

HEALTH TECHNOLOGY BRIEFING DECEMBER 2020

Pembrolizumab with or without standard adjuvant therapy after resection for non-small-cell lung cancer - adjuvant

NIHRIO ID	28449	NICE ID	10365
Developer/Company	Merck Sharp & Dohme Ltd	UKPS ID	654465

Licensing and market availability plans	Currently in phase III clinical development.
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SUMMARY

Adjuvant pembrolizumab with or without standard adjuvant treatment is in clinical development for the treatment of early-stage operable non-small cell lung cancer (NSCLC) after resection. NSCLC is the most common type of lung cancer. Early-stage lung cancer is typically treated with surgery to remove either part of or the whole of the lung, with adjuvant (additional treatment given after the primary treatment) chemotherapy and/or radiotherapy. Treatment with immunotherapy after surgery may provide better long-term survival prospects for patients with early-stage operable NSCLC.

Pembrolizumab is an immunotherapy drug administered by intravenous infusion. It works by improving the activity of white blood cells (T-cells) by blocking a protein, PD-L1, thereby increasing the ability of the immune system to kill cancer cells. If licensed, with or without standard adjuvant treatment, pembrolizumab will offer an additional treatment option for patients with early-stage, operable NSCLC who currently have few well tolerated and effective therapies available.

This briefing reflects the evidence available at the time of writing and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information. A version of the briefing was sent to the company for a factual accuracy check. The company was available to comment.

PROPOSED INDICATION

Adjuvant treatment of adults with early stage NSCLC after resection, with or without standard adjuvant therapy.¹

TECHNOLOGY

DESCRIPTION

Pembrolizumab 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 (PD-L)-1 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

In the phase III trial (NCT02504372, MK-3475-091/KEYNOTE-091) pembrolizumab 200mg is administered intravenously (IV), every 3 weeks, for one year (expected maximum 18 doses).¹

INNOVATION AND/OR ADVANTAGES

This is a new indication for pembrolizumab. It is not currently licensed for the treatment of NSCLC after surgical resection.²

The benefit of adjuvant chemotherapy in NSCLC has plateaued at around 5.4% improvement in 5-year overall survival and is hampered by toxicities having a major impact on treatment compliance. It is hypothesized that immunotherapy (i.e. pembrolizumab) works best in the context of minimal residual disease. Adjuvant treatment with pembrolizumab after surgery could therefore provide an increased cure rate for NSCLC.³

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Pembrolizumab is currently licenced as a monotherapy in the UK for:²

- The treatment of advanced (unresectable or metastatic) melanoma in adults.
- Adjuvant treatment of adults with stage III melanoma and lymph node involvement who have undergone complete resection.
- First-line treatment of metastatic NSCLC in adults whose tumours express PD-L1 with a $\geq 50\%$ tumour proportion score (TPS) with no epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) positive tumour mutations.
- The treatment of locally advanced or metastatic NSCLC in adults whose tumours express PD-L1 with a $\geq 1\%$ TPS and who have received at least one prior chemotherapy regimen. Patients with EGFR or ALK positive tumour mutations should also have received targeted therapy before receiving pembrolizumab.
- The treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant and brentuximab vedotin (BV), or who are transplant-ineligible and have failed BV.

- The treatment of locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy.
- The treatment of locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD L1 with a combined positive score (CPS) ≥ 10 .
- As monotherapy or in combination with platinum and 5-fluorouracil (5-FU) chemotherapy, is indicated for the first-line treatment of metastatic or unresectable recurrent head and neck squamous cell carcinoma (HNSCC) in adults whose tumours express PD-L1 with a CPS ≥ 1 .
- The treatment of recurrent or metastatic HNSCC in adults whose tumours express PD-L1 with a $\geq 50\%$ TPS and progressing on or after platinum-containing chemotherapy.

Pembrolizumab is currently licenced as a combination therapy in the UK in combination with:²

- axitinib for the first-line treatment of advanced renal cell carcinoma in adults
- pemetrexed and platinum chemotherapy 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.
- carboplatin and either paclitaxel or nab-paclitaxel for the first-line treatment of metastatic squamous non-small cell lung carcinoma in adults.

