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HEALTH TECHNOLOGY BRIEFING
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Selpercatinib for metastatic RET fusion-positive non-small cell lung cancer

NIHRIO ID	27907	**NICE ID**	10287
Developer/Company	Eli Lilly and Co Ltd	**UKPS ID**	653793

Licensing and market availability plans	Currently in phase II clinical trials

*COMMERCIAL IN CONFIDENCE

SUMMARY

Selpercatinib is in clinical development for the treatment of 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. Around 2% of these patients will have tumours that contain fusion mutations in the RET gene. Cells in these tumour produce altered RET signalling receptors that allow uncontrolled cancer growth. Currently the only treatment options that attempt to inhibit RET fusion-positive tumour activity are nonselective multikinase inhibitors.

Selpercatinib is a first-in-class oral precision cancer medicine designed to selectively bind to cancers that harbour genetic abnormalities in the RET proteins. This binding inhibits the RET receptor signalling which in turn inhibits the tumour cell growth and may also prevent resistance to the treatment from developing. 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

Metastatic RET fusion-positive non-small cell lung cancer (NSCLC).[1]

TECHNOLOGY

DESCRIPTION

Selpercatinib (LOXO-292) is a highly selective, ATP-competitive small molecule inhibitor of the rearranged during transfection (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 currently in clinical development for the treatment of patients with advanced RET-altered solid tumours including metastatic RET-fusion positive NSCLC. In the phase I/II clinical trial (NCT03157128) the drug is administered orally and the company have proposed a dose of 160mg twice a day.[1]

INNOVATION AND/OR ADVANTAGES

Selpercatinib is a first-in-class oral RET inhibitor.[4] Until recently, only multikinase inhibitors (MKIs) with nonselective RET inhibitory activity have been available for patients with RET-altered cancers – clinical experience has been disappointing, with only modest activity in RET-fusion positive lung cancers and substantial side effects.[5]

In contrast to MKIs, selpercatinib possesses nanomolar potency against diverse RET alterations (including anticipated acquired resistance mutations), high selectivity for RET, and favourable pharmacokinetic properties, including high bioavailability, predictable exposure, significant central nervous system (CNS) penetration, and a low potential for drug interactions.[5]

Currently, NICE guidelines for NSCLC do not include recommendations specifically for RET-fusion positive cases.[6]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Selpercatinib is not licensed for any indication in the EU/UK.

In September and October 2018, selpercatinib received breakthrough therapy designation from the FDA for the 3 indications explored in the LIBRETTO-001 trial including NSCLC.[7]

Selpercatinib is in phase II development for medullary thyroid cancer, colon cancer and other advanced solid tumours harbouring RET-fusions or activating RET mutations as well as infantile myofibromatosis and fibrosarcoma.[1,8] A phase III trial is planned for RET fusion-positive NSCLC.[9]

PATIENT GROUP

DISEASE BACKGROUND

Lung cancer is classified into two main types: small-cell lung cancer (SCLC) or NSCLC. NSCLC comprises approximately 87% 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).[10] Metastatic cancers refer to cancers that have spread from where they started to other parts of the body, metastatic cancers cannot be cured.[11]

About 2% of patients with NSCLC have fusions between the RET gene and other genes, such as KIF5B-RET and CCDC6-RET.[5] The RET gene codes for a tyrosine kinase receptor on the cell membrane that is involved in cell growth and apoptosis (cell death) pathways. RET gene fusions can lead to the activation of RET receptors, disrupting regular cell signalling and allowing cancer cells to evade cell death and proliferate, causing tumour growth.[12]

Common risk factors for the development of lung cancer include tobacco smoking, exposure to air pollution, radon gas, silica and asbestos, previous lung disease such as COPD, family history of lung cancer, previous radiotherapy treatment and lowered immunity.[13] RET-fusion mutations are most common in patients with the adenocarcinoma subtype of NSCLC, in patients younger than 60 years, females, and former light smokers, or never smokers.[14]

