Health Technology Briefing
February 2022

Pembrolizumab and chemotherapy for resectable non-small-cell lung cancer

Company/Developer	Merck Sharp & Dohme Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 24150	NICE ID: 10341	UKPS ID: 651329

Licensing and Market Availability Plans

Currently in phase III clinical development.

Summary

Pembrolizumab in combination with platinum doublet chemotherapy is in clinical development as neoadjuvant therapy followed by pembrolizumab adjuvant monotherapy for adults with resectable stage II, IIIA and resectable IIIB (T3-4N2) non-small cell lung cancer (NSCLC). NSCLC is the most common type of lung cancer. T3-4 broadly refers to the size of the tumour (greater than 5cm) and N2 refers to the cancer being in the lymph nodes in the centre of the chest or windpipe of the lungs. These stages of lung cancer have not spread to other parts of the body and can be treated with resection (surgery to remove either part of or the whole of the lung) and adjuvant (additional treatment given after the primary treatment) chemotherapy and/or radiotherapy. However, the long-term outlook for patients undergoing this treatment pathway is still poor. Treatment with medicines prior to surgery (neoadjuvant) may provide better long-term survival prospects for patients with early-stage operable NSCLC.

Pembrolizumab is a drug administered intravenously (IV) that binds to the programmed cell death-1 (PD-1) receptor and improves the activity of the immune system to kill cancer cells. If licensed in combination with chemotherapy as a neoadjuvant therapy and as an adjuvant monotherapy, pembrolizumab will offer an additional treatment option for patients with early-stage, operable NSCLC who currently have few well tolerated and effective therapies available.

Proposed Indication

Pembrolizumab, in combination with platinum-containing chemotherapy as neoadjuvant treatment and then continued as monotherapy as adjuvant treatment, is indicated for the treatment of resectable stage II, IIIA, or IIIB (T3-4N2) non-small cell lung carcinoma in adults.[1]

Technology

Description

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

In the phase III trial (NCT03425643), pembrolizumab 200mg was administered as follows:[1]

- Neoadjuvant: Prior to surgery, participants receive up to 4 cycles (cycle length: 3 weeks) of pembrolizumab [200 mg, IV; given on cycle day 1] in combination with platinum doublet neoadjuvant chemotherapy, consisting of cisplatin [75 mg/m^2, IV; given on cycle day 1] and either gemcitabine [1000 mg/m^2, IV; given on cycle days 1 and 8] or pemetrexed [500 mg/m^2, IV; given on cycle day 1].
- Adjuvant: 4-12 weeks following surgery, participants receive 13 cycles (cycle length: 3 weeks) of pembrolizumab [200 mg, IV; given on cycle day 1].

Key Innovation

Surgery is the best option for patients with early-stage NSCLC. However, the rate of local and metastatic recurrences following surgery alone is high, especially in NSCLC patients with N2 lymph node involvement. The addition of adjuvant or neoadjuvant chemotherapy improves five year survival by 5%-10%.[3] It has been suggested that neoadjuvant treatment with immune checkpoint inhibitors may extend survival in early-stage NSCLC by enhancing systemic immunity and eradicating micrometastatic disease.[4]

Robust and durable antitumour activity has been previously demonstrated with pembrolizumab in patients with advanced NSCLC, both as a monotherapy in the first- and second-line settings (in patients with PD-L1 tumour proportion score [TPS] ≥50% and ≥1%, respectively) and when combined with pemetrexed-carboplatin or paclitaxel and carboplatin.[5-9] Pembrolizumab with carboplatin and paclitaxel has been recently recommended by NICE in patients with untreated metastatic squamous NSCLC.[10] Studies have also suggested neoadjuvant pembrolizumab is a feasible therapy in surgical lung cancer patients and is associated with tolerable toxicity and does not compromise tumour resection.[11]

If licensed in combination with chemotherapy as a neoadjuvant therapy and as an adjuvant monotherapy, pembrolizumab will offer an additional treatment option for patients with early-stage, operable NSCLC who currently have no approved neoadjuvant/adjuvant immunotherapy treatment options.

