Health Technology Briefing
December 2021

Selpercatinib for previously untreated advanced RET fusion-positive non-small cell lung cancer

Company/Developer	Eli Lilly and Company Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 31194	NICE ID: 10732	UKPS ID: 661217

Licensing and Market Availability Plans

Currently in phase I/II clinical development.

Summary

Selpercatinib is in clinical development for the treatment of advanced or metastatic RET fusion-positive non-small cell lung cancer (NSCLC). NSCLC is the most common type of lung cancer and at the metastatic stage the disease has already spread from the lungs to other sites. Advanced is when the cancer has progressed locally. Around 2% of patients with NSCLC will have a mutation or abnormal arrangement of a gene called RET (rearranged during transfection), which can allow uncontrolled cancer growth. Current treatment options are nonselective, meaning they do not inhibit RET receptors specifically.

Selpercatinib is an orally administered selective cancer medicine that blocks the activity of abnormal proteins that are encouraged by the RET gene mutation, this prevents the growth and spread of cancer cells. Selpercatinib is being developed for NSCLC and other advanced solid tumours with RET genetic alterations with early results indicating significantly improved outcomes. If licensed, selpercatinib will offer a first-in-class treatment option for RET-fusion positive NSCLC, who currently have no highly selective therapies available.

Proposed Indication

Selpercatinib for the treatment of adults with advanced or metastatic RET (rearranged during transfection) fusion-positive NSCLC.[1]

Technology

Description

Selpercatinib (LOXO-292) is a highly selective, ATP-competitive small molecule inhibitor of the RET receptor tyrosine kinase.[2] In RET-altered cancers (which include fusions and activating point mutations), gene alterations cause overactive RET signalling, allowing tumour proliferation and survival. Such cancers are often dependent on a single activated kinase which renders them highly susceptible to small molecule inhibitors targeting RET, such as selpercatinib.[2,3]

Selpercatinib is in clinical development for the treatment of advanced or metastatic RET fusion-positive NSCLC. In the phase III clinical trial (LIBRETTO-431; NCT04194944), selpercatinib is administered orally at a dose of 160mg twice daily.[1,4]

Key Innovation

Multitargeted kinase inhibitors that have some measure of RET inhibition have only shown limited clinical benefit and off-target toxic effects due to the multiple non-RET kinases being inhibited. Selpercatinib is a highly selective inhibitor of RET kinase and spares non-RET kinases from inhibition.[5] Studies have suggested that NSCLC patients with driver oncogenes such as RET may benefit less from chemotherapy-immunotherapy combinations and may benefit from a targeted therapy such as selpercatinib, as a first line treatment. Selpercatinib was designed to inhibit RET signalling as well as anticipated acquired resistance mechanisms that could otherwise limit the activity of this therapeutic approach.[4]

If approved, selpercatinib would provide a treatment option for patients with untreated advanced RETfusion-positive NSCLC.

Regulatory & Development Status

Selpercatinib is currently licensed in the UK as monotherapy for the following indications:[6]

- Adults with advanced RET fusion-positive NSCLC who require systemic therapy following prior treatment with immunotherapy and/or platinum-based chemotherapy.
- Adults with advanced RET fusion-positive thyroid cancer who require systemic therapy following prior treatment with sorafenib and/or lenvatinib.
- Adults and adolescents 12 years and older with advanced RET-mutant medullary thyroid cancer (MTC) who require systemic therapy following prior treatment with cabozantinib and/or vandetanib.

Selpercatinib is currently in phase II/III clinical development for:[7]

- Medullary thyroid cancer (MTC)
- Advanced solid tumours, lymphomas or histiocytic disorders with activating RET gene alterations
- RET-altered thyroid cancer

Patient Group

Disease Area and Clinical Need

Primary lung cancer, which starts in the lung, is divided into small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). NSCLC accounts for around 80-85% of lung cancers in the UK.[8] There are three main types of NSCLC:[8]

- Adenocarcinoma – starts in the mucus making gland cells in the lining of airways
- Squamous cell cancer – develops in the flat cells that cover the surface of the airways
- Large cell carcinoma – the cancer appears large and round under the microscope

