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Pembrolizumab (KEYTRUDA®) in combination with carboplatin-paclitaxel/Nab-paclitaxel for metastatic squamous non small cell lung cancer, first line

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LAY SUMMARY

Squamous non-small cell lung cancer (NSCLS) is a type of lung cancer that is slow growing and mostly present in males that smoke. People with this type of lung cancer are often unaware until the first symptoms start to manifest. By this time the cancer has often progressed to more advanced stages, limiting the chances of survival. Current therapeutic options depend on the stage of the cancer at the time of diagnosis. Available treatments involve surgery and chemotherapy or radiotherapy.

Pembrolizumab is an immuno-oncology drug administered intravenously that stimulates the body's immune system to fight cancer cells. Pembrolizumab targets and blocks a protein called PD-L1 on the surface of certain immune cells called T-cells. Blocking the PD-L1 protein triggers the T-cells to find and kill cancer cells. Pembrolizumab is already approved for use in other types of cancers. If licensed in the UK, pembrolizumab in combination with chemotherapy would provide a new treatment option for lung cancer patients who currently have a poor life expectancy and few therapies available.

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TARGET GROUP

Squamous Non-Small Cell Lung Cancer (metastatic) – first line; in combination with carboplatin-paclitaxel/nab-paclitaxel

TECHNOLOGY

DESCRIPTION

Pembrolizumab (KEYTRUDA®; MK-3475; SCH-900475) is a humanized monoclonal immunoglobulin (Ig) G4 antibody directed against human cell surface receptor PD-1 (programmed death-1 or programmed cell death-1) with potential immune checkpoint inhibitory and antineoplastic activities. Upon administration, pembrolizumab binds to PD-1, an inhibitory signalling receptor expressed on the surface of activated T cells, and blocks the binding to and activation of PD-1 by its ligands, which results in the activation of T-cell-mediated immune responses against tumour cells. The ligands for PD-1 include programmed cell death ligand 1 (PD-L1), overexpressed on certain cancer cells, and programmed cell death ligand 2 (PD-L2), which is primarily expressed on antigen-presenting cells (APCs). Activated PD-1 negatively regulates T-cell activation and plays a key role in tumour evasion from host immunity.[1]

Pembrolizumab is currently licensed in the EU for use in advanced (unresectable or metastatic) melanoma, metastatic or unresectable non-small cell lung cancer (NSCLC) in adults whose tumours express PD-L1 and who have had chemotherapy, as monotherapy is indicated for the first-line treatment of metastatic non-small cell lung carcinoma (NSCLC) in adults whose tumours express PD-L1 with a ≥50% tumour proportion score (TPS) with no EGFR or ALK positive tumour mutations[a], and in relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant and brentuximab vedotin (BV) treatment, or who are transplant-ineligible and have failed BV.[2] The most common side effects reported with pembrolizumab in clinical trials include fatigue, pruritus, rash, diarrhoea, and nausea.[3]

Pembrolizumab is also in clinical trials for first and second line treatment of gastric or gastroesophageal junction adenocarcinoma. Phase III trials of pembrolizumab are registered for head and neck cancer, colorectal cancer, multiple myeloma, bladder/renal cancer, urothelial cancer, mesothelioma, liver cancer, non-small cell lung cancer and small cell lung cancer.[4]

In the currently recruiting trial (NCT02775435) pembrolizumab 200 mg is administered by intravenous (IV) infusion prior to chemotherapy on Day 1 of each 21-day cycle for up to 35 cycles.[24]

INNOVATION and/or ADVANTAGES

Drugs targeting the PD-1 pathway may provide antitumor immunity, especially in PD-L1 positive tumours. Various cancers, such as melanoma, hepatocellular carcinoma, glioblastoma, lung, kidney, breast, ovarian, pancreatic, and oesophageal cancers, as well as haematological malignancies, have positive PD-L1 expression, and this expression has been correlated with poor prognosis.[5]

[a] Information provided by company

If approved to use in combination with carboplatin-paclitaxel/Nab-paclitaxel chemotherapy regimens for the first line treatment of metastatic squamous NSCLC, pembrolizumab has the potential to prolong the time without cancer progression.

DEVELOPER

Merck Sharp & Dohme Corp.