Regulatory & Development Status

Pembrolizumab is currently licenced as a monotherapy for several indications including but not limited to:[2]

- locally advanced or metastatic NSCLC in adults whose tumours express PD-L1 with a ⩾ 1% tumour proportion score (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.
- first-line treatment of metastatic NSCLC in adults whose tumours express PD-L1 with a ⩾ 50% TPS with no EGFR or ALK positive tumour mutations

Pembrolizumab is currently licenced in combination with:[2]
- axitinib OR lenvatinib, for the first-line treatment of advanced renal cell carcinoma in adults
- lenvatinib for the treatment of advanced recurrent endometrial carcinoma in adults who have disease progression on or following prior treatment with a platinum-containing therapy in any setting and who are not candidates for curative surgery or radiation
- 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 NSCLC in adults
- platinum and 5-fluorouracil (5-FU) chemotherapy, for the first-line treatment of metastatic or unresectable recurrent head and neck squamous cell carcinoma in adults whose tumours express PD-L1 with a CPS ⩾ 1
- platinum and fluoropyrimidine based chemotherapy, for the first-line treatment of patients with locally advanced unresectable or metastatic carcinoma of the oesophagus or HER-2 negative gastroesophageal junction adenocarcinoma in adults whose tumours express PD-L1 with a CPS ⩾ 10
- chemotherapy for the treatment of locally recurrent unresectable or metastatic triple negative breast cancer in adults whose tumours express PD-L1 with a CPS ≥10 and who have not received prior chemotherapy for metastatic disease

Pembrolizumab in combination with chemotherapy is in phase III clinical trials for small cell lung cancer, urothelial carcinoma, head and neck cancer and cervical cancer and in phase II trials for oesophageal cancer, gastric cancer, ovarian cancer and cervical cancer.[12]

Patient Group

Disease Area and Clinical Need

NSCLC is the most common type of lung cancer. The three main types are adenocarcinoma, squamous cell carcinoma and large cell carcinoma. Adenocarcinoma is the most common type and starts in the mucus making gland cells 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 in large cell carcinoma the cancer cells appear large and round under the microscope.[13] In stage IIA NSCLC, the cancer is at least 4cm in size, at stage IIB it may have spread to lymph nodes within the lung and at stage IIIA/B it has spread to lymph nodes in the centre of the chest on the same side as the affected lung or different areas nearby the lungs.[14] A person's risk of developing lung cancer depends on many factors including age, genetics and exposure to risk factors including: smoking, workplace chemicals (e.g., asbestos, silica), air pollution and ionising radiation.[15] There are usually no signs or symptoms in the early stages. Symptoms of lung cancer develop as the condition progresses. The main symptoms of lung cancer include a continuous or persistent worsening cough, recurrent chest infections, coughing up blood, an ache or pain when breathing or coughing, persistent breathlessness, persistent tiredness or lack of energy, loss of appetite or unexplained weight loss.[16]

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.[17] According to the National Cancer Registration and Analysis Service (NCRAS), there were 10,519 diagnosed cases of stage II and III lung cancer in 2017, this represents 27% of the overall number of lung cancer cases diagnosed for that year.[18] In the UK it is estimated that up to 85% of lung cancer cases are NSCLC, applying this figure to the number of stage II/III lung cancer cases diagnosed in 2017, it can be estimated that approximately 8,941 cases diagnosed with stage II/III in 2017 were NSCLC.[13] Additionally, around 18% of people with NSCLC had surgical resection with curative intent in England and Wales in 2017.[19] In England between 2013 and 2017, the age-standardised net lung cancer survival for stage II was 73% at one year and 34.1% at five years, and for stage III was 48.7% at one year and 12.6% at five years.[20] In 2020, there were 28,730 registrations of deaths in England and Wales for malignant neoplasms of the trachea, bronchus and lung in England (ICD-10 code C34).[21]