Key symptoms of lung cancer include a cough, breathlessness, coughing up blood, chest pain, weight loss and loss of appetite, fatigue and chest infections.[15]

CLINICAL NEED AND BURDEN OF DISEASE

Lung cancer was the third most common cancer in the UK in 2016, with incidence rates of 77.4 per 100,000 men and 67.2 per 100,000 women.[16] In 2017, there were 38,888 new registrations of malignant neoplasms of bronchus and lung in England (ICD-10 code C34).[17] In the UK 87% of lung cancers are NSCLC and around 2% of those are RET-fusion positive.[10,12] If these figures are applied to 2017 registrations, there were potentially 676 new cases of RET-fusion positive NSCLC.

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.[18]

2013-2017 figures report a 1-year age-standardised survival rate of 40.6% and a 5-year age-standardised survival rate of 16.2% for all lung cancer patients in England. For patients diagnosed with stage IV lung cancer, when the condition is metastatic, the survival rates are 19.3% and 2.9% respectively.[19]

Lung cancer was one of the most common causes of cancer death in 2017, accounting for approximately 21% of all cancer deaths.[20] In 2018 there were 29,604 registrations of death from cancer in England for malignant neoplasms of bronchus and lung (ICD-10 code C34).[21]

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 early stage (I, II and III) NSCLC are surgery, chemotherapy, radiotherapy, chemoradiotherapy and immunotherapy.[22]

At advanced stage (III and 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.[22] There are specific treatment pathways for cancers positive for EGFR-TK, ALK or ROS-1 gene mutations but not for RET-fusions/mutations.[23]

CURRENT TREATMENT OPTIONS

Depending on their PD-L1 tumour expression, first line treatment for NSCLC (without a mutation or fusion protein for a NICE recommended mutation specific treatment):[23]

- Pembrolizumab with pemetrexed and platinum chemotherapy in combinations or pembrolizumab or chemotherapy as monotherapies.

Patients who progress after platinum-based therapy receive:[23]

- Immunotherapy treatment with pembrolizumab, nivolumab or without PD-L1 expression; atezolizumab.
- Chemotherapy with docetaxel and the multikinase inhibitor nintedanib.
- Best supportive care

PLACE OF TECHNOLOGY

If licensed, selpercatinib will offer a treatment option for patients with metastatic RET fusion-positive non-small cell lung cancer (NSCLC), who currently have no highly selective therapies available.[1]

CLINICAL TRIAL INFORMATION

Trial	LIBRETTO-001, NCT03157128, LOXO-RET-17001, EudraCT2017-000800-59; 12 years and older; LOXO-292; Phase I/II.
Sponsor	Loxo Oncology, Inc.
Status	Ongoing
Source of Information	Trial registry[1,24] Press release[25]
Location	EU (including UK), USA, Canada and other countries.
Design	Single group assignment, open label
Participants	N=970; aged 12 and older For phase 1 • Patients with a locally advanced or metastatic solid tumour who: o have progressed on or are intolerant to standard therapy, or o no standard therapy exists, or in the opinion of the Investigator, are not candidates for or would be unlikely to tolerate or derive significant clinical benefit from standard therapy, or o decline standard therapy • Prior MKIs with anti-RET activity are allowed

