National Institute for Health Research

NIHR Innovation Observatory
Evidence Briefing: August 2017

Lorlatinib (PF-06463922) for advanced ALK or ROS1 positive non-small cell lung cancer – second line

NIHRIO (HSRIC) ID: 14896 NICE ID: 9656

LAY SUMMARY

Lung cancer is the second most common type of cancer. The most common type of lung cancer is non-small cell lung cancer (NSCLC). NSCLC has three sub-types that can be further grouped by their specific genetic mutation. Two of these types are ALK-positive and ROS1-positive lung cancer, both of which fuse with other genes and promote cancer tumour growth. Patients with ALK-positive and ROS1-positive NSCLC are similar in that they are often younger, have no history of smoking and have a particular type of NSCLC called adenocarcinoma (a cancerous tumour of the lung).

Lorlatinib is a new drug under development for the sub-group of advanced non-small cell lung cancer who are ALK or ROS1 positive and have already undergone gene treatment with drugs that specifically target this type of cancer. Lorlatinib is currently being evaluated in phase II clinical trials as an oral dose at 100 mg daily. If marketed it will become an additional targeted treatment for this sub-group of ALK or ROS1 positive patients.

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.

TARGET GROUP

Non-small cell lung cancer (NSCLC); advanced or metastatic; anaplastic lymphoma kinase (ALK)-positive or ROS1-positive, previously treated with one or more ALK inhibitors – second line

TECHNOLOGY

DESCRIPTION

Lorlatinib (PF-06463922) is a new biological entity under development for the treatment of advanced ALK-positive and ROS1-positive NSCLC.[1]

Lorlatinib acts by inhibiting the ALK and ROS1 receptor tyrosine kinases, with potent activity against a broad spectrum of ALK resistant mutations. By inhibiting ALK phosphorylation and ROS1 activity, lorlatinib inhibits the downstream signalling, thereby inducing the apoptosis process, which results in the inhibition of tumour cells proliferation.[1]

Loratinib is currently in phase II clinical trials as a treatment for ALK positive or ROS1 positive advanced NSCLC who have previously been treated with one or more ALK inhibitors. The recommended Phase II dose for orally administered PF-06463922 has been defined by dose escalation in the phase I study.[2]

Lorlatinib is also in a phase III clinical trial for the first-line treatment for advanced ALK-positive NSCLC.[3]

Lorlatinib does not currently have Marketing Authorisation in the EU for any indication.

INNOVATION and/or ADVANTAGES

If licensed, lorlatinib will offer an additional treatment option for ALK-positive or ROS1-positive advanced NSCLC previously treated with one or more ALK inhibitors as it is a targeted therapy for the specific gene rearrangements.

DEVELOPER

Pfizer Ltd

AVAILABILITY, LAUNCH or MARKETING

Loratinib was designated orphan drug status in the USA in 2015 and was awarded Breakthrough Therapy in 2017 by FDA for the treatment of ALK-positive metastatic (NSCLC) who have previously received 1 or more ALK inhibitors.[1]

PATIENT GROUP

BACKGROUND

Lung cancer is the second most common cancer.[4] NSCLC is the most common type of lung cancer, accounting for approximately 85-90% of all lung cancers.[5] This can be further classified into 3 histological subtypes: large cell undifferentiated carcinoma, squamous cell carcinoma and adenocarcinoma.[6] Cigarette smoking is the single biggest risk factor for developing lung cancer,

accounting for about 90% of cases.[7] Due to the usually asymptomatic nature of lung cancer in the early stages, it is often diagnosed at an advanced stage resulting in a poor prognosis.[8] Common symptoms can include coughing, haemoptysis, dyspnoea, persistent chest infections and chest pain.[7,8] Other symptoms may include unilateral paralysis of the diaphragm, Pancoast's syndrome and metastases, which most frequently spread to the liver, bone, brain and adrenal glands.[7]

