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HEALTH TECHNOLOGY BRIEFING
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Pembrolizumab in combination with olaparib as maintenance therapy for non-small-cell lung cancer following first line treatment

NIHRIO ID	27355	**NICE ID**	10489
Developer/Company	Merck Sharp & Dohme	**UKPS ID**	653249

Licensing and market availability plans	Currently in phase III clinical trials

SUMMARY

Pembrolizumab in combination with olaparib is currently in development as a maintenance treatment of non-small cell lung cancer (NSCLC) in those that have not progressed following first line treatment. NSCLC makes up the majority of lung cancers in the UK and most patients are diagnosed at the advanced/metastatic stage where curative treatment with surgery is unsuitable. There are currently a number of first-line treatment options to control the advanced/metastatic disease, but there are limited maintenance treatment options to reduce the risk of progression.

Pembrolizumab delivered via intravenous infusion is a type of immunotherapy that stimulates the body's immune system to fight cancer cells. Olaparib is administered orally in tablet form and can lead to cancer cell death by blocking DNA repair by the PARP enzyme. Pembrolizumab is currently recommended as a first line treatment of NSCLC and evidence suggests that the addition of olaparib may improve its effectiveness. If licensed, pembrolizumab in combination with olaparib will offer an additional maintenance treatment for patients with advanced NSCLC.

PROPOSED INDICATION

Pembrolizumab, in combination with olaparib, for the maintenance treatment of metastatic, non-squamous NSCLC.[1]

TECHNOLOGY

DESCRIPTION

Pembrolizumab (Keytruda, MK-3475) is a humanised monoclonal anti-programmed cell death-1 (PD-1) antibody which binds to the 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]

Olaparib (Lynparza) is a potent inhibitor of human poly (ADP-ribose) polymerase enzymes (PARP-1, PARP-2, PARP-3) 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.[3]

Pembrolizumab in combination with olaparib is in development as maintenance therapy for non-small-cell lung cancer following first line treatment. In a phase III clinical trial (NCT03976323, KEYLYNK-006), the treatment schedule is as following:[4]

- Induction phase – patients receive 4 cycles of treatment consisting of pembrolizumab, pemetrexed and carboplatin AUC or cisplatin on day 1 of each 21 day cycle.
- Maintenance phase – patients receive pembrolizumab 200mg via IV infusion on day 1 of each 21 day cycle, for up to cycles. This is in combination with olaparib 300mg via oral tablet twice daily.

INNOVATION AND/OR ADVANTAGES

Pemetrexed is currently the only maintenance therapy option for advanced NSCLC that has not progressed following first line treatment, hence the need for more treatment options.[5]

Pembrolizumab is a PD-L1 antibody currently used as a first-line treatment for NSCLC. PARP inhibitors such as olaparib have been demonstrated to upregulate PD-L1, improving its effectiveness. As a result, there may be potential therapeutic benefit for the use of pembrolizumab and olaparib in combination for this indication.[6]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Pembrolizumab and olaparib in combination do not currently have Marketing Authorisation for any indication in the EU/UK. Both pembrolizumab and olaparib have Marketing Authorisation in the EU/UK as monotherapies and other combinations for several indications.[2,3]

The most common adverse events of pembrolizumab monotherapy or in combination with chemotherapy or other anti-tumour medicines include anaemia, neutropenia, thrombocytopenia, hypothyroidism, decreased appetite, hypokalaemia, headache, dizziness, peripheral neuropathy, dysgeusia, dyspnoea, cough, diarrhoea, abdominal pain, nausea,

vomiting, constipation, rash, pruritus, alopecia, musculoskeletal pain, arthralgia, fatigue, asthenia, oedema, pyrexia and blood creatinine increased.[2]

Olaparib monotherapy has been associated with adverse reactions generally of mild or moderate severity (CTCAE grade 1 or 2) and generally not requiring treatment discontinuation. The most frequently observed adverse reactions across clinical trials in patients receiving olaparib monotherapy (⩾ 10%) were nausea, vomiting, diarrhoea, dyspepsia, fatigue, headache, dysgeusia, decreased appetite, dizziness, cough, dyspnoea, anaemia, neutropenia, thrombocytopenia and leukopenia.[3]

Pembrolizumab in combination with olaparib is in phase II/III clinical trials for the following:[7]

- prostate cancer
- triple negative breast neoplasms
- solid tumours
- cholangiocarcinoma,
- head and neck cancer
- epithelial ovarian cancer
- advanced gastric adenocarcinoma.

