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HEALTH TECHNOLOGY BRIEFING SEPTEMBER 2020

Pembrolizumab in addition to platinum-pemetrexed chemotherapy for metastatic EGRF mutant non-squamous non-small-cell lung cancer – second line

NIHRIO ID	24213	**NICE ID**	10176
Developer/Company	Merck Sharp & Dohme	**UKPS ID**	651330

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Licensing and market availability plans	Currently in phase III clinical trials.

SUMMARY

Pembrolizumab in addition to platinum-pemetrexed chemotherapy is in clinical development for epithelial growth factor receptor (EGRF) mutation positive metastatic non-squamous non-small-cell lung cancer (NSCLC). NSCLC makes up the majority of lung cancers in the UK. Stage IV (advanced or metastatic) NSCLC is when the cancer has spread beyond the lung which was initially affected to other organs. Overexpression of EGFR is known to accelerate the growth of cancer cells. The majority of NSCLC patients will develop resistance to first-line treatment with tyrosine kinase inhibitors so there is a need to develop effective second line treatments.

Pembrolizumab is a type of immunotherapy delivered intravenously that stimulates the body's immune system to fight cancer cells. Pembrolizumab targets and blocks a protein called PD-1 that is expressed on the surface of certain immune cells called T-cells. Blocking PD-1 triggers the T-cells to find and kill cancer cells. Pembrolizumab in addition to platinum-pemetrexed may offer a second line treatment option for patients whose disease has progressed on or after prior EGFR tyrosine kinase inhibitor therapy.

PROPOSED INDICATION

Second-line treatment in patients with metastatic EGFR mutant NSCLC, whose disease has progressed on or after prior EGFR tyrosine kinase inhibitor therapy.[3]

TECHNOLOGY

DESCRIPTION

Pembrolizumab is a humanised monoclonal immunoglobin (Ig) G4 antibody directed against human cell surface receptor programmed cell death-1 (PD-1). Upon intravenous administration, pembrolizumab binds to PD-1 (programmed cell death-1) which is an inhibitory signalling receptor expressed on the surface of activated T-cells. This blocks the binding to and activation of PD-1 by its ligands PD-L1 (programmed cell death ligand-1) and PD-L2 (programmed cell death ligand-2) which are expressed on antigen presenting cells. Activated PD-1 negatively regulates T-cell activation and plays a key role in tumour evasion from host immunity. Therefore, by preventing the activation of PD-1, pembrolizumab potentiates T-cell responses including anti-tumour responses.[1,2]

Pembrolizumab in addition to pemetrexed and platinum chemotherapy is currently in clinical development for the second-line treatment of metastatic EGFR mutant NSCLC, whose disease has progressed on or after prior EGFR tyrosine kinase inhibitor therapy. In the clinical trial (KEYNOTE-789; NCT03515837), participants receive up to 35 cycles of 200mg pembrolizumab via intravenous (IV) infusion on day 1 of each 3-week cycle (Q3W) plus pemetrexed 500mg/m^2 via IV infusion plus platinum- chemotherapy (either carboplatin area under the curve (AUC) 5 via intravenous (IV) infusion Q3W for 4 cycles or cisplatin 75 mg/m^2 via IV infusion Q3W for 4 cycles).[3]

INNOVATION AND/OR ADVANTAGES

Despite initial response to first-line tyrosine kinase inhibitors, 70% of NSCLC patients with classical EGFR mutations will develop resistance to tyrosine kinase inhibitors, on average after 9-16 months of treatment.[4]

Immune checkpoint inhibitors, specifically PD-1 directed agents such pembrolizumab, have changed the treatment paradigm of NSCLC. Initial studies have demonstrated a survival advantage with these agents in patients with recurrent NSCLC and recent data suggests that addition of these agents to chemotherapy may improve survival compared with chemotherapy alone.[5]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Pembrolizumab is currently licenced as a monotherapy in the UK for the treatment of:[2]

- advanced (unresectable or metastatic) melanoma in adults
- as an 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 >50% tumour proportion score with no EGFR or ALK positive tumour mutations
- locally advanced or metastatic NSCLC in adults whose tumours express >1% tumour proportion score and who have received at least one prior chemotherapy regimen

- adult patients with relapsed or refractory Hodgkin lymphoma who have failed autologous stem cell transplant and brentuximab vedotin or who are transplant ineligible and have failed BV
- treatment of locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy
- 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 > 10
- recurrent or metastatic head and neck squamous cell carcinoma in adults whose tumours express PD-L1 with a >50% tumour proportion score and progressing on or after platinum-containing chemotherapy

Pembrolizumab in combination with pemetrexed and platinum chemotherapy is licensed in the UK for the first-line treatment of metastatic non-squamous NSCLC in adults whose tumours have no EGFR or ALK positive mutations.[2]

The most common adverse events of pembrolizumab (affecting more than one in ten people) include anaemia, neutropenia, thrombocytopenia, hypokalaemia, decreased appetite, dizziness, headache, peripheral neuropathy, dysgeusia, diarrhoea, nausea, vomiting, constipation, abdominal pain, rash, alopecia, pruritus, musculoskeletal pain, arthralgia, fatigue, asthenia, oedema, dyseusia, increased blood creatinine and increased alanine aminotransferase.[2]

Pembrolizumab is currently in phase II and III clinical trials for the treatment of multiple malignant conditions such as breast cancer, colorectal cancer, cervical cancer, prostate cancer.[6]

PATIENT GROUP

DISEASE BACKGROUND

There are two major types of lung cancer, NSCLC and small cell lung cancer. NSCLC is the most common type of lung cancer, accounting for about 85% of lung cancers. NSCLC can be further classified into adenocarcinoma (which starts in the mucus making glands in the lining of the airways), squamous cell cancer (which 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).[7] Metastatic cancer is a cancer that has spread from the part of the body where it started, the cancer is named and treated based on the part of the body where the cancer started.[8]