AVAILABILITY, LAUNCH or MARKETING

Due to its success in clinical trials, pembrolizumab was approved by the U.S. Food and Drug Administration early to allow quick patient access and was given breakthrough therapy and orphan drug designation. In the EU, pembrolizumab (as Keytruda) has been approved to treat advanced cases of melanoma, the most common type of lung malignancy, non-small cell lung cancer, and Classical Hodgkin Lymphoma.[2]

PATIENT GROUP

BACKGROUND

Lung cancer is classified as one of two main histologic types: small cell lung cancer (SCLC) or non-small cell lung cancer (NSCLC).[6] NSCLC can be further divided into different subtypes, including nonsquamous and squamous NSCLC.[7] Squamous cell (epidermoid) carcinoma starts in early versions of squamous cells, which are flat cells that line the inside of the airways in the lungs. They are often linked to a history of smoking and tend to be found in the central part of the lungs, near a main airway (bronchus)[6] which results in symptoms such as collapsed lung, coughing up blood and pneumonia presenting much earlier on in the development of the disease making it easier to detect.[7]

Squamous cell carcinoma is usually slow growing and more commonly found in men.[7] In recent years, there has been a gradual decline in the incidence of this form of lung cancer.[7]

CLINICAL NEED and BURDEN OF DISEASE

NSCLC is the more common type of lung cancer, found in approximately 85% to 90% of patients with lung cancer with an estimated 450,000 cases worldwide in 2012.[6] In the UK, about 87 out of 100 lung cancers are NSCLC. In 2014, there were 46,403 new cases of lung cancer and 35,895 deaths in the UK.[8] There are three common types: adenocarcinoma, squamous cell cancer and large cell carcinoma. They are grouped together because they behave and respond to treatment in a similar way.[7]

NSCLC is often asymptomatic until it has become well advanced. Upon initial NSCLC diagnosis, 20% of patients have localized disease, 25% of patients have regional metastasis, and 55% of patients have distant metastasis.[9] Often, the first sites of metastases are the regional lymph nodes and other nearby tissues, such as the pericardium, diaphragm, or mediastinal pleura. Metastasis to another lobe of the same lung usually occurs before metastasis to the opposite lung, which generally occurs in the later stages of progression. Finally, distant metastases to the kidney, adrenal gland, bones, or brain mark the advanced stages of disease progression.[10]

Lung cancer has the lowest 5-year relative survival rate and squamous NSCLC is an aggressive form of lung cancer.[11] The prognosis for patients diagnosed with NSCLC depends on the stage of the disease

at diagnosis. Patients who are diagnosed in the earliest stages can have a 5 year survival rate between 53-78%, however, those diagnosed at the latest stage may be looking at a 5 year survival rate of 2-13%.[7] The incidence of NSCLC increases with age; 60% occur in patients aged 60 years and older, and 30% to 40% occur in patients aged 70 years and older. The median age of individuals diagnosed with NSCLC in developed countries is 68 years.[12] In the UK, there were 35,419 deaths (6.2%) due to lung cancer (sub-type not specified) in 2012.[13]

In the latest Hospital Episode Statistics (2015/2016) there were 110,013 finished consultant episodes, 89,945 admissions to hospital and 266,522 finished consultant episodes bed days for malignant neoplasms of bronchus and lung (ICD-10 code C34).[14]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Lung cancer (non-small-cell, squamous, metastatic) - nivolumab (after chemotherapy) (GID-TAG506). Expected publication date: TBC.
- NICE technology appraisal. Pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer (TA447). June 2017
- NICE technology appraisal. Pembrolizumab for treating PD-L1-positive non-small-cell lung cancer after chemotherapy (TA428). January 2017.
- NICE technology appraisal. Necitumumab for untreated advanced or metastatic squamous non-small-cell lung cancer (TA 411). September 2016.
- NICE guidelines. Lung cancer: diagnosis and management (CG121). April 2011
- NICE Quality Standard. Lung cancer in adults. March 2012.

NHS ENGLAND and POLICY 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. 2016 Clinical Commissioning Policy: Robotic assisted lung resection for primary lung cancer. 16024/P
- NHS England. 2013 Clinical Commissioning Policy: Stereotactic Ablative Body Radiotherapy for Non-Small Cell Lung Cancer (Adult). B01/P/a

OTHER GUIDANCE

- European Society for Medical Oncology. Metastatic non-small cell lung cancer (NSCLC): ESMO clinical practice guidelines for diagnosis, treatment and follow-up. 2014.[15]
- Scottish Intercollegiate Guidelines Network. Management of lung cancer (137). 2014.[16]
- National Comprehensive Cancer Network. The NCCN clinical practice guidelines in oncology. Non-small cell lung cancer. 2013.[17]

CURRENT TREATMENT OPTIONS

Surgery is the treatment of choice for patients with non–small cell lung cancer (NSCLC) stages I through IIIA. In addition, patients with resected lung cancer have a high risk of relapse and are treated with adjuvant chemotherapy. Patients with stage IIIB and IV NSCLC are usually offered chemotherapy with

the option of surgery. Radiation is an option for treatment in patients who are not candidates for surgery.[18]