Oncogenic fusion genes consisting of echinoderm microtubule-associated protein-like 4 and anaplastic lymphoma kinase (ALK) are present in a subgroup of NSCLC.[9] 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.[10] Patients with ALK-rearranged (ALK-positive) NSCLC are highly responsive to small-molecule tyrosine kinase inhibitors of ALK.[11] Although crizotinib was the first ALK inhibitor tested, and was superior to chemotherapy in treating advanced ALK-positive NSCLC,[12] most patients tend to relapse within the first year of treatment.[11] It is found that approximately a third of patients develop a resistance due to amplification of the ALK fusion gene or to a secondary mutation within the ALK tyrosine kinase domain following crizotinib,[13] therefore various next-generation ALK inhibitors that can overcome the most common ALK resistance mutations have underdone clinical studies.[11]

Significant overlap exists between ALK-positive and ROS-1 positive patients, as patients are often younger, have no history of smoking and have a histologic diagnosis of adenocarcinoma.[14] However, ALK and ROS1 arrangements rarely occur in the same tumour, as each one defines a distinct NSCLC molecular subgroup.[15] ROS1 receptor tyrosine kinase is activated by chromosomal rearrangement in a variety of human cancers, including NSCLC[16] and the ROS1 oncogene encodes an orphan receptor tyrosine kinase related to ALK.[17] Whilst crizotinib acts as a ROS1 inhibitor and often generates tumour regression in patients with NSCLC,[18] ultimately disease progression follows.[19]

CLINICAL NEED and BURDEN OF DISEASE

Lung cancer accounted for 13% of all new cases of cancer in the UK and in 2014.[20] In 2015, there were 37,637 (20,017 males and 17,620 females) cases of lung cancer registered in England.[21] Twelve per cent of cases of lung cancer are classified as small cell lung cancer, 87% as NSCLC and 1% are carcinoid,[20] and approximately half of patients with NSCLC have metastatic disease at diagnosis.[22]

ALK rearrangements are found in an estimated 3 to 7% of patients with NSCLC,[11] which translates into more than 60,000 patients globally, acquiring this specific NSCLC sub-type.[12] ROS1 rearrangements occur in approximately 1% of NSCLC patients[15] and world-wide an estimated 15,000 cases are considered to be driven by ROS1 fusions.[18]

In 2015/2016, there were 89,945 hospital admissions for malignant neoplasm of the bronchus and lung (ICD code C34) in England, resulting in 266,522 bed days and 110,013 finished consultant episodes.[23]

As lung cancer is the most common cause of cancer death in the UK (2014), it accounts for 22% of all cancer deaths. In males, it is the most common cause of cancer death in the UK (23% of all male cancer deaths), and it is also the most common cause of cancer death in females in the UK (21% of all female cancer deaths). In 2014, there were 35,895 lung cancer deaths in the UK: 19,563 (55%) in males and 16,332 (45%) in females.[20]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal. Nivolumab for previously treated locally advanced or metastatic non-squamous non-small-cell lung cancer. In development
- 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. Crizotinib for previously treated anaplastic lymphoma kinase-positive advanced non-small-cell lung cancer (TA422). December 2016.
- NICE technology appraisal. Osimertinib for treating locally advanced or metastatic EGFR T790M mutation-positive non-small-cell lung cancer. (TA416). October 2016.
- NICE technology appraisal. Crizotinib for untreated anaplastic lymphoma kinase-positive advanced non-small-cell lung cancer (TA406). September 2016.
- NICE technology appraisal. Ramucirumab for previously treated locally advanced or metastatic non-small-cell lung cancer (TA403). August 2016.
- NICE technology appraisal. Pemetrexed maintenance treatment for non-squamous non-small-cell lung cancer after pemetrexed and cisplatin (TA402). August 2016.
- NICE technology appraisal. Erlotinib and gefitinib for treating non-small-cell lung cancer that has progressed after prior chemotherapy (TA374). December 2015.
- NICE technology appraisal. Nintedanib for previously treated locally advanced, metastatic, or locally recurrent non‑small‑cell lung cancer (TA347). July 2015.
- NICE technology appraisal. Pemetrexed maintenance treatment following induction therapy with pemetrexed and cisplatin for non-squamous non-small-cell lung cancer (TA309). April 2014.
- NICE technology appraisal. Afatinib for treating epidermal growth factor receptor mutation-positive locally advanced or metastatic non-small-cell lung cancer (TA310). April 2014.
- NICE technology appraisal. Crizotinib for previously treated non-small-cell lung cancer associated with an anaplastic lymphoma kinase fusion gene (TA296). September 2013.

