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HEALTH TECHNOLOGY BRIEFING
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Pembrolizumab in addition to lenvatinib for PD-L1 positive (⩾1%) non-small-cell lung cancer – first line

NIHRIO ID	27193	**NICE ID**	10282
Developer/Company	Merck Sharp & Dohme Ltd.	**UKPS ID**	653314

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

SUMMARY

Lenvatinib in addition to pembrolizumab is in clinical development for the treatment of adults with treatment-naïve, metastatic, stage IV, non-small cell lung cancer (NSCLC), with Programmed cell Death-Ligand 1 (PD-L1) expression in ≥1% of tumour cells. NSCLC makes up the majority of lung cancers in the UK. Stage IV (advanced/metastatic) NSCLC is when the cancer has spread beyond the lung that was initially affected, most often to the liver, the adrenal glands, the bones, and the brain. Most patients with NSCLC are diagnosed at the advanced/metastatic stage where curative treatment with surgery is unsuitable. While current treatments exist for advanced NSCLC, significant unmet medical need remains for more effective treatment options with manageable safety profiles for patients in the first line setting.

Lenvatinib is a tyrosine kinase inhibitor that targets several different growth factor receptors including vascular endothelial growth factor (VEGFR) and fibroblast growth factor receptors (FGFR). By blocking these receptors, lenvatinib can reduce tumour growth. Pembrolizumab is a drug that works by improving the activity of white blood cells in killing cancer cells by blocking a protein, PD-L1. If licenced, lenvatinib (administered orally) in addition to pembrolizumab (administered intravenously) could provide an additional treatment option for adults with PD-L1 positive NSCLC.

PROPOSED INDICATION

Indication was deemed CiC. Pivotal trial evaluated pembrolizumab with or without lenvatinib in adults with treatment-naïve, metastatic non-small cell lung cancer, stage IV, programmed cell death-ligand 1 (PD-L1) expression in ≥1% of tumour cells.[1]

TECHNOLOGY

DESCRIPTION

Lenvatinib (Kisplyx; Lenvima) is a multiple receptor tyrosine kinase inhibitor (TKI) with a novel binding mode that selectively inhibits the kinase activities of all vascular endothelial growth factor (VEGF) receptors, in addition to other proangiogenic and oncogenic pathway-related RTKs including all fibroblast growth factor (FGF) receptors, the platelet-derived growth factor (PDGF) receptor PDGFRα, KIT and RET that are involved in tumour proliferation.[2,3] Pembrolizumab is already a licenced first line therapy for PD-L1 positive NSCLC.[4]

The proposed dose and the dose used in the phase III trials (NCT03829332) is 200 mg of pembrolizumab via intravenous infusion on day 1 of each 3-week cycle for up to 35 administrations (up to approximately 2 years) in combination with 20 mg of lenvatinib via oral capsule once daily on days 1-21 of each 3-week cycle until progressive disease or unacceptable toxicity.[1]

INNOVATION AND/OR ADVANTAGES

Pembrolizumab and lenvatinib are both anti-tumour drugs, the former being approved as a monotherapy for several NSCLC indications in the UK.[5] Studies in mouse tumour models showed that treatment with lenvatinib combined with an anti–programmed cell death-1 (PD-1) monoclonal antibody demonstrated superior antitumor activity compared with either compound individually.[6]

In a phase II clinical trial, the combination of lenvatinib and pembrolizumab demonstrated a manageable safety profile and encouraging antitumor activity in patients with selected advanced solid tumours. In the trial, there were 21 patients with NSCLC, 7 of whom were evaluable for the 24-week objective response rate, which was 33% (95% CI, 14.6%-57.0%). The median duration of response was 10.9 months (95% CI, 2.4 months-NE), and the median progression-free survival was 5.9 months (95% CI, 2.3-13.8 months). The study investigators concluded from this study that the combination of lenvatinib and pembrolizumab demonstrated a manageable safety profile and promising antitumor activity in patients with selected solid tumor types.[7]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Pembrolizumab is already a licenced first line therapy for PD-L1 positive NSCLC.[4]

Lenvatinib is currently licenced as a monotherapy for treatment of adult patients with progressive, locally advanced or metastatic, differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma (DTC), refractory to radioactive iodine (RAI) and for the treatment of adult patients with advanced or unresectable hepatocellular carcinoma (HCC) who have received no prior systemic therapy.[2] It is also currently licenced in combination with everolimus for the treatment of adult patients with advanced renal cell carcinoma (RCC) following one prior vascular endothelial growth factor (VEGF)-targeted therapy.[3]

Very common adverse events (occurs in ⩾1 in 10 patients) of lenvatinib include: urinary tract infection, hypothyroidism, hypocalcaemia, thrombocytopenia, decreased weight and appetite, insomnia, headache, dysgeusia, dizziness, hypertension, haemorrhage, diarrhoea, vomiting, oral pain and inflammation, constipation, dyspepsia, dysphonia, dry mouth, rash, alopecia, pain, palmar erythema, palmar-plantar erythrodysaesthesia syndrome, myalgia, proteinuria, arthralgia, peripheral oedema, fatigue and asthenia.[3]

Lenvatinib plus pembrolizumab is in phase III clinical development for tumours including malignant melanoma, hepatocellular carcinoma, renal cell carcinoma, head and neck squamous cell carcinoma, non-small cell lung cancer and urothelial carcinoma. This combination is also in phase II clinical development for advanced solid tumours like gastric, thyroid and breast cancer.[8]

