Health Technology Briefing
December 2023

Pembrolizumab with or without olaparib following pembrolizumab with chemoradiation therapy for previously untreated, advanced, stage III non-small-cell lung cancer

Company/Developer	Merck Sharp & Dohme Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 29961	NICE ID: Not available	UKPS ID: 666145

Licensing and Market Availability Plans

Currently in phase III clinical development.

Summary

Pembrolizumab with or without olaparib following pembrolizumab with chemoradiation therapy is currently in development for treatment of adults with unresectable, locally advanced, stage III non-small-cell lung cancer (NSCLC). NSCLC is the most common form of lung cancer. Advanced cancer often refers to cancer that cannot be cured. Stage III NSCLC is considered "locally advanced," meaning that it has spread regionally, in the area near the original tumour. The main risk factor for lung cancer is smoking. Some symptoms of lung cancer include a persistent cough, repeated chest infections, breathlessness, unexplained pain, weight loss or tiredness. Lung cancer remains the leading cause of cancer deaths, and there is need for more treatment options to prolong survival and preserve quality of life.

Pembrolizumab is designed to bind to a receptor called programmed death-1 (PD-1) and stops the cancer switching off these immune cells, thereby increasing the immune response to tumour cells. Olaparib is designed to block the action of an enzyme in cancer cells and stop the cells from growing further. If licensed, pembrolizumab with or without olaparib following pembrolizumab with chemoradiation therapy, would offer an additional treatment option for patients with previously untreated, locally advanced, stage III NSCLC.

Proposed Indication

Treatment of adults with unresectable, locally advanced, stage III non-small-cell lung cancer (NSCLC).[1]

Technology

Description

Pembrolizumab (Keytruda) is a humanised monoclonal antibody that binds to programmed cell death-1 receptors, blocking their interactions with programmed death ligand (PD-L)-1 and PD-L2. As the programmed death 1 (PD-1) receptor has been shown to be involved in the control of T-cell immune responses, pembrolizumab is designed to enhance T-cell responses, including anti-tumour responses, by blocking PD-1 that binds to PD-L1 and PD-L2, which may both be expressed in tumours.[2] Olaparib (Lynparza) 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 either as a standalone treatment or in combination with established chemotherapies or new hormonal agents.[3]

In the phase III clinical trial (NCT04380636), patients were administered pembrolizumab 200 milligrams (mg) intravenously (IV) every 3 weeks (Q3W) in combination with 3 cycles of the investigator's choice of platinum doublet chemotherapy and concurrent standard thoracic radiotherapy (60 Gray (Gy) over 6 weeks) followed by pembrolizumab plus olaparib twice a day (BID) for approximately 1 year.[1]

Key Innovation

Concurrent chemoradiotherapy is a standard therapy for patients with stage III NSCLC.[4] Radiotherapy potentially 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.[5] The phase II trial (NCT02492568) showed that pembrolizumab preceded by radiotherapy 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.[6] PARP inhibitors such as olaparib have been shown to upregulate PD-L1 expression in preclinical studies, suggesting a therapeutic benefit of combining anti-PD-L1 therapy (pembrolizumab) with a PARP inhibitor (olaparib).[7] If licensed, pembrolizumab with or without olaparib following the combination of pembrolizumab and chemoradiation, would offer an additional treatment option for patients with previously untreated, locally advanced, stage III NSCLC.

Regulatory & Development Status

Pembrolizumab and olaparib do not currently have Marketing Authorisation in the UK/EU as a combination but do as monotherapies or in combination with other drugs.

Pembrolizumab currently has Marketing Authorisation in the UK as a combination therapy for:[2]

- NSCLC
- Head and neck squamous cell carcinoma (HNSCC)
- Renal cell carcinoma (RCC)
- Oesophageal carcinoma
- Triple-negative breast cancer (TNBC)
- Endometrial carcinoma

- Cervical cancer

Pembrolizumab currently has Marketing Authorisation in the UK as a monotherapy for:[2]

- Melanoma
- NSCLC
- Classic Hodgkin lymphoma
- Urothelial carcinoma
- HNSCC
- RCC
- Microsatellite instability high or mismatch repair deficient cancers (including colorectal cancer, advanced or recurrent endometrial carcinoma and unresectable or metastatic gastric, small intestine or biliary cancer)
- TNBC as adjuvant after surgery

Olaparib currently has Marketing Authorisation in the UK as a combination therapy for:[3]

- Ovarian cancer
- Prostate cancer

Pembrolizumab and olaparib in combination are also in phase II and III clinical trials for several other indications, but not limited to:[8]

- Solid tumours
- Small cell lung cancer
- Uveal melanoma
- Ocular melanoma
- Endometrial carcinoma