- NICE technology appraisal. Erlotinib for the first-line treatment of locally advanced or metastatic EGFR-TK mutation-positive non-small-cell lung cancer (TA258). June 2012.
- NICE technology appraisal. Erlotinib monotherapy for maintenance treatment of nonsmall-cell lung cancer (TA227). June 2011.
- NICE technology appraisal. Gefitinib for the first-line treatment of locally advanced or metastatic non-small-cell lung cancer (TA192). July 2010.
- NICE technology appraisal. Pemetrexed for the maintenance treatment of non-small-cell lung cancer (TA190). June 2010.
- NICE clinical guideline. Lung cancer: The diagnosis and treatment of lung cancer (CG121). April 2011.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. National Chemotherapy Algorithms: non-small cell lung cancer. DRAFT v0.6. 2014.
- American Society of Clinical Oncology. Molecular Testing for Selection of Lung Cancer Patients for EGFR and ALK Tyrosine Kinase Inhibitors: American Society of Clinical Oncology Endorsement of the CAP/IASLC/AMP Guideline. October 2014.
- European Society for Medical Oncology. Metastatic non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. August 2014.
- Scottish Intercollegiate Guidelines Network. Management of Lung Cancer (SIGN 137). February 2014.
- London Cancer Alliance. LCA Lung Cancer Clinical Guidelines. December 2013.
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- American Society of Clinical Oncology. The role of CT screening for Lung Cancer in clinical practice. The evidence based practice guideline of the American College of Chest Physicians and the American Society for Clinical Oncology. May 2012.

OTHER GUIDANCE

- Besse B, Adjei A, Baas P, Meldgaard P, Nicolson M, Paz-Ares L, Reck M, Smit EF, Syrigos K, Stahel R, Felip E. 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 Mar 25;25(8):1475-84.
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CURRENT TREATMENT OPTIONS

The aim of treatment for locally advanced or metastatic NSCLC is to prolong survival, improve quality of life, and control disease-related symptoms.[24] Treatment strategies should take into account the tumour histology and molecular pathology, as well as the patient's age, performance status, co-morbidities, and preferences. Patients who smoke should be encouraged to cease, as cessation improves treatment outcomes.[25]

Current guidelines recommend that palliative chemotherapy should be offered to patients with stage III/IV NSCLC and good performance status (WHO 0 or 1 or a Karnofsky score of 80–100).[26] Induction chemotherapy for advanced NSCLC should be a combination of a single third generation drug (docetaxel, gemcitabine, paclitaxel, or vinorelbine) plus a platinum drug (either carboplatin or cisplatin);[27] if patients cannot tolerate a platinum combination (or are WHO performance status 2), a single agent chemotherapy with a third generation drug is recommended.[24] In the first and subsequent treatment line setting, afatinib, erlotinib and gefitinb are all options for epidermal growth factor receptor tyrosine kinase mutation (EGFRTK) positive metastatic NSCLC patients.[26]

Pemetrexed in combination with cisplatin is recommended if the tumour has been confirmed as adenocarcinoma or large-cell carcinoma on the basis of best survival figures and toxicity profiled. Pemetrexed is recommended as maintenance therapy after treatment with platinum-based chemotherapy in combination with gemcitabine, paclitaxel and docetaxel (switch maintenance) if the tumour is adenocarcinoma or large-cell carcinoma.[26]

