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HEALTH TECHNOLOGY BRIEFING DECEMBER 2020

Lorlatinib for advanced ALK-positive non-small cell lung cancer – first line

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Developer/Company	Pfizer Ltd	**UKPS ID**	655553

Licensing and market availability plans	In phase III clinical trials

SUMMARY

Lorlatinib is being investigated for the treatment of advanced anaplastic lymphoma kinase (ALK) positive non-small cell lung cancer (NSCLC). NSCLC comprises the majority of lung cancers in the UK. Symptoms of lung cancer include a persistent cough, shortness of breath, coughing up blood, aches and pains in the chest or shoulder, loss of appetite, weight loss and fatigue. While current treatments exist for ALK-postive NSCLC, significant unmet medical need remains for more effective treatment options as treatment with current options inevitably leads to further progression of the disease over time.

Lorlatinib is administered orally in tablet form and works by acting as an inhibitor to tyrosine kinases which function as 'on'/'off' enzymes in cellular proteins. This prevents cancer cells from growing so can control the spread of the cells. If licensed, lorlatinib would offer an additional first-line treatment option for adult patients with ALK-positive NSCLC.

PROPOSED INDICATION

First-line treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC).[a]

TECHNOLOGY

DESCRIPTION

Lorlatinib is a selective, adenosine triphosphate (ATP)-competitive inhibitor of ALK and c-ros oncogene 1 (ROS1) tyrosine kinases. In non-clinical studies, lorlatinib inhibited catalytic activities of non-mutated ALK and clinically relevant ALK mutant kinases in recombinant enzyme and cell-based assays. Lorlatinib demonstrated marked antitumour activity in mice bearing tumour xenografts that express echinoderm microtubule-associated protein-like 4 (EML4) fusions with ALK variant 1 (v1), including ALK mutations L1196M, G1269A, G1202R, and I1171T. Two of these ALK mutants, G1202R and I1171T, are known to confer resistance to alectinib, brigatinib, ceritinib, and crizotinib. Lorlatinib was also capable of penetrating the blood-brain barrier. Lorlatinib demonstrated activity in mice bearing orthotopic EML4-ALK or EML4-ALK^{L1196M} brain tumour implants.[1]

Lorlatinib is currently in clinical trials for adult patients with advanced ALK-postive NSCLC. In the phase III clinical trial (NCT03052608), participants receive 100mg lorlatinib (4 x 25mg) tablets orally each day.[2]

INNOVATION AND/OR ADVANTAGES

Lorlatinib is effective against ALK-positive NSCLC that has spread to the brain. Very few other effective treatments are available for patients whose cancer has spread to the brain, and the side effects with lorlatinib are manageable.[3]

In a phase III trial (NCT03052608), the percentage of patients who were alive without disease progression at 12 months was 78% in the lorlatinib group which shows the efficacy of lorlatinib as a first-line treatment.[4,5]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Lorlatinib is licensed in the EU/UK for the treatment of NSCLC after progression despite treatment with other ALK tyrosine kinase inhibitors (TKIs), including alectinib, ceritinib and crizotinib.[3]

The most common side effects with lorlatinib (which may affect more than 1 in 5 people) are hypercholesterolaemia (high blood cholesterol levels), hypertriglyceridaemia (high blood levels of triglycerides, a type of fat), oedema (build-up of fluid), peripheral neuropathy (nerve damage in the hands and feet), problems with thinking, learning and memory, tiredness, weight gain, arthralgia (joint pain), effects on mood and diarrhoea.[3]

It is currently in phase II clinical development for treatment on ALK+ or ROS1+ NSCLC in combination with crizotinib and binimetinib.[6]

[a] Information provided by Pfizer on UK PharmaScan

PATIENT GROUP

DISEASE BACKGROUND

Lung cancer is classified into two main types: small-cell lung cancer (SCLC) or 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).[7] In stage IV the cancer has spread, either to both lungs, the chest or beyond.[8]

Tobacco smoking remains the main cause of lung cancer and the geographical and temporal patterns of the disease largely reflect tobacco consumption during previous decades. 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. COPD). [9] Other factors include family history of lung cancer and certain genetic mutations.[10]

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.[11,12]

Oncogenic fusion genes consisting of echinoderm microtubule-associated protein-like 4 (EML4) and anaplastic lymphoma kinase (ALK) are present in a subgroup of NSCLC.[13] The EML4-ALK fusion gene is expressed in a distinct subgroup of NSCLC, that typically occur in younger patients who have never smoked or have a history of light smoking and that has adenocarcinoma histologic characteristics.[14]