For locally advanced or metastatic NSCLC, the aim of treatment is to prolong survival, improve quality of life, and control disease-related symptoms.[19] Treatment strategies should take into account the tumour histology and molecular pathology, as well as the patient's age, performance status, comorbidities, and preferences. Patients who smoke should be encouraged to cease, as cessation improves treatment outcomes.[20] Current NICE Pathways reflect these recommendations.[21]

In England, NICE clinical guideline 121 (CG121) is currently being updated in the effectiveness of chemotherapy and radiotherapy for treatment of non‐small‐cell lung cancer (NSCLC) and the first-line treatment of limited-stage and extensive-stage small‐cell lung cancer (SCLC). The newly updated guideline is expected to be published in January 2019. In advance to this update, the NICE pathway for lung cancer recommends the use of pembrolizumab for first-line chemotherapy for advanced or metastatic non-small-cell lung cancer.[22]

For people with locally advanced or metastatic NSCLC whose disease has progressed after non-targeted chemotherapy, NICE recommends chemotherapy combination of a single third-generation drug (docetaxel, gemcitabine, paclitaxel or vinorelbine) plus a platinum drug. Either carboplatin or cisplatin may be administered, taking account of their toxicities, efficacy and convenience.[22,21]

Treatment choices may be influenced by the presence of genetic markers (such as mutations in EGFR-TK), histology (squamous or non-squamous) and previous treatment experience. Supportive care may be considered for some people for whom chemotherapy is unsuitable or may not be tolerated.[23]

EFFICACY and SAFETY

Trial	Pembrolizumab with or without chemotherapy, KEYNOTE-407, NCT02775435; phase III
Sponsor	Merck Sharp & Dohme Corp.
Status	Ongoing
Source of Information	Trial registry[24]
Location	Australia, Canada, China, France, Germany, Hungary, Italy, Japan, Korea, Republic of, Mexico, Netherlands, Poland, Russian Federation, Spain, Thailand, Turkey, United States
Design	Randomised, placebo/controlled
Participants	N=560 (planned); aged 18-65 years; stage IV squamous NSCLC; no prior systemic treatment for metastatic NSCLC.
Schedule	Randomised to pembrolizumab 200 mg by intravenous (IV) infusion prior to chemotherapy on Day 1 of each 21-day cycle for up to 35 cycles PLUS investigator's choice of paclitaxel (200 mg/m^2 by i.v. infusion on Day 1 of each 21-day cycle for 4 cycles) or nab-paclitaxel (100 mg/m^2 by i.v. infusion on Days 1, 8, 15 of each 21-day cycle for 4 cycles) PLUS carboplatin AUC 6 by i.v. infusion on Day 1 of each 21-day cycle for 4 cycles; or, randomised to normal saline by i.v. infusion prior to chemotherapy on Day 1 of each 21-day cycle for up to 35 cycles PLUS investigator's choice of paclitaxel (200 mg/m^2 by IV infusion on Day 1 of each 21-day cycle for 4 cycles) or nab-paclitaxel (100 mg/m^2 by i.v. infusion on Days 1, 8, 15 of each 21-day cycle for 4 cycles) PLUS carboplatin AUC 6 by i.v. infusion on Day 1 of each 21-day cycle for 4 cycles.

Follow-up	Active treatment for 21-day cycle for up to 35 cycles. Follow up of up to 2 years.
Primary Outcomes	Progression free survival and overall survival
Secondary Outcomes	Objective Response Rate (ORR) per RECIST 1.1 as assessed by a blinded central imaging vendor.
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Not reported

ESTIMATED COST and IMPACT

COST

Pembrolizumab is already marketed in the UK for other indications. The list price per 50mg vial is £1,315.[25] The company has agreed a patient access scheme with the Department of Health, and this scheme provides a discount to the list price of pembrolizumab. The level of the discount is commercial in confidence. [26]

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☒ Reduced mortality/increased length of survival

☐ Reduced symptoms or disability

☐ Other:

☐ No impact identified

IMPACT ON HEALTH and SOCIAL CARE SERVICES

☐ Increased use of existing services

☐ Decreased use of existing services

☐ Re-organisation of existing services

☐ Need for new services

☐ Other:

☒ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

☐ Increased drug treatment costs

☐ Reduced drug treatment costs

☐ Other increase in costs

☐ Other reduction in costs

☐ Other: ☒ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified ☒ None identified

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