It is recommended that patients progressing after first-line chemotherapy be offered docetaxel or erlotinib monotherapy as a second-line treatment option or crizotinib for previously treated ALK positive advanced NSCLC. Nintedanib in combination with docetaxel is recommended, within its marketing authorisation, as an option for treating locally advanced, metastatic or locally recurrent non-small-cell lung cancer of adenocarcinoma histology that has progressed after first-line chemotherapy. Pembrolizumab is recommended for use within the Cancer Drugs Fund as an option for untreated PD-L1-positive metastatic non-small-cell lung cancer in adults, only if:

- their tumours express PD-L1 with at least a 50% tumour proportion score and have no epidermal growth factor receptor- or anaplastic lymphoma kinase-positive mutations
- pembrolizumab is stopped at 2 years of uninterrupted treatment and no documented disease progression
- the conditions in the managed access agreement for pembrolizumab are followed.

Osimertinib is recommended as an option for use within the Cancer Drugs Fund for treating locally advanced or metastatic EGFR T790M mutation-positive non-small-cell lung cancer in adults whose disease has progressed only after first-line treatment with an EGFR-TK inhibitor.[26]

EFFICACY and SAFETY

Trial	NCT01970865, EudraCT-2013-002620-17, PF-06463922 (lorlatinib), phase I/II
Sponsor	Pfizer Ltd
Status	Ongoing
Source of Information	GlobalData[1] and Trial registry[2]
Location	EU (incl UK), USA, Canada, Australia and other countries
Design	Non-randomised, uncontrolled, open-label study

Participants	n=340 (planned); ≥ aged 18 years; ALK-positive or ROS1; advanced or metastatic; including patients with previously treated with one or more ALK inhibitors. Phase 1: ALK-positive NSCLC and ROS1-positive patients must either be treatment naïve in the advanced setting or have had disease progression after at least 1 previous ALK/ROS1 inhibitor therapy(ies). Phase 2: ALK-positive NSCLC patients must either be or have had: • Treatment naïve (ie, no prior chemotherapy in the metastatic disease setting and no prior ALK inhibitor therapy allowed). • Disease progression after crizotinib only. No prior chemotherapy is allowed in the metastatic disease setting. • Disease progression after crizotinib and 1 or 2 prior regimens of chemotherapy in the metastatic disease setting. • Disease progression after 1 prior ALK inhibitor therapy other than crizotinib. Patients may have had any number of prior chemotherapy regimens in any disease setting. • Disease progression after 2 prior ALK inhibitor therapies. Patients may have had any number of prior chemotherapy regimens in any disease setting. • Disease progression after 3 prior ALK inhibitor therapies. Patients may have had any number of prior chemotherapy regimens in any disease setting. ROS1-positive NSCLC patients may be: • Treatment naïve (ie, no prior chemotherapy in the metastatic disease setting and no prior ROS inhibitor therapy). • Any number of prior therapies (ie, chemotherapy and/or ROS inhibitor therapies). Tumor Requirements: All Patients must have at least one measurable target extracranial lesion according to RECIST v1.1. In addition patients with asymptomatic CNS metastases (including patients asymptomatic by means of stable or decreasing doses of steroids within the last 2 weeks prior to study entry) will be eligible. Patients who have leptomeningeal disease (LM) or carcinomatous meningitis (CM) are eligible. • Adequate Bone Marrow, Pancreatic Function, Renal Function and Liver Function. • Negative Serum pregnancy test for females of childbearing potential Exclusion Criteria • Radiation therapy (except palliative to relieve bone pain) within 2 weeks of study entry. Whole brain radiation must have completed at least 4 weeks prior to study entry. • Systemic anti-cancer therapy completed within a minimum of 5 half-lives of study entry. • Prior therapy with an antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways, including, but not limited to, anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-cytotoxic T lymphocyte associated antigen 4 (anti-CTLA-4) antibody. • Active and clinically significant bacterial, fungal, or viral infection including hepatitis B (HBV), hepatitis C (HCV), known human immunodeficiency virus (HIV), or acquired immunodeficiency syndrome (AIDS) related illness. • Clinically significant cardiovascular disease (that is, active or <3 months prior to enrolment): cerebral vascular accident/stroke, myocardial infarction, unstable angina, congestive heart failure (New York Heart Association Classification Class ≥ II), second-degree or third-degree AV block (unless