The most common adverse events of pembrolizumab monotherapy include: anaemia, hyperthyroidism, decreased appetite, headache, dyspnoea, cough, diarrhoea, abdominal pain, nausea, vomiting, constipation, rash, pruritus, musculoskeletal pain, arthralgia, fatigue, asthenia, oedema and pyrexia.²

Pembrolizumab is currently in phase III and phase II clinical trials for many cancer indications including gastric, cervical, head and neck, urothelial and breast cancer.⁴

PATIENT GROUP

DISEASE BACKGROUND

Lung cancer is classified into two main types: small-cell lung cancer (SCLC) or NSCLC. NSCLC comprises approximately 87% of lung cancers.⁵ 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).⁶

The stages of lung cancer are as follows:^{7,8}

Stage I: the cancer is small and is contained inside the lung. It has not spread to lymph nodes. IA is smaller than 3cm across. IB the cancer is between 3 cm and 4 cm in size.

Stage IIA: the cancer is between 4cm and 5cm in size but has not spread to any lymph nodes.

Stage IIB:

- the cancer is up to 5cm in size and has spread into nearby lymph nodes or
- the cancer is between 5cm and 7cm but has not spread into any lymph nodes or
- there is more than one area of cancer in one lobe of the lung or

- the cancer has spread into structures close to the lung

Stage III: the cancer is in more than one lobe of the lung, or it has spread to lymph nodes or nearby structures in the chest.

Stage IV: the cancer has spread to the other lung or to a distant part of the body such as the liver or bones.

Common risk factors for the development of lung cancer include tobacco smoking, exposure to air pollution, radon gas, silica and asbestos, previous lung disease such as COPD, family history of lung cancer, previous radiotherapy treatment and lowered immunity.⁹

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 phlegm with blood, aches and pains in the chest or shoulder, recurrent chest infections, loss of appetite, weight loss and fatigue.¹⁰

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 47,800 new lung cancer cases in the UK yearly. Incidence rates for lung cancer in the UK are highest in people aged 85 to 89 years (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 the UK it is estimated that up to 87% of lung cancer cases are NSCLC.¹²

In England in 2017, there were 38,888 newly diagnosed cases of malignant neoplasm of the bronchus and lung (ICD-10 code C34).¹³ According to the National Cancer Registration and Analysis Service (NCRAS), 18,175 of the cases in 2017 were stage I-III lung cancer.¹⁴

In 2019/20 there were 111,188 hospital admissions with primary diagnosis malignant neoplasm of bronchus and lung (ICD-10 code C34), and 132,969 finished consultant episodes (FCEs), resulting in 243,883 FCE bed days.¹⁵

In England, between 2013 to 2017, the age-standardised net cancer survival rate at 1-year for stage I, II and III were 87.7%, 73.0% and 48.7% respectively. The age-standardised net cancer survival rate at 5-years for stage I, II and III were 56.6%, 34.1% and 12.6% respectively.¹⁶

Lung cancer was one of the most common causes of cancer death in 2017, accounting for approximately 21% of all cancer deaths.¹⁷ In 2019 there were 29,443 registrations of death from malignant neoplasms of bronchus and lung in adults in England and Wales (ICD-10 code C34).¹⁸

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Treatment for NSCLC differs by stage. For stage I and II NSCLC, the main treatment option is surgery, consisting of either a lobectomy (removal of part of the lung) or a pneumonectomy (removal of all of the lung), potentially followed by adjuvant chemotherapy. For patients that

are not well enough to undergo surgery, treatment consists of either radiotherapy or radiofrequency ablation. For stage III NSCLC, surgery is carried out if the surgeon deems the tumour to be excisable, potentially followed by chemotherapy and/or radiotherapy. If surgery is not possible, patients may undergo treatments including immunotherapy, chemotherapy or radiotherapy.⁷

CURRENT TREATMENT OPTIONS

Currently, patients may be offered a cisplatin-based combination chemotherapy regimen for adjuvant chemotherapy after surgery.¹⁹