PATIENT GROUP

DISEASE BACKGROUND

Lung cancer is classified into two main types: small-cell lung cancer (SCLC) or non-small cell lung cancer (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).[9] In stage IV the cancer has spread, either to both lungs, the chest or beyond.[10]

PD-L1 is a type 1 transmembrane protein that belongs to the B7 ligands family and may be expressed both on hematopoietic cells and non-hematopoietic cells. Expression of PD-L1 on tumour cells promotes down-regulation and self-tolerance of the immune system from rejecting the tumour by supressing T-cell inflammatory activity through binding the regulatory T-cell receptor, PD-1.[11]

Tobacco smoking remains the main cause of lung cancer and the geographical and temporal patterns of the disease largely reflect tobacco consumption during the previous decades. Both smoking prevention and smoking cessation can lead to a reduction in a large fraction of 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.[12]

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.[13]

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.[14,15]

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.[12]

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.[16]

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.[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 the 47% of the overall number of lung cancer cases diagnosed for that year.[18] 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.[9]

Survival rates for lung cancer depend on at which stage of disease the cancer is identified.[16] 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.[19] 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.[16] 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.[20]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Treatment of NSCLC depends on the stage of the cancer and the general health of the patient. The main treatment options for stage I, II and III NSCLC are surgery, chemotherapy and radiotherapy. 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.[21]

CURRENT TREATMENT OPTIONS

The following are recommended for first-line treatment of patients with advanced nonsquamous (stages IIIB and IV) NSCLC, and no specific modifications to the EGFR or ALK genes:

- PD-L1 under 50% (no gene mutation, fusion protein or biomarker):[22]
    - Atezolizumab plus bevacizumab, carboplatin and paclitaxel
    - Pembrolizumab, with pemetrexed and platinum chemotherapy
    - Pemetrexed in combination with cisplatin
- PD-L1 50% or over (no gene mutation, fusion protein or biomarker):[4]
    - 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.[15] Pembrolizumab with carboplatin and paclitaxel is also recommended as an option for adults with untreated metastatic squamous NSCLC for use within the Cancer Drugs Fun (CDF).[23]

PLACE OF TECHNOLOGY

If licenced, pembrolizumab in addition to lenvatinib will offer an additional treatment option for people with adults with treatment-naïve, metastatic, stage IV, non-small cell lung cancer with programmed cell death-ligand 1 (PD-L1) expression in ≥1% of tumour cells.[1]

CLINICAL TRIAL INFORMATION

Trial	**LEAP-007, NCT03829332, EudraCT 2018-003794-98; A Phase 3, Randomized, Double-blind Trial of Pembrolizumab (MK-3475) With or Without Lenvatinib (E7080/MK-7902) in Participants With Treatment-naïve, Metastatic Non-small Cell Lung Cancer (NSCLC) Whose Tumours Have a Tumour Proportion Score (TPS) Greater Than or Equal to 1% (LEAP-007)** **Phase III** **Location: EU (not UK), Canada, United states and other countries.**
Trial design	Randomised, double blind, parallel assignment, active comparator.
Population	n = 620 (planned), aged 18 years and older, stage IV NSCLC, programmed cell death-ligand 1 (PD-L1) expression in ⩾1% of tumour cells.
Intervention(s)	Pembrolizumab 200 mg via intravenous (IV) infusion on day 1 of each 3-week cycle for up to 35 administrations (up to approximately 2 years) PLUS lenvatinib 20 mg via oral capsule once daily (QD) on days 1-21 of each 3-week cycle until progressive disease or unacceptable toxicity.
Comparator(s)	Pembrolizumab 200 mg via IV infusion on day 1 of each 3-week cycle for up to 35 administrations (up to approximately 2 years) PLUS placebo for lenvatinib via oral capsule QD on days 1-21 of each 3-week cycle until progressive disease or unacceptable toxicity.
Outcome(s)	Primary Outcome(s): • Progression-free survival (PFS) as assessed by response evaluation criteria in solid tumours Version 1.1 (RECIST 1.1) [Time frame: up to approximately 24 months] • Overall Survival (OS) [Time frame: up to approximately 60 months] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

ESTIMATED COST

Lenvatinib is already marketed in the UK; 30 x 4 mg or 10mg capsules cost £1,437.00.[24]

Pembrolizumab is already marketed in the UK. The NHS indicative price is:[25]

- A 100 mg/4 ml concentrate for solution for infusion vial costs £2630.00

- A 50 mg powder for concentrate for solution for infusion vial costs £1315.00

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance in development. Veliparib with carboplatin and paclitaxel for untreated non-squamous non-small-cell lung cancer (ID1277). Expected date of issue to be confirmed.
- NICE technology appraisal guidance in development. Pembrolizumab for untreated PD-L1 positive non-small-cell lung cancer with at least 1% tumour proportion score (ID1247). Expected date of issue to be confirmed.
- NICE technology appraisal guidance in development. Durvalumab with tremelimumab for untreated non-small-cell lung cancer with no EGFR- or ALK-positive mutations (ID1143). Expected date of issue to be confirmed.
- NICE technology appraisal guidance. Pembrolizumab with carboplatin and paclitaxel for untreated metastatic squamous non-small-cell lung cancer (TA600). September 2019.
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NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

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OTHER GUIDANCE

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ADDITIONAL INFORMATION

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