Recommended Treatment Options

There are currently no recommended neoadjuvant treatments for stage II, or IIIA-B patients with NSCLC. The National Institute for Health and Care Excellence (NICE) currently recommends that people with stage I–II NSCLC that are suitable for surgery are not offered neoadjuvant treatment outside a clinical trial.[22]

Adjuvant chemotherapy (cisplatin-based combination chemotherapy regimen) should be offered with resected stage II and III NSCLC. Pre-existing comorbidity, time from surgery and postoperative recovery need to be taken into account in this decision taken in a multidisciplinary tumour board.[22,23]

Clinical Trial Information

Trial	**MK-3475-671/KEYNOTE-671**; NCT03425643, 2017-001832-21; A Phase III, Randomized, Double-blind Trial of Platinum Doublet Chemotherapy +/- Pembrolizumab (MK-3475) as Neoadjuvant/Adjuvant Therapy for Participants With Resectable Stage II, IIIA, and Resectable IIIB (T3-4N2) Non-small Cell Lung Cancer (NSCLC) (KEYNOTE-671) **Phase III** – Active, not recruiting **Location(s):** 11 EU countries, UK, Canada, USA and other countries. **Primary completion date:** January 2024
Trial design	Randomised, parallel assignment, double-blinded
Population	N=786, previously untreated and pathologically confirmed resectable Stage II, IIIA, or IIIB (N2) NSCLC; aged 18 years and older
Intervention(s)	• Neoadjuvant: Prior to surgery, participants receive up to 4 cycles (cycle length: 3 weeks) of pembrolizumab [200 mg, IV; given on cycle day 1] in combination with platinum doublet neoadjuvant chemotherapy, consisting of cisplatin [75 mg/m^2, IV; given on cycle day 1] and either Gemcitabine [1000 mg/m^2, IV; given on cycle days 1 and 8] or Pemetrexed [500 mg/m^2, IV; given on cycle day 1]. • Adjuvant: 4-12 weeks following surgery, participants receive 13 cycles (cycle length: 3 weeks) of pembrolizumab [200 mg, IV; given on cycle day 1].
Comparator(s)	As above with matched pembrolizumab placebo
Outcome(s)	Primary Outcomes: • Event Free Survival (EFS) [Time frame: up to 5 years] • Overall Survival (OS) [Time frame: up to 5 years]

	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 £2,630 for 100 mg/4 ml concentrate for solution for infusion vial.[24]

Relevant Guidance

NICE Guidance

- NICE technology appraisal guidance in development. Atezolizumab with chemotherapy for neoadjuvant and adjuvant treatment of resectable non-small-cell lung cancer (GID-TA10777). Expected publication date: To Be Confirmed.
- NICE technology appraisal guidance in development. Nivolumab with chemotherapy for neoadjuvant treatment of early non-small-cell lung cancer (GID-TA10632). Expected publication date: To Be Confirmed.
- NICE technology appraisal guidance in development. Pembrolizumab for adjuvant treatment of resected non-small-cell lung cancer (GID-TA10784). Expected publication date: To Be Confirmed.
- NICE technology appraisal guidance in development. Atezolizumab for adjuvant treatment of resected non-small-cell lung cancer (GID-TA10751). Expected publication date: July 2022.
- NICE Guideline. Lung cancer: diagnosis and management (NG122). 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 2.2021, NCCN Clinical Practice Guidelines in Oncology. 2021.[25]
- 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.[23]
- European Society for Medical Oncology. Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2016.[26]
- European Society for Medical Oncology. ESMO Consensus Guidelines: Non-small-cell lung cancer first-line/second and further lines in advanced disease. 2014.[27]
- Scottish Intercollegiate Guidelines Network. Management of lung cancer (SIGN 137). 2014.[28]

Additional Information

References

1 ClinicalTrials.gov. *Efficacy and Safety of Pembrolizumab (MK-3475) With Platinum Doublet Chemotherapy as Neoadjuvant/Adjuvant Therapy for Participants With Resectable Stage II, IIIA, and Resectable IIIB (T3-4N2) Non-small Cell Lung Cancer (MK-3475-671/KEYNOTE-671)*. *Trial ID: NCT03425643*. 2018. Status: Recruiting. Available from: https://ClinicalTrials.gov/show/NCT03425643 [Accessed 12 January 2022].

