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HEALTH TECHNOLOGY BRIEFING
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Pembrolizumab in combination with ipilimumab for advanced non-small cell lung cancer

NIHRIO ID	20564	NICE ID	10207
Developer/Company	Merck Sharp & Dohme Ltd	UKPS ID	651299

Licensing and market availability plans	Currently in phase III clinical trials

SUMMARY

Pembrolizumab in combination with ipilimumab is under development for the treatment of advanced non-small cell lung cancer (NSCLC), which comprises the majority of lung cancers in the UK. Symptoms of lung cancer include a persistent cough, shortness of breath, coughing up blood, aches and pains in the chest or shoulder, loss of appetite, weight loss and fatigue. While current treatments exist for NSCLC, significant unmet medical need remains for more effective treatment options. Combining different technologies targeting complementary pathways might result in additional or complementary antitumor activity.

Pembrolizumab is a humanised monoclonal anti - programmed cell death - 1 (PD - 1) antibody. Pembrolizumab works by improving the activity of white blood cells in killing cancer cells by blocking PD-L1. Ipilimumab increases the activity of T-cells against cancer cells. If licensed, this combination of pembrolizumab and ipilimumab administered intravenously could offer a treatment for patients with NSCLC whose tumours express high levels of PD-L1.

PROPOSED INDICATION

Treatment of patients with advanced non-small cell lung cancer (NSCLC) whose tumours express high levels of programmed cell death ligand 1 (PD-L1) (Tumour Proportion Score (TPS) ⩾50%).[a]

TECHNOLOGY

DESCRIPTION

Pembrolizumab (Keytruda, MK-3475) is a humanised monoclonal anti-programmed cell death-1 (PD-1) antibody (IgG3/kappa isotope with a stabilising sequence alteration in the Fc region) produced in Chinese hamster ovary cells by recombinant DNA technology. 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.[1]

In the phase III clinical trial (NCT03302234, KEYNOTE-598), participants receive 200mg of pembrolizumab by intravenous (IV) infusion on day 1 of each 3 week cycle for up to 35 cycles of treatment plus 1mg/kg of ipilimumab by IV infusion on day 1 of each 6 week cycle for up to 18 cycles of treatment.[2]

INNOVATION AND/OR ADVANTAGES

Pembrolizumab and ipilimumab are both anti-tumour drugs with different mechanisms of action and are both licensed as monotherapies for certain types of cancer. Combining immunotherapies such as anti–PD-1 and anti–CTLA-4 agents, which target complementary pathways in the cancer-immunity cycle, might result in additive or synergistic antitumor activity compared with single-agent therapy.[3]

In a phase II trial, it was determined that this combination of drugs showed anti-tumour activity but it was also associated with meaningful toxicity.[4]

[a] Information provided by Merck Sharp and Dohme Ltd on UK PharmaScan

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

The combination of pembrolizumab and ipilimumab is not currently licensed for any indication in the UK. Pembrolizumab is currently licensed as a monotherapy for NSCLC in adults whose tumours expressed PD-L1 with a ≥ 50% TPS, with no EGFR (epidermal growth factor receptor) or ALK (anaplastic lymphoma kinase) positive mutations.[1]

Pembrolizumab is currently licenced as a combination treatment in the UK:[1]

- as monotherapy or in combination with platinum and 5-fluorouracil chemotherapy, is indicated for the first-line treatment of metastatic or unresectable recurrent HNSCC in adults whose tumours express PD-L1 with a CPS ≥ 1.
- in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of metastatic non-squamous non-small cell lung carcinoma in adults whose tumours have no EGFR or ALK positive mutations.
- in combination with carboplatin and either paclitaxel or nab-paclitaxel, is indicated for the first-line treatment of metastatic squamous non-small cell lung carcinoma in adults.
- in combination with axitinib, is indicated for the first-line treatment of advanced renal cell carcinoma in adults

Very common adverse events of pembrolizumab as a monotherapy (affecting more than one in ten people) include anaemia, hypothyroidism, headache, decreased appetite, dyspnoea, cough, diarrhoea, abdominal pain, nausea, vomiting, constipation, rash, pruritus, musculoskeletal pain, arthralgia, fatigue, asthenia, oedema and pyrexia.[1]