	• A RET gene alteration is not required initially. Once adequate PK exposure is achieved, evidence of RET gene alteration in tumour and/or blood is required as identified through molecular assays, as performed for clinical evaluation. • Measurable or non-measurable disease as determined by RECIST 1.1 or RANO as appropriate to tumour type. • Eastern Cooperative Oncology Group (ECOG) score of 0, 1, or 2 or Lansky Performance Score (LPS) ≥ 40% (age < 16 years) with no sudden deterioration 2 weeks prior to the first dose of study treatment. • Adequate hematologic, hepatic and renal function. • Life expectancy of at least 3 months. For phase 2 As for phase 1 with the following modifications: • For Cohorts 1 and 3 Subjects must have received prior standard therapy appropriate for their tumour type and stage of disease, or in the opinion of the Investigator, would be unlikely to tolerate or derive clinical benefit from appropriate standard of care therapy. • Cohorts 1-4: enrolment will be restricted to patients with evidence of a RET gene alteration in tumour. However, a positive germline DNA test for a RET gene mutation is acceptable in the absence of tumour tissue testing for patients with MTC. • Cohorts 1-4: at least one measurable lesion as defined by RECIST 1.1 or RANO, as appropriate to tumour type and not previously irradiated. • Cohort 4: radiographic PD within the previous 14 months. • Cohort 5: (up to 150 patients): o Cohorts 1-4 without measurable disease; o MTC not meeting the requirements for Cohorts 3 or 4; (a known RET mutation is not required) o MTC syndrome spectrum cancers (e.g., MTC, pheochromocytoma), cancers with neuroendocrine features/differentiation, or poorly differentiated thyroid cancers with other RET alteration/activation may be allowed with prior Sponsor approval; o cfDNA positive for a RET gene alteration not known to be present in a tumour sample. • Cohort 6: Patients who otherwise are eligible for Cohorts 1-5 who discontinued another RET inhibitor due to intolerance may be eligible with prior Sponsor approval.
Schedule	The trial will be conducted in 2 parts: phase 1 (dose escalation) and phase 2 (dose expansion). In phase 1, subjects receive multiple doses of LOXO-292. In phase 2, subjects receive LOXO-292 to assess the maximum tolerated dose (MTD)/recommended dose. A dose of 160 mg twice a day (BID) has been selected as the recommended phase 2 dose (RP2D).
Follow-up	Treatment every 28 dys for approximately 12 mths and observation for up to 2 yrs.
Primary Outcomes	Phase 1:

	• Maximum tolerated dose (Time frame: the first 28 days of treatment (cycle 1)) • Recommended Phase 2 dose (Time frame: the first 28 days of treatment (cycle 1) and every cycle (28 days) for approximately 12 months (or earlier if the patient discontinues from the study)) Phase 2: • Objective Response Rate (ORR), (Time frame: approximately every 8 weeks for one year, then every 12 weeks, and 7 days after the last dose (for up to 2 years) in patients who have not progressed).
Secondary Outcomes	Phase 1: • Frequency, severity, and relatedness of Treatment emergent adverse events (TEAEs) and serious adverse events (SAEs), changes in haematology and blood chemistry values, assessments of physical examinations, vital signs, and electrocardiograms (ECGs). (Time frame: from the time of informed consent, for approximately 24 months (or earlier if the patient discontinues from the study), and through safety follow-up (28 days after the last dose)) • Plasma concentration of LOXO-292 and pharmacokinetic (PK) parameters, including but not limited to area under the curve from time 0 to 24 hours (AUC0-24), maximum drug concentration (Cmax), time to maximum plasma concentration (Tmax), and degree of accumulation. (Time frame: day 8 of cycle 1 and day 8 after Intra-patient dose escalation (Phase 1 only)) • ORR based on RECIST 1.1 or RANO, as appropriate to tumour type. (Time frame: approximately every 8 weeks for one year, then every 12 weeks, 7 days after the last dose (for up to 2 years) in patients who have not progressed.) Phase 2: • ORR (by Investigator) (Time frame: approximately every 8 weeks for one year, then every 12 weeks, 7 days after the last dose (for up to 2 years) in patients who have not progressed.) • Best change in tumour size from baseline (by IRC and Investigator) (Time frame: approximately every 8 weeks for one year, then every 12 weeks, 7 days after the last dose (for up to 2 years) in patients who have not progressed.) • Duration of response (DOR) (by IRC and Investigator) (Time frame: approximately every 8 weeks for one year, then every 12 weeks, 7 days after the last dose (for up to 2 years) in patients who have not progressed.) • CNS ORR (by IRC) (Time frame: approximately every 8 weeks for one year, then every 12 weeks, 7 days after the last dose (for up to 2 years) in patients who have not progressed.) • CNS DOR (by IRC) (Time frame: approximately every 8 weeks for one year, then every 12 weeks, 7 days after the last dose (for up to 2 years) in patients who have not progressed.) • Time to any and best response (by IRC and Investigator) (Time frame: every 8 weeks for one year, then every 12 weeks, 7 days after the last dose (for up to 2 years) in patients who have not progressed.) • CBR (by IRC and Investigator) (Time frame: approximately every 8 weeks for one year, then every 12 weeks, 7 days after the last dose (for up to 2 years) in patients who have not progressed.) • Progression-free survival (PFS) (by IRC and Investigator) (Time frame: approximately every 8 weeks for one year, then every 12