PATIENT GROUP

DISEASE BACKGROUND

Lung cancer is one of the most common and serious types of cancer. There are usually no signs or symptoms in the early stages of lung cancer, but many people with the condition eventually develop symptoms such as a persistent cough, coughing up blood, persistent breathlessness, unexplained tiredness and weight loss, and/or an ache or pain when breathing or coughing.[8]

Smoking cigarettes is the single biggest risk factor for lung cancer and is responsible for more than 70% of cases. Other risk factors include passive smoking, radon (a radioactive gas), and exposure to chemicals such as arsenic, asbestos, beryllium, cadmium, coal/coke, silica and nickel.[9]

Lung cancer can be categorised into two main groups: small cell lung cancer or NSCLC. The latter is the most common type. There are three main types of NSCLC:[10]

- Adenocarcinoma – starts in the mucus making gland cells in the lining of airways
- Squamous cell cancer – develops in the flat cells that cover the surface of the airways
- Large cell carcinoma – the cancer appears large and round under the microscope

In addition to being diagnosed by type of lung cancer, patients will also have the cancer graded. Grading is based on how cells look under a microscope, and gives an estimate of how quickly or slowly the cancer is growing, and whether it is likely to spread.[11] Advanced lung cancer means that the cancer has spread from where it started in the lung. It is also called metastatic cancer. Advanced cancer cannot usually be cured, but treatment can control it, help symptoms and improve quality of life.[12]

CLINICAL NEED AND BURDEN OF DISEASE

Lung cancer is the third most common cancer in the UK, accounting for 13% of all new cancer cases in 2017. There are around 48,000 new lung cancer cases in the UK yearly. Incidence rates for lung cancer in the UK are highest in people aged 85 to 89 (2015-2017). Incidence

rates for lung cancer are projected to fall by 7% in the UK between 2014 and 2035, to 88 cases per 100,000 people by 2035.[13]

In 2020/21, there were 86,043 hospital admissions with primary diagnosis malignant neoplasm of bronchus and lung (ICD-10 code C34), and 103,856 finished consultant episodes (FCEs), resulting in 170,030 FCE bed days.[14]

According to the National Cancer Registration and Analysis Service (NCRAS), there were 18,213 diagnosed cases of stage IV lung cancer in 2017, this represents 47% of the overall number of lung cancer cases diagnosed for that year.[15] In the UK it is estimated that up to 85% of lung cancer cases are NSCLC, applying this figure to the number of stage IV lung cancer cases diagnosed in 2017, it can be estimated that approximately 15,481 cases diagnosed with stage IV in 2017 were NSCLC.[10]

In England between 2013 and 2017, the age-standardised net lung cancer survival for stage IV was 19.3% at one year and 2.9% at five years.[16] There are around 35,100 lung cancer deaths in the UK every year (based on data from 2016-2018). Mortality rates for lung cancer are projected to fall by 21% in the UK between 2014 and 2035.[17]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Treatment of NSCLC depends on the stage of the cancer and the general health of the patient. At advanced (stage III) or metastatic (stage IV) disease, where patients are not candidates for surgical resection or definitive chemoradiation, treatment aims to control the cancer for as long as possible and help with symptoms. Treatment generally include chemotherapy, targeted drugs, radiotherapy and symptom control treatment.[18]

Recommended maintenance treatment options for advanced or metastatic NSCLC in those that have not progressed following first line treatment are limited.[5]

CURRENT TREATMENT OPTIONS

Currently NICE recommends pemetrexed as an option for the maintenance treatment of locally advanced or metastatic NSCLC in adults when their disease has not progressed immediately after 4 cycles of pemetrexed and cisplatin induction therapy.[5,19]

PLACE OF TECHNOLOGY

If licensed, pembrolizumab in combination with olaparib will offer an additional maintenance treatment for patients with metastatic non-squamous NSCLC.