PLACE OF TECHNOLOGY

If licenced, pembrolizumab with or without standard adjuvant therapy would provide an additional treatment option for patients with early stage NSCLC after resection.¹

CLINICAL TRIAL INFORMATION

Trial	PEARLS, MK-3475-091/KEYNOTE-091, NCT02504372, 2015-000575-27 ; A Randomized, Phase 3 Trial With Anti-PD-1 Monoclonal Antibody Pembrolizumab (MK-3475) Versus Placebo for Patients With Early Stage NSCLC After Resection and Completion of Standard Adjuvant Therapy Phase III – Active, not recruiting Location(s) : EU (including the UK), Canada, Australia, Brazil and other countries Primary completion date : August 2021
Trial design	Randomised, parallel assignment, triple masked.
Population	N = 1177, previously untreated and pathologically confirmed Stage IB with T \geq 4 cm or II-IIIa NSCLC after complete surgical resection, aged 18 years and older
Intervention(s)	Participants receive pembrolizumab 200 mg, intravenously (IV), every 3 weeks, for one year
Comparator(s)	Matched placebo
Outcome(s)	Primary outcome(s); <ul style="list-style-type: none"> Disease-free Survival (DFS) [Time Frame: Up to approximately 78 months] 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 for a vial of pembrolizumab (25 mg) is £2630.00 (hospital only).²⁰

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: Chemotherapy (Adult). B15/S/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a.
- NHS England. Clinical Commissioning Policy: Stereotactic Ablative Body Radiotherapy for Non-Small-Cell Lung Cancer (Adult). B01/P/a. April 2013.

OTHER GUIDANCE

- European Society for Medical Oncology. Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment follow-up. 2018.²¹
- European Society for Medical Oncology. Early and locally advanced non-small-cell-lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment, and follow-up. 2017.²²
- National Comprehensive Cancer Network (NCCN). Non-Small Cell Lung Cancer, Version 5.2017, NCCN Clinical Practice Guidelines in Oncology. 2017.²³
- Scottish Intercollegiate Guidelines Network (SIGN) Management of lung cancer: A national clinical guideline. 2014.²⁴

ADDITIONAL INFORMATION

REFERENCES

- 1 Clinicaltrials.gov. *Study of Pembrolizumab (MK-3475) vs Placebo for Participants With Non-small Cell Lung Cancer After Resection With or Without Standard Adjuvant Therapy (MK-3475-091/KEYNOTE-091) (PEARLS)*. Trial ID: NCT02504372. 2015. Status: Active, not recruiting. Available from: <https://clinicaltrials.gov/ct2/show/study/NCT02504372>
- 2 Electronic Medicines Compendium. *KEYTRUDA 50 mg powder for concentrate for solution for infusion*. 2020. Available from: https://www.medicines.org.uk/emc/product/6947/smpc#PHARMACODYNAMIC_PROPS [Accessed 18 October 2020].
- 3 O'Brien M, Hasan B, Dafni U, Menis J, Peters S, De Waele M, et al. EORTC-ETOP randomized, phase 3 trial with anti-PD-1 monoclonal antibody pembrolizumab versus placebo for patients with early stage non-small cell lung cancer (NSCLC) after resection and standard adjuvant chemotherapy: PEARLS (NCT02504372). *Journal of Clinical Oncology*. 2017;34(15). Available from: https://ascopubs.org/doi/abs/10.1200/JCO.2016.34.15_suppl.TPS8571.