The RET receptor tyrosine kinase can be abnormally activated by chromosomal rearrangements producing RET gene fusions in 1–2% of patients with NSCLC and they appear to be associated with a high risk of brain metastases.[4,5] Advanced lung cancer means that the cancer has spread from where it started in the lung. It is also called metastatic cancer. Unfortunately, advanced cancer cannot usually be cured, but treatment can control it, help symptoms and improve quality of life.[9] There are usually no signs or symptoms in the early stages of lung cancer, but many people with the condition eventually develop symptoms such as a persistent cough, coughing up blood, persistent breathlessness, unexplained tiredness, weight loss, and/or an ache or pain when breathing or coughing.[10] Smoking cigarettes is the single biggest risk factor for lung cancer and is responsible for more than 70% of cases. Other risk factors include passive smoking, radon (a radioactive gas), and exposure to chemicals such as arsenic, asbestos, beryllium, cadmium, coal/coke, silica and nickel.[11]

Lung cancer is the third most common cancer in the UK, accounting for 13% of all new cancer cases (2016-2018). There are around 48,500 new lung cancer cases in the UK yearly. Incidence rates for lung cancer in the UK are highest in people aged 85 to 89 (2016-2018). 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.[12] In England 2020-21, there were 35,679 finished consultant episodes (FCE) with a primary diagnosis of malignant neoplasm of bronchus or lung, unspecified (ICD-10 code C34.9), resulting in 61,090 FCE bed days and 20,004 day cases.[13]

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.[14] There are around 35,100 lung cancer deaths in the UK every year (based on data from 2016-2018). Mortality rates for lung cancer are projected to fall by 21% in the UK between 2014 and 2035.[12] In England and Wales in 2020 there were 379,999 deaths with malignant neoplasm of bronchus and lung, unspecified (ICD-10 code C34.9) recorded as the underlying cause.[15]

Recommended Treatment Options

Treatment of NSCLC depends on the stage of the cancer, the grade, and the general health of the patient. The main treatment options for stage I, II and III NSCLC are surgery, chemotherapy and radiotherapy. At advanced stage III disease, where patients are not candidates for surgical resection or definitive chemoradiation and stage IV metastatic disease, treatment aims to control the cancer for as long as possible and help with symptoms. Treatment generally includes chemotherapy, targeted drugs, immunotherapy, radiotherapy and symptom control treatment.[16]

There are specific treatment pathways for cancers positive for EGFR-TK, ALK or ROS-1 gene mutations, but not for RET-fusions/mutations.[17] First-line treatment options for patients with stage IIIB-IIIC and IV non-squamous NSCLC include:

- Brigatinib, alectinib, cerittinib or crizotinib for ALK-positive mutations[18]
- Osimertinib, dacomitinib, afatinib, erlotinib, gefitinib or ramucirumab with erlotinib for EGFR-TK mutations[19]
- Entrectinib or crizotinib for ROS1-positive mutations[20]

- Pembrolizumab combination or atezolizumab combination or pemetrexed with cisplatin or platinum doublet chemotherapy, or nivolumab with ipilimumab and platinum-doublet chemotherapy for PD-L1 under 50%[21]
- Atezolizumab monotherapy, pembrolizumab with pemetrexed and platinum chemotherapy, pembrolizumab, or nivolumab with ipilimumab and platinum-doublet chemotherapy for PD-L1 ≥50%[22]

Clinical Trial Information	
Trial	**LIBRETTO-431;** NCT04194944; 2019-001979-36; A Multicentre, Randomised, Open-Label, Phase 3 Trial Comparing Selpercatinib to Platinum-Based and Pemetrexed Therapy With or Without Pembrolizumab as Initial Treatment of Advanced or Metastatic RET Fusion-Positive Non-Small Cell Lung Cancer **Phase III –** Recruiting **Location(s):** 10 EU countries, UK, Canada and other countries **Primary completion date:** January 2023
Trial Design	Randomised, open label, parallel assignment, multicentre
Population	N=250; aged 18 years and older; Subjects with stage IIIB-IIIC or IV non-squamous NSCLC that is not suitable for radical surgery or radiation therapy, and a RET gene fusion in tumour.
Intervention(s)	Selpercatinib (oral) 160mg twice a day (BID) continuously in 21-day cycles.[4]
Comparator(s)	• Pemetrexed IV plus the investigator's discretion of carboplatin IV or cisplatin IV with or without pembrolizumab IV. • Pemetrexed IV plus the investigator's discretion of carboplatin IV or cisplatin IV with pembrolizumab IV.
Outcome(s)	Primary outcome measures: • Progression Free Survival (PFS) by Blinded Independent Central Review (BICR) (with Pembrolizumab) [Time Frame: Baseline to Progressive Disease or Death from Any Cause (Estimated at up to 24 Months)] PFS by BICR (with Pembrolizumab) • PFS by BICR (with or without Pembrolizumab) [Time Frame: Baseline to Progressive Disease or Death from Any Cause (Estimated at up to 24 Months)] PFS by BICR (with or without Pembrolizumab)
Results (efficacy)	-
Results (safety)	-