PATIENT GROUP

DISEASE BACKGROUND

Lung cancer is classified into two main types: small-cell lung cancer (SCLC) or NSCLC. NSCLC comprises approximately 80 to 85% of lung cancers in the UK. There are three common types of NSCLC; adenocarcinoma (the most common type which starts in the mucus making glands in the lining of the airways), squamous cell cancer (develops in the flat cells that cover the surface of the airways and tends to grow near the centre of the lung) and large cell carcinoma (cancer cells which appear large and round under the microscope).[5] In stage IV the cancer has spread, either to both lungs, the chest or beyond.[6]

Tobacco smoking remains the main cause of lung cancer and the geographical and temporal patterns of the disease largely reflect tobacco consumption during previous decades. Smoking prevention and cessation can lead to a large reduction in lung cancers. In countries with active tobacco control measures, the incidence of lung cancer has begun to decline in men and is reaching a plateau for women. An increase in the proportion of NSCLC in never-smokers has been observed, especially in Asian countries. These new epidemiological data have resulted in 'non-smoking-associated lung cancer' being considered a distinct disease entity, where specific molecular and genetic tumour characteristics have been identified.[7]

Several other factors have been described as lung cancer risk factors including; exposure to radiation certain chemicals (e.g. asbestos, silica and diesel engine exhaust fumes) and previous lung disease (e.g. tuberculosis and COPD). Other factors include family history of lung cancer and certain genetic mutations.[8]

Symptoms of lung cancer include a persistent cough (which may be more painful, have a different sound or bring up coloured mucus), shortness of breath, coughing up blood, aches and pains in the chest or shoulder, loss of appetite, weight loss and fatigue.[9, 10]

CLINICAL NEED AND BURDEN OF DISEASE

Primary lung cancer remains the most common malignancy after non-melanocytic skin cancer, and deaths from lung cancer exceed those from any other malignancy worldwide.[7]

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.[11]

In 2018/19 there were 107,010 hospital admissions with primary diagnosis malignant neoplasm of bronchus and lung (ICD-10 code C34), and 128,985 finished consultant episodes (FCEs), resulting in 249,196 FCE bed days.[12] 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 the 47% of the overall number of lung cancer cases diagnosed for that year.[13] In the UK 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.[5]

Survival rates for lung cancer depend on at which stage of disease the cancer is identified.[11] 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.[14] There are around 35,300 lung cancer deaths in the UK every year (based on data from 2015-2017). Mortality rates for lung cancer are projected to fall by 21% in the UK between 2014 and 2035.[11] In England and Wales in 2018 there were 29,604 deaths with malignant neoplasm of bronchus and lung (ICD-10 codes C34) recorded as the underlying cause.[15]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Treatment of NSCLC depends on the stage of the cancer and the general health of the patient. At stage IV NSCLC, 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.[16]

CURRENT TREATMENT OPTIONS

The following are recommended for first-line treatment of patients with advanced nonsquamous NSCLC, and no specific modifications to the EGFR or ALK genes:[17]

- PD-L1 50% or over (no gene mutation, fusion protein or biomarker):
  - Pembrolizumab with pemetrexed and platinum chemotherapy
  - Pembrolizumab

For treatment of squamous NSCLC, NICE recommends platinum-based chemotherapy as an option for people with previously untreated stage III or IV NSCLC and good performance status. Pembrolizumab monotherapy is also recommended as an option for untreated PD-L1-positive metastatic NSCLC if the tumour expresses PD-L1 with at least 50% tumour proportion score and has no EGFR- or ALK-positive mutations. Pembrolizumab with carboplatin and paclitaxel is also recommended as an option for adults with untreated metastatic squamous NSCLC for use within the Cancer Drugs Fund (CDF).[18]

PLACE OF TECHNOLOGY

If licensed, pembrolizumab in combination with ipilimumab will offer a treatment for patients with advanced NSCLC whose tumours express high levels of PD-L1 (TPS⩾50%).[b]