CLINICAL TRIAL INFORMATION

Trial	**KEYLYNK-006**; NCT03976323; 2018-004720-11; A Phase 3 Study of Pembrolizumab in Combination With Pemetrexed/Platinum (Carboplatin or Cisplatin) Followed by Pembrolizumab and Maintenance Olaparib vs Maintenance Pemetrexed in the First-Line Treatment of Participants With Metastatic Non-squamous Non-Small-Cell Lung Cancer **Phase III** – active, not recruiting

	Location(s): 6 EU countries, UK, US, Canada and other countries **Primary completion date:** August 2024
Trial design	Randomised, parallel assignment, open-label, active-controlled
Population	N~792; 18 years and older; have a histologically or cytologically confirmed diagnosis non-squamous NSCLC; have stage IV non-squamous NSCLC
Intervention(s)	For the Induction Phase, participants receive 4 cycles: • Pembrolizumab 200 mg IV on day 1 of each 21-day cycle (cycles 1 through 4) PLUS pemetrexed 500 mg/m^2 IV on day 1 of each 21-day cycle (cycles 1 through 4) PLUS platinum chemotherapy, investigator's choice: carboplatin area under the curve (AUC) 5 mg/mL/min IV on day 1 of 21-day cycle (Cycles 1 through 4) OR cisplatin 75 mg/m^2 IV on day 1 of 21-day cycle (Cycles 1 through 4). • If the participant has a complete or partial response or stable disease to induction therapy, the participant is randomised to maintenance therapy. • For the maintenance phase, participants receive Pembrolizumab 200 mg IV on day 1 of each 21-day cycle for up to 31 cycles PLUS maintenance oral olaparib 300 mg twice daily. In the maintenance phase, the participant continues to receive maintenance olaparib until progressive disease, physician decision or intolerable toxicity.
Comparator(s)	For the Induction Phase, participants receive 4 cycles: • Pembrolizumab 200 mg IV on day 1 of each 21-day cycle (cycles 1 through 4) PLUS pemetrexed 500 mg/m^2 IV on day 1 of each 21-day cycle (cycles 1 through 4) PLUS platinum chemotherapy, investigator's choice: carboplatin area under the curve (AUC) 5 mg/mL/min IV on day 1 of 21-day cycle (Cycles 1 through 4) OR cisplatin 75 mg/m^2 IV on day 1 of 21-day cycle (Cycles 1 through 4). • If the participant has a complete or partial response or stable disease to induction therapy, the participant is randomized to maintenance therapy. • For the maintenance phase, participants receive Pembrolizumab 200 mg IV on day 1 of each 21 day-cycle for up to 31 cycles PLUS maintenance pemetrexed IV 500 mg/m^2 on day 1 of each 21-day cycle. In the maintenance phase, the participant continues to receive maintenance pemetrexed until progressive disease, physician decision or intolerable toxicity.
Outcome(s)	• Progression-free Survival (PFS) Per Response Evaluation Criteria in Solid Tumours Version 1.1 (RECIST 1.1) [Time frame: Up to approximately 3 years] • Overall Survival (OS) [Time frame: Up to approximately 5 years] See trial record for full list of other outcomes

Results (efficacy)	-
Results (safety)	-

ESTIMATED COST

For pembrolizumab, the NHS indicative price for a vial of pembrolizumab (100 mg/4 ml) is £2630.00.[20]

For olaparib, the NHS indicative price is £2317.50 for 56 x 100 mg and 150 mg tablets and £3,550 for 448 x 50 mg capsules.[21]

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal. Atezolizumab monotherapy for untreated advanced non-small-cell lung cancer. [TA705]. June 2021.
- NICE technology appraisal. Pembrolizumab with pemetrexed and platinum chemotherapy for untreated, metastatic, non-squamous non-small-cell lung cancer. [TA683]. March 2021.
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- NICE technology appraisal. Pemetrexed maintenance treatment for non-squamous non-small-cell lung cancer after pemetrexed and cisplatin. [TA402]. August 2016.
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- NICE guideline. Lung cancer: diagnosis and management (NG122). March 2019.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

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OTHER GUIDANCE

- National Comprehensive Cancer Network (NCCN). Non–Small Cell Lung Cancer, Version 5.2017, NCCN Clinical Practice Guidelines in Oncology. 2017.[22]
- European Society for Medical Oncology. Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2016.[23]
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ADDITIONAL INFORMATION

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