2 electronic Medicines Compendium (eMC). *KEYTRUDA 25 mg/mL concentrate for solution for infusion.* 2021. Available from: https://www.medicines.org.uk/emc/product/2498 [Accessed 12 January 2022].

3 Catania C, Muthusamy B, Spitaleri G, del Signore E, Pennell NA. The new era of immune checkpoint inhibition and target therapy in early-stage non-small cell lung cancer. A review of the literature. *Clinical Lung Cancer*. 2021 2021/11/11/. Available from: https://doi.org/10.1016/j.cllc.2021.11.003.

4 Forde PM, Chaft JE, Felip E, Broderick S, Girard N, Awad MM, et al. Checkmate 816: A phase 3, randomized, open-label trial of nivolumab plus ipilimumab vs platinum-doublet chemotherapy as neoadjuvant treatment for early-stage NSCLC. *Journal of Clinical Oncology*. 2017 2017/05/20;35(15_suppl):TPS8577-TPS. Available from: https://doi.org/10.1200/JCO.2017.35.15_suppl.TPS8577.

5 Fernando HC, Yang J, Ferraro GL, Keller SM. Randomized, double-blind phase 3 study evaluating neoadjuvant platinum-based chemotherapy with perioperative pembrolizumab or placebo in resectable stage IIB or IIIA NSCLC: KEYNOTE-671. *Journal of Clinical Oncology*. 2018 2018/05/20;36(15_suppl):TPS8583-TPS. Available from: https://doi.org/10.1200/JCO.2018.36.15_suppl.TPS8583.

6 Reck M, Rodríguez–Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A, et al. Updated Analysis of KEYNOTE-024: Pembrolizumab Versus Platinum-Based Chemotherapy for Advanced Non–Small-Cell Lung Cancer With PD-L1 Tumor Proportion Score of 50% or Greater. *Journal of Clinical Oncology*. 2019 2019/03/01;37(7):537-46. Available from: https://doi.org/10.1200/JCO.18.00149.

7 Gadgeel S, Rodríguez-Abreu D, Speranza G, Esteban E, Felip E, Dómine M, et al. Updated Analysis From KEYNOTE-189: Pembrolizumab or Placebo Plus Pemetrexed and Platinum for Previously Untreated Metastatic Nonsquamous Non-Small-Cell Lung Cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2020 May 10;38(14):1505-17. Available from: https://doi.org/10.1200/jco.19.03136.

8 Paz-Ares L, Luft A, Vicente D, Tafreshi A, Gümüş M, Mazières J, et al. Pembrolizumab plus Chemotherapy for Squamous Non–Small-Cell Lung Cancer. *New England Journal of Medicine*. 2018 2018/11/22;379(21):2040-51. Available from: https://doi.org/10.1056/NEJMoa1810865.

9 Herbst RS, Baas P, Kim D-W, Felip E, Pérez-Gracia JL, Han J-Y, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *The Lancet*. 2016;387(10027):1540-50. Available from: https://doi.org/10.1016/S0140-6736(15)01281-7.

10 (NICE) NIfHaCE. *Pembrolizumab with carboplatin and paclitaxel for untreated metastatic squamous non-small-cell lung cancer.* 2022. Available from: https://www.nice.org.uk/guidance/ta770 [Accessed 12 January 2022].

11 Eichhorn F, Klotz LV, Kriegsmann M, Bischoff H, Schneider MA, Muley T, et al. Neoadjuvant anti-programmed death-1 immunotherapy by pembrolizumab in resectable non-small cell lung cancer: First clinical experience. *Lung Cancer*. 2021 2021/03/01/;153:150-7. Available from: https://doi.org/10.1016/j.lungcan.2021.01.018.