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.[9]

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.[15]

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.[16] 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.[17] 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.[7]

Survival rates for lung cancer depend on at which stage of disease the cancer is identified.[15] 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.[18] 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.[15] In England and Wales in 2019

there were 29,443 deaths with malignant neoplasm of bronchus and lung (ICD-10 codes C34) recorded as the underlying cause.[19]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Treatment of NSCLC depends on the stage of the cancer and the general health of the patient. 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.[20]

CURRENT TREATMENT OPTIONS

Current first line treatment options for ALK-positive NSCLC are:[21]

- Alectinib
- Certinib
- Crizotinib

PLACE OF TECHNOLOGY

If licensed, lorlatinib will provide an additional first-line treatment for adult patients with ALK-positive NSCLC.

CLINICAL TRIAL INFORMATION

Trial	**B7461006;** NCT03052608**;** EudraCT2016-003315-35**;** A phase 3, randomised, open-label study of lorlatinib (PF-06463922) monotherapy versus crizotinib monotherapy in the first-line treatment of patients with advanced ALK-positive non-small cell lung cancer **Phase III** - recruiting **Location(s):** US, Canada, EU (incl. UK) plus other countries **Primary completion date:** March 2020
Trial design	Randomised, parallel assignment, open-label, active controlled
Population	N = 280; 18 years and older; histologically or cytologically confirmed diagnosis of locally advanced or metastatic ALK-positive NSCLC; at least 1 extracranial measurable target lesion not previously irradiated; central nervous system metastases allowed if asymptomatic and not currently requiring corticosteroid treatment.
Intervention(s)	Lorlatinib, 100 mg (4 x 25 mg) oral tables, daily, continuously
Comparator(s)	Crizotinib, 250 mg (1 x 250) oral capsules, twice a day, continuously
Outcome(s)	Progression-free survival (PFS) based on blinded independent central review (BICR) assessment [Time frame: from time of Study Start up to 33 months} See trial record for full list of other outcomes

Results (efficacy)	• Median follow-up for PFS by BICR was 18.3 months (95% CI 16.4, 20.1) for lorlatinib (n=149) and 14.8 months (95% CI 12.8, 18.4) for crizotinib (n=147). • PFS by BICR was significantly prolonged with lorlatinib vs crizotinib (HR 0.28; 95% CI 0.191, 0.413; stratified 1-sided p<0.001). Lorlatinib median PFS was NE (not estimable) (95% CI NE, NE) vs crizotinib 9.3 months (95% CI 7.6, 11.1). • PFS by investigator (INV), Objective Response (OR) and Intracranial Objective Response (IC-OR) by BICR were improved with lorlatinib vs crizotinib.[5]
Results (safety)	• Grade 3–4 adverse events (AE)/AEs leading to treatment discontinuation: 72.5%/6.7% for lorlatinib; 55.6%/9.2% for crizotinib. The majority of Grade 3–4 AEs for lorlatinib were laboratory abnormalities, the most common of which were lipid abnormalities.[5]

ESTIMATED COST

The cost of lorlatinib for a pack of 90 x 25mg tablets is £5283.00, a pack of 120 x 25mg tablets is £7044.00. For a pack of 30 x100mg tablets, the cost is £5283.00.[22]

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Brigatinib for ALK-positive advanced non-small-cell lung cancer that has not been previously treated with an ALK inhibitor. (GID-TA10351). Expected date; January 2021.
- NICE technology appraisal. Alectinib for untreated ALK-positive advanced non-small-cell lung cancer. (TA536). August 2018.
- NICE technology appraisal. Ceritinib for untreated ALK-positive non-small-cell lung cancer. (TA500). January 2018.
- NICE technology appraisal. Crizotinib for untreated anaplastic lymphoma kinase-positive advanced non-small-cell lung cancer. (TA406). September 2016.
- NICE guideline. Lung cancer: diagnosis and management (NG122). March 2019.
- NICE quality standard. Lung cancer in adults (QS17). 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 5.2017, NCCN Clinical Practice Guidelines in Oncology. 2017.[23]

- European Society for Medical Oncology. Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2016.[24]
- European Society for Medical Oncology. ESMO Consensus Guidelines: Non-small-cell lung cancer first-line/second and further lines in advanced disease. 2014.[25]
- Scottish Intercollegiate Guidelines Network. Management of lung cancer (SIGN 137). 2014.[26]

ADDITIONAL INFORMATION

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