A clinically significant proportion of patients with NSCLC have EGFR mutations.[9] The EGFR gene is an oncogene and thus plays a crucial role in the development and subsequent progression of lung cancers.[10] EGFR is a transmembrane receptor whose function is to regulate cell proliferation and apoptosis via signal transduction pathways.[11] Dysregulation of EGFR leads to increased intracellular pathways activity, via tyrosine kinase auto-phosphorylation, resulting in directly or indirectly, cell proliferation angiogenesis, invasion and metastasis.[12]

A person's risk of developing lung cancer depends on many factors including age, genetics and exposure to risk factors. 79% of lung cancer cases are preventable caused by things such as smoking, workplace exposures, air pollution and ionising radiation.[13] Symptoms of lung cancer include a persistent cough that does not go away after 2 or 3 weeks, a long-standing cough

that gets worse, chest infections that keep coming back, 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.[14]

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 and with a European age standardised incidence rate of 78.0 per 100,000 in 2017.[15,16] 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.[15]

In 2019/20 there were 111,188 hospital admissions with a primary diagnosis malignant neoplasm of bronchus and lung (ICD-10 code C34) resulting in 132,969 finished consultant episodes (FCEs), resulting in 243,883 FCE bed days.[17] 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.[18] In the UK it is estimated that 85% of lung cancers 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 were stage IV NSCLC.[18,19]

Survival for lung cancer depends on the stage at diagnosis.[20] In England 2013-2017 followed up to 2018 the 1 year survival rate for people with stage IV lung cancer was 19.3% and the 5 year survival rate was 2.9%.[21] In 2017 there were 30,131 registrations of death from cancer in England for malignant neoplasms of trachea, bronchus and lung in England (ICD-10 code C33-34).[22]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Treatment of NSCLC depends on the stage of cancer and the general health of the patient.[23] The main treatment option for the locally advanced or metastatic disease includes surgery, systemic anti-cancer therapy (SACT) and radiotherapy.[24]

At stage IV, NSCLC treatment aims to control the cancer for as long as possible and help with symptoms. Treatment generally includes chemotherapy, targeted drugs, radiotherapy and symptom control treatment to help patients breathe more easily.[25]

CURRENT TREATMENT OPTIONS

NICE guidelines currently recommends the following treatment options for patients whose disease has progressed following first-line treatment with an EGFR-TK inhibitor:

- Osimertinib[26]
- Atezolizumab plus bevacizumab, carboplatin and paclitaxel[27]
- Pemetrexed with carboplatin or other platinum doublet chemotherapy after progression on afatinib, erlotinib, gefitinib or osimertinib[28]

PLACE OF TECHNOLOGY

If licensed, pembrolizumab in addition to platinum-pemetrexed chemotherapy will offer a second line treatment for patients with metastatic EGFR mutant NSCLC whose disease has progressed on or after tyrosine kinase inhibitor therapy.

CLINICAL TRIAL INFORMATION

Trial	**KEYNOTE-789,** NCT03515837, EudraCT 2017-004188-11; A Randomized, Double-Blind, Phase 3 Study of Pemetrexed + Platinum Chemotherapy With or Without Pembrolizumab (MK-3475) in TKI-resistant EGFR-mutated Tumours in Metastatic Non-squamous Non-small Cell Lung Cancer (NSCLC) Participants **Phase III –** Active, not recruiting **Locations:** 5 EU countries (incl UK), USA and Canada **Estimated primary completion date:** 15 June 2023
Trial design	Randomised, Double-Blind, Parallel Assignment, Active-Controlled Study
Population	N=480; adults aged 18 years and older; histologically or cytologically confirmed diagnosis of stage IV non-squamous NSCLC.
Intervention(s)	• 200mg pembrolizumab (intravenous infusion) • 500mg/m^2 pemetrexed (intravenous infusion) • Platinum chemotherapy [carboplatin AUC 5 (intravenous infusion) **or** cisplatin 75mg/m^2 (intravenous infusion)]
Comparator(s)	• 500mg/m^2 pemetrexed (intravenous infusion) • Platinum chemotherapy [carboplatin AUC 5 (intravenous infusion) **or** cisplatin 75mg/m^2 (intravenous infusion)]
Outcome(s)	Primary outcome measures: • Progression-free survival per response evaluation criteria in solid tumours version 1.1 (RECIST 1.1) [Time Frame: Up to approximately 32 months] • Overall Survival [Time Frame: Up to approximately 59 months] See trial record for full list of outcome measures
Results (efficacy)	-
Results (safety)	-

ESTIMATED COST

Pembrolizumab is already marketed in the UK; a 100mg/4ml concentrate for solution for infusion vial (25mg/ml) costs £2,630.[29]

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal. Atezolizumab in combination for treating metastatic non-squamous non-small-cell lung cancer (TA584). June 2019.
- NICE technology appraisal. Osimertinib for treating locally advanced or metastatic EGFR T790M mutation-positive non-small-cell lung cancer (TA416). October 2016.
- NICE guideline. Lung cancer: diagnosis and management (NG122). March 2019.
- NICE quality standard. Lung cancer in adults (QS17). December 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

- European Society for Medical Oncology (ESMO). Metastatic Non-Small-Cell Lung Cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2019.[30]
- British Medical Journal (BMJ). Lung cancer: diagnosis and management: summary of updated NICE guidance. 2019.[31]
- Scottish Intercollegiate Guideline Network (SIGN). Management of lung cancer. 2014. [32]

ADDITIONAL INFORMATION

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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.