CLINICAL TRIAL SUMMARY INFORMATION

Trial	**KEYNOTE-598;** NCT03302234; EudraCT 2016-004364-20; A Phase 3, Randomized, Double-Blind Study of Pembrolizumab Plus Ipilimumab vs Pembrolizumab Plus Placebo in Previously Untreated, Stage IV, Metastatic Non-small Cell Lung Cancer Subjects Whose Tumors Are PD-L1 Positive (TPS ≥ 50%) **Phase III – Active, not recruiting** **Location(s):** EU (inc UK), US, Canada and other countries **Primary Completion Date:** Feb 2023
Trial design	Randomised, parallel assignment, quadruple-blinded
Population	N=568; 18 years and older; has a histologically or cytologically confirmed diagnosis of Stage IV metastatic NSCLC; has a life expectancy of >3 months; has Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
Intervention(s)	Participants receive 200 mg of pembrolizumab by intravenous (IV) infusion on day 1 of each 3-week cycle for up to 35 cycles of treatment plus 1 mg/kg of ipilimumab by IV infusion on day 1 of each 6-week cycle for up to 18 cycles of treatment.
Comparator(s)	Participants receive 200 mg of pembrolizumab by IV infusion on day 1 of each 3-week cycle for up to 35 cycles of treatment plus placebo by IV infusion on day 1 of each 6-week cycle for up to 18 cycles of treatment.
Outcome(s)	• Overall Survival (OS) [Time frame: up to 27 months] OS is the time from randomisation to death due to any cause. • Progression-free Survival (PFS) [Time frame: up to 27 months] PFS is the time from randomisation to first documented disease progression per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) by Blinded Independent Central Review (BICR). See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

ESTIMATED COST

Pembrolizumab is already marketed in the UK. The NHS indicative price is:[19]

- A 25mg/ml concentrate for solution for infusion vial costs £2630.00
- A 50 mg powder for concentrate for solution for infusion vial costs £1315.00

Ipilimumab is already marketed in the UK. The NHS indicative prices for ipilimumab solution for infusion vials are as follows:[20]

- Ipilimumab 5mg/ml concentrate for solution for infusion vials (1 vial) costs £15000.00.

[b] Information provided by Merck Sharpe & Dohne on UK PharmaScan

- Ipilimumab 50mg/10ml concentrate for solution for infusion vials (1 vial) costs £3750.00.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Durvalumab with tremelimumab for untreated non-small-cell lung cancer with no EGFR- or ALK-positive mutations (TA10186). Expected date of issue to be confirmed.
- NICE technology appraisal. Pembrolizumab with carboplatin and paclitaxel for untreated metastatic squamous non-small-cell lung cancer (TA600). September 2019.
- NICE technology appraisal. Pembrolizumab with pemetrexed and platinum chemotherapy for untreated, metastatic, non-squamous non-small-cell lung cancer (TA557). January 2019.
- NICE technology appraisal. Pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer (TA531). July 2018.
- NICE technology appraisal. Necitumumab for untreated advanced or metastatic squamous non-small-cell lung cancer (TA411). September 2016.
- NICE technology appraisal. Gefitinib for the first-line treatment of locally advanced or metastatic non-small-cell lung cancer (TA192). July 2010.
- NICE technology appraisal. Pemetrexed for the first-line treatment of non-small cell lung cancer (TA181). September 2009.
- NICE technology appraisal. Pemetrexed for the treatment of non-small-cell lung cancer (TA124). August 2007.
- NICE guideline. Lung cancer: diagnosis and management (NG122). March 2019.
- NICE quality standard. Lung cancer in adults (QS17). March 2019.

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). Non–Small Cell Lung Cancer, Version 5.2017, NCCN Clinical Practice Guidelines in Oncology. 2017.[21]
- European Society for Medical Oncology. Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2016.[22]
- European Society for Medical Oncology. ESMO Consensus Guidelines: Non-small-cell lung cancer first-line/second and further lines in advanced disease. 2014.[23]
- Scottish Intercollegiate Guidelines Network. Management of lung cancer (SIGN 137). 2014.[24]

ADDITIONAL INFORMATION

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