	weeks, 7 days after the last dose (for up to 2 years) in patients who have not progressed.) • OS (Time frame: approximately every 8 weeks for one year, then every 12 weeks, 7 days after the last dose (for up to 2 years) in patients who have not progressed.) • Frequency, severity and relatedness of TEAEs and SAEs, changes in haematology and blood chemistry values, assessments of physical examinations, vital signs and ECGs. (Time frame: from the time of informed consent, for approximately 24 months (or earlier if the patient discontinues from the study), and through safety follow-up (28 days after the last dose)) • Plasma concentrations of LOXO-292 and PK parameters, including but not limited to AUC0-24, Cmax, and Tmax. (Time frame: day 8 of cycle 1 and day 8 after Intra-patient dose escalation).
Key Results	Interim results: • 68% ORR in the registration dataset (n=105) of RET-fusion positive NSCLC patients who had previously received chemotherapy • 85% ORR in treatment-naïve RET-fusion positive NSCLC patients • as of the data cut-off date of June 17, 2019, median DOR was 20.3 months (95% CI: 13.8-24.0) and median PFS was 18.4 months (95% CI: 12.9-24.9) • selpercatinib was well-tolerated, with only 9 patients (1.7%) discontinuing therapy due to treatment-related toxicity.
Adverse effects (AEs)	Interim results: • Most commonly observed adverse events, regardless of attribution, were dry mouth, diarrhoea, hypertension, increased liver enzymes, fatigue, constipation, and headache.
Expected reporting date	Primary completion date is March 2022.

ESTIMATED COST

The cost of selpercatinib is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Avelumab for treating non-small-cell lung cancer after platinum-based chemotherapy (TA10341). Expected date of issue to be confirmed.

- NICE Technology appraisal. Pembrolizumab with pemetrexed and platinum chemotherapy for untreated, metastatic, non-squamous non-small-cell lung cancer (TA557). January 2019.
- NICE technology appraisal. Durvalumab for treating locally advanced unresectable non-small-cell lung cancer after platinum-based chemoradiation (TA578). May 2019.
- NICE Technology appraisal. Pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer (TA531). July 2018.
- NICE technology appraisal. Atezolizumab for treating locally advanced or metastatic non-small-cell lung cancer after chemotherapy (TA520). May 2018.
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NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

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- NHS England. Clinical Commissioning Policy: Stereotactic Ablative Body Radiotherapy for Non-Small-Cell Lung Cancer (Adult). B01/P/a. April 2013.

OTHER GUIDANCE

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- European Society for Medical Oncology. Early and locally advanced non-small-cell-lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2017.[27]
- National Comprehensive Cancer Network (NCCN). Non–Small Cell Lung Cancer, Version 5.2017, NCCN Clinical Practice Guidelines in Oncology. 2017.[28]
- Scottish Intercollegiate Guidelines Network (SIGN) Management of lung cancer: A national clinical guideline. 2014.[29]

ADDITIONAL INFORMATION

A diagnostic test will be required to identify patients with RET-fusion positive cancer. Ideally Next Generation Sequenceing, however RET driven cancers can also be detected by other single gene tests e.g. Fluorescence in situ hybridization (FISH).[a]

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