- 4 Clinicaltrials.gov. *Search: Pembrolizumab | Phase 2, 3*. 2020. Available from: https://clinicaltrials.gov/ct2/results?term=Pembrolizumab&age_v=&gndr=&type=&rslt=&phase=1&phase=2&Search=Apply [Accessed 15 October 2020].
- 5 National Health Service. *Overview -Lung cancer*. 2019. Available from: <https://www.nhs.uk/conditions/lung-cancer/> [Accessed 19 October 2020].
- 6 Cancer Research UK. *Lung cancer: Stages, types and grades*. 2017. Available from: <https://www.cancerresearchuk.org/about-cancer/lung-cancer/stages-types-grades/types> [Accessed 19 October 2020].
- 7 Cancer Research UK. *Treatment for non small cell lung cancer (NSCLC)*. 2019. Available from: <https://about-cancer.cancerresearchuk.org/about-cancer/lung-cancer/treatment/non-small-cell-lung-cancer> [Accessed 19 October 2020].
- 8 American Cancer Society. *Non-Small Cell Lung Cancer Stages*. 2019. Available from: <https://www.cancer.org/cancer/lung-cancer/detection-diagnosis-staging/staging-nscl.html> [Accessed 19 October 2020].
- 9 Cancer Research UK. *Lung cancer: Risks and causes*. 2019. Available from: <https://www.cancerresearchuk.org/about-cancer/lung-cancer/risks-causes> [Accessed 19 October 2020].
- 10 Cancer Research UK. *Lung cancer symptoms*. 2019. Available from: <https://www.cancerresearchuk.org/about-cancer/lung-cancer/symptoms> [Accessed 19 October 2020].
- 11 Cancer Research UK. *Lung cancer statistics*. 2017. Available from: <https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/lung-cancer#heading-Zero> [Accessed 19 October 2020].
- 12 Cancer Research UK. *Types of lung cancer*. 2020. Available from: <https://www.cancerresearchuk.org/about-cancer/lung-cancer/stages-types-grades/types> [Accessed 19 October 2020].
- 13 Office for National Statistics. *Cancer registration statistics, England*. 2019. Available from: <https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancerregistrationstatisticscancerregistrationstatisticsengland> [Accessed 19 October 2020].
- 14 National Cancer registration and Analysis Service (NCRAS). *Stage breakdown by CCG 2017*. 2019. Available from: http://www.ncin.org.uk/publications/survival_by_stage [Accessed 19 October 2020].
- 15 NHS Digital. *Hospital Episode Statistics for England. Admitted Patient Care statistics, 2019-20*. Available from: <https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2019-20> [Accessed 18 October 2020].
- 16 Office for National Statistics (ONS). *Cancer Survival in England: adults diagnosed between 2013 and 2017 and followed up to 2018*. Available from: <https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancersurvivalratescancersurvivalinenglandadultsdiagnosed> [Accessed 18 October 2020].
- 17 Cancer Research UK. *Lung cancer mortality statistics*. 2019. Available from: <https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/lung-cancer/mortality> [Accessed 17 November 2020].
- 18 Office for National Statistics. *Deaths registered in England and Wales – 21st century mortality: 2019*. Available from: <https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/datasets/the21stcenturymortalityfilesdeathsdataset>
- 19 National Institute for Health and Care Excellence. *Lung cancer: diagnosis and management*. 2019. Available from: <https://www.nice.org.uk/guidance/ng122> [Accessed 2 November 2020].
- 20 British National Formulary (BNF). *PEMBROLIZUMAB*. 2015. Available from: <https://bnf.nice.org.uk/medicinal-forms/pembrolizumab.html> [Accessed 2 November 2020].

- 21 Planchard D, Popat S, Kerr K, Novello S, Smit EF, Faivre-Finn C, et al. Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology*. 2018. Available from: <https://doi.org/10.1093/annonc/mdy275>.
- 22 Postmus PE, Kerr KM, Oudkerk M, Senan S, Waller DA, Vansteenkiste J, et al. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology*. 2017. Available from: <https://doi.org/10.1093/annonc/mdx222>.
- 23 David SE, Douglas EW, Dara LA, Wallace A, Jessica B, Lucian RC, et al. Non-Small Cell Lung Cancer, Version 5.2017, NCCN Clinical Practice Guidelines in Oncology. *Journal of the National Comprehensive Cancer Network*. 2017. Available from: <https://doi.org/10.6004/jnccn.2017.0050>.
- 24 Scottish Intercollegiate Guidelines Network. *Management of lung cancer (SIGN 137)*. Last Update Date: Available from: <https://www.sign.ac.uk/media/1075/sign137.pdf> [Accessed 2 November 2020].

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