Patient Group

Disease Area and Clinical Need

NSCLC is the most common form of lung cancer. Around 80 to 85% of lung cancer cases in the UK are NSCLC. The three main types are adenocarcinoma, squamous cell carcinoma and large cell carcinoma.[9] Advanced cancer often refers to cancer that cannot be cured. However, some advanced cancers can be controlled over a long period and are considered an ongoing (or chronic) illness.[10] The stage of lung cancer refers to the size of cancer, how aggressive it is and where, if at all, it has spread. Stage III NSCLC is considered "locally advanced," meaning that it has spread regionally in the area near the original tumour.[11] Risk factors for lung cancer include smoking, second-hand smoke, exposure to workplace chemicals, radiation exposure, air pollution, and family history of lung cancer.[12] Symptoms of lung cancer can include a persistent cough, repeated chest infections, breathlessness, unexplained pain, weight loss, or tiredness. However, early stages of lung cancer may not always be symptomatic.[13]

Lung cancer is the third most common cancer in the UK, accounting for 13% of all new cancer cases (2016 - 2018).[14] Between 2017 and 2019 in the UK, there were 34,771 deaths due to lung cancer; the age-standardised mortality rate was 55.5 per 100,000.[15] In England (2017) the one year age-standardised survival rate for stage III lung cancer was 48.7%, dropping to 12.6% survival rate after 5 years.[16] In England, 2022-23, there were 122,866 finished consultant episodes (FCE) and 104,232 admissions for malignant neoplasm of bronchus and lung (ICD-10 code C34) which resulted in 217,569 FCE bed days and 80,131 day cases.[17]

Recommended Treatment Options
Treatment for lung cancer includes surgery, chemotherapy, radiotherapy, immunotherapy, and other targeted therapy drugs. Patients may be offered one or more different treatments depending on the stage, histology and type of lung cancer as well as their general health.[18] The National Institute for Health and Care Excellence (NICE) currently recommends durvalumab for locally advanced unresectable NSCLC in adults whose tumours express PD-L1 on 1% or more of cells and whose disease has not progressed after platinum-based chemoradiation.[19]

Clinical Trial Information

Trial	**KEYLYNK-012,** NCT04380636; EudraCT 2019-003237-41; A Phase 3 Study of Pembrolizumab (MK-3475) in Combination With Concurrent Chemoradiation Therapy Followed by Pembrolizumab With or Without Olaparib vs Concurrent Chemoradiation Therapy Followed by Durvalumab in Participants With Unresectable, Locally Advanced, Stage III Non-Small Cell Lung Cancer (NSCLC) **Phase III** - Recruiting **Locations:** 12 EU countries, UK, USA, Canada, and other countries **Primary completion date:** July 2026
Trial Design	Randomised, parallel assignment, triple masked, active comparator controlled
Population	N=870 (estimated); aged 18 years or older; has pathologically (histologically or cytologically) confirmed diagnosis of NSCLC (Stage IIIA, IIIB, or IIIC) and have not received prior treatment for stage III NSCLC
Intervention(s)	Pembrolizumab 200 mg (IV Q3W in combination with 3 cycles of the investigator's choice of platinum doublet chemotherapy and concurrent standard thoracic radiotherapy (60 Gy over 6 weeks) followed by pembrolizumab plus olaparib 300 mg BID for approximately 1 year
Comparator(s)	• 3 cycles of the investigator's choice of platinum doublet chemotherapy with concurrent standard thoracic radiotherapy (60 Gy over 6 weeks) followed by durvalumab 10 mg/kg every 2 weeks (Q2W) for approximately 1 year • Pembrolizumab plus chemoradiation followed by pembrolizumab plus olaparib placebo
Outcome(s)	Primary outcomes: • Progression-Free Survival (PFS) According to Response Evaluation Criteria in Solid Tumours Version 1.1 (RECIST 1.1) as Assessed by Blinded Independent Central Review (BICR) [Time Frame: Up to approximately 48 months] • Overall Survival (OS) [Time Frame: Up to approximately 72 months] See trial record for full list of outcomes.
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The NHS indicative cost of one vial of pembrolizumab 25mg/ml is £2,630.[20] The NHS indicative cost of a pack of 56 100mg tablets of olaparib is £2,317.50.[21]

Relevant Guidance

NICE Guidance

- NICE technology appraisal guidance. Durvalumab for maintenance treatment of unresectable non-small-cell lung cancer after platinum-based chemoradiation (TA798). June 2022.
- NICE guideline. Lung cancer: diagnosis and management (NG122). March 2019. Updated July 2023.
- NICE quality standard. Lung cancer in adults (QS17). March 2012. Updated December 2019.

NHS England (Policy/Commissioning) Guidance

- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.

Other Guidance

- National Health Service Northern Cancer Alliance. Lung Cancer Clinical Guidelines. May 2019.[22]
- European Society for Medical Oncology (ESMO). Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment, and follow-up. July 2017.[23]
- London Cancer Alliance. LCA Lung Cancer Clinical Guidelines. March 2016.[24]

Additional Information

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