12 Clinicaltrials.gov. *Search for: pembrolizumab AND platinum chemotherapy | Phase 2, 3.* 2021. Available from: https://clinicaltrials.gov/ct2/results?term=pembrolizumab+AND+platinum+chemotherapy&age_v=&gndr=&type=&rslt=&phase=1&phase=2&Search=Apply [Accessed 12 January 2022].

13 Cancer Research UK. *Types of lung cancer.* Available from: https://www.cancerresearchuk.org/about-cancer/lung-cancer/stages-types-grades/types [Accessed 12 January 2022].
14 Cancer Research UK. *Stages and grades of lung cancer.* Available from: https://www.cancerresearchuk.org/about-cancer/lung-cancer/stages-types-grades/stages-grades [Accessed 12 January 2022].
15 Cancer Research UK. Risks and causes. 2019. Available from: https://www.cancerresearchuk.org/about-cancer/lung-cancer/risks-causes.
16 National Health Service (NHS). *Lung Cancer: Symptoms.* Available from: https://www.nhs.uk/conditions/lung-cancer/symptoms/ [Accessed 12 January 2022].
17 NHS Digital. *Hospital Admitted Patient Care Activity, 2020-21: Diagnosis*. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2020-21 [Downloaded 12 January 2022].
18 National Cancer Registration and Analysis Service (NCRAS). *Stage breakdown by CCG 2017.* 2017. Available from: http://www.ncin.org.uk/publications/survival_by_stage [Accessed 12 January 2022].
19 Royal College of Physicians. *National Lung Cancer Audit annual report 2018*. 2020. Available from: https://www.rcplondon.ac.uk/projects/outputs/nlca-annual-report-2018.
20 Office for National Statistics. *Cancer survival in England - adults diagnosed.* Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancersurvivalratescancersurvivalinenglandadultsdiagnosed [Accessed 12 January 2022].
21 Office for National Statistics (ONS). *Deaths registered in England and Wales – 21st century mortality.* 2021. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/datasets/the21stcenturymortalityfilesdeathsdataset [Accessed 12 January 2022].
22 National Insititute for Health and Care Excellence (NICE). *Lung cancer: diagnosis and management.* 2019. Available from: https://www.nice.org.uk/guidance/ng122/resources/lung-cancer-diagnosis-and-management-pdf-66141655525573 [Accessed 22 January 2022].
23 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 2020. *Annals of Oncology*. 2017;28:iv1-iv21. Available from: https://doi.org/10.1093/annonc/mdx222.
24 British National Formulary (BNF). *Pembrolizumab.* 2018. Available from: https://bnf.nice.org.uk/medicinal-forms/pembrolizumab.html [Accessed 22 January 2022].
25 Ettinger DS, Wood DE, Aisner DL, Akerley W, Bauman JR, Bharat A, et al. NCCN Guidelines Insights: Non–Small Cell Lung Cancer, Version 2.2021: Featured Updates to the NCCN Guidelines. *Journal of the National Comprehensive Cancer Network*. 2021 01 Mar. 2021;19(3):254-66. Available from: https://doi.org/10.6004/jnccn.2021.0013.
26 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.* 2020. Available from: https://www.esmo.org/guidelines/lung-and-chest-tumours/clinical-practice-living-guidelines-metastatic-non-small-cell-lung-cancer [Accessed 12 January 2022].
27 Besse B, Adjei A, Baas P, Meldgaard P, Nicolson M, Paz-Ares L, et al. 2nd ESMO Consensus Conference on Lung Cancer: non-small-cell lung cancer first-line/second and further lines of treatment in advanced disease. *Annals of Oncology*. 2014;25(8):1475-84. Available from: https://doi.org/10.1093/annonc/mdu123.
28 Scottish Intercollegiate Guidelines Network. *Management of lung cancer (SIGN 137).* . Available from: https://www.sign.ac.uk/media/1075/sign137.pdf [Accessed 12 January 2022].

NB: This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.