Trial	**LIBRETTO-001;** NCT03157128; 2017-000800-59; A Study of Oral LOXO-292 in Patients With Advanced Solid Tumors, Including RET Fusion-Positive Solid Tumors, Medullary Thyroid Cancer, and Other Tumors With RET Activation (LIBRETTO-001) **Phase I/II –** Recruiting

	Location(s): 5 EU countries, UK, USA, Canada and other countries **Primary completion date:** November 2022
Trial Design	Open label, single group assignment.
Population	N=989; aged 12 years and older; Subjects with advanced solid tumours, including RET-fusion-positive solid tumours, medullary thyroid cancer (MTC) and other tumours with RET activation.
Intervention(s)	• Phase I: Selpercatinib (oral) doses ranging from 20mg once daily to 240mg twice daily • Phase II: Selpercatinib (oral) 160mg twice daily
Comparator(s)	NA.
Outcome(s)	Primary outcome measures: • Phase I: Maximum tolerated dose (MTD) [Time Frame: The first 28 days of treatment (Cycle 1)] Incidence rate and category of dose limiting toxicities (DLTs) during the first 28-day cycle of LOXO-292 (selpercatinib) treatment See trial record for full list of other outcomes.
Results (efficacy)	In the first 105 consecutively enrolled patients with RET fusion–positive NSCLC who had previously received at least platinum-based chemotherapy, the percentage with an objective response was 64% (95% confidence interval [CI], 54 to 73). The median duration of response was 17.5 months (95% CI, 12.0 to could not be evaluated), and 63% of the responses were ongoing at a median follow-up of 12.1 months. Among 39 previously untreated patients, the percentage with an objective response was 85% (95% CI, 70 to 94), and 90% of the responses were ongoing at 6 months. Among 11 patients with measurable central nervous system metastasis at enrollment, the percentage with an objective intracranial response was 91% (95% CI, 59 to 100).[5]
Results (safety)	The most common adverse events of grade 3 or higher were hypertension (in 14% of the patients), an increased alanine aminotransferase level (in 12%), an increased aspartate aminotransferase level (in 10%), hyponatremia (in 6%), and lymphopenia (in 6%). A total of 12 of 531 patients (2%) discontinued selpercatinib because of a drug-related adverse event.[5]

Estimated Cost

The estimated cost of a 28-day cycle of selpercatinib is £8,736.00.[23]

Relevant Guidance

NICE Guidance

- NICE technology appraisal guidance in development. Pralsetinib for treating RET-positive advanced non-small-cell lung cancer (ID3875). Expected publication date: April 2022.

- NICE technology appraisal guidance in development. Selpercatinib for RET fusion-positive advanced non-small-cell lung cancer (ID3743). Expected publication date: January 2022.
- NICE guideline. Lung cancer: diagnosis and management (NG122). 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.
- NHS England. Clinical Commissioning Policy: Stereotactic Ablative Body Radiotherapy for Non-Small-Cell Lung Cancer (Adult). B01/P/a. April 2013.

Other Guidance

- National Comprehensive Cancer Network (NCCN). NCCN Guidelines Insights: Non–Small Cell Lung Cancer, Version 2.2021. 2021.[24]
- European Society for Medical Oncology (ESMO). Early and locally advanced non-small-cell lung cancer: an update of the ESMO Clinical Practice Guidelines focusing on diagnosis, staging and systemic and local therapy. 2021.[25]
- European Society for Medical Oncology (ESMO). Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment follow-up. 2020.[26]

Additional Information

The presence of a RET gene fusion (NSCLC and non-medullary thyroid cancer) or mutation (MTC) should be confirmed by a validated test prior to initiation of treatment with selpercatinib.[6]

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