	paced) or any AV block with PR >220 msec. Ongoing cardiac dysrhythmias of NCI CTCAE Grade ≥2, uncontrolled atrial fibrillation of any grade, bradycardia defined as <50 bpm (unless patient is otherwise healthy such as long-distance runners, etc.), machine-read ECG with QTc >470 msec, or congenital long QT syndrome. • History of extensive, disseminated, bilateral or presence of Grade 3 or 4 interstitial fibrosis or interstitial lung disease including a history of pneumonitis, hypersensitivity pneumonitis, interstitial pneumonia, interstitial lung disease, obliterative bronchiolitis and pulmonary fibrosis. • Current use or anticipated need for food or drugs that are known strong or moderate CYP3A4 inhibitors, inducers and substrates; drugs that are CYP2C9 substrates; drugs that are sensitive CYP2B6 substrates; drugs that are strong CYP2C19 inhibitors; drugs that are strong CYP2C8 inhibitors; and drugs that are P-gp substrates.
Schedule	Subjects receive 100 mg once a day starting dose of lorlatinib orally in Phase I dose escalation until recommended Phase II dose determined in cycles lasting 21 days.
Follow-up	Subjects are enrolled in six expansion cohorts (EXP) based upon the prior tx (EXP 1-5, ALK+) and rearrangement status (EXP 6, ROS1+) in this study.
Primary Outcomes	**Phase I** Number of patients with Dose-limiting toxicities (DLT) - First Cycle Cycle 1 Dose Limiting Toxicities (DLTs). (Phase 1) - One (1) cycle (21 days) To assess safety and tolerability of PF-06463922 as a single agent at increasing dose levels in patients with advanced ALK+ or advanced ROS1+ NSCLC in order to estimate the Maximum Tolerated Dose (MTD) and select the Recommended Phase 2 Dose (RP2D) **Phase II** Percentage of patients with Overall and Intracranial Objective Response - Every 6 weeks from the time of patient enrolment up to 4 years Percentage of patients with objective response based assessment of intracranial and overall confirmed complete remission (CR) or confirmed partial remission (PR) according to a modified Response Evaluation Criteria in Solid Tumours (RECIST)v 1.1.
Secondary Outcomes	See trial for exhaustive list
Key Results	Interim Phase I results: N=54 (including ALK+ N=41, ROS1+ N=12) and Interim Phase II results: ALK+ EXP 2-5 (N=82) PF-06463922 is has demonstrated clinical activity in subjects with advanced ALK+ or ROS1+ non-small cell lung cancer.
Adverse effects (AEs)	Interim Phase II results: ALK+ EXP2-5 Lorlatinib 100mg once-daily: The most common severe (grade 3) side effects of lorlatinib were hypercholesterolemia (16.4%) and hypertriglyceridemia (14.7%), successfully managed with lipid-lowering agents. Other common but lower grade AEs include oedema, peripheral neuropathy, and cognitive effects. With 3.4%, permanent treatment discontinuations due to AEs were infrequent.

Expected reporting date	Study completion date reported as April 2018.

COST

The cost of lorlatinib is not yet known.

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

INFORMATION FROM

Information was received from Pfizer Ltd

UK PharmaScan ID number: 645794

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