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Health Technology Briefing
February 2023

Selpercatinib for treating advanced solid tumours with RET gene fusion in people aged 12 years and older

Company/Developer	Eli Lilly and Company Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 36044	NICE TSID: 11850	UKPS ID: 666914

Licensing and Market Availability Plans

Currently in phase I/II clinical trials.

Summary

Selpercatinib is in clinical development for the treatment of advanced solid tumours with a mutation in the gene known as RET, which is involved in cell signalling or cell communication. Solid tumours are abnormal masses of tissue that usually do not contain cysts or liquid areas. A cancer cell's RET gene can move or fuse to another gene, which is referred to as RET gene fusions. When this occurs, cancer cells can spread and grow rapidly. RET fusions in people with solid tumours are associated with more aggressive forms of diseases and poorer outcomes for patients. Inhibiting RET in cancer tumours has shown to slow the growth of cancer cells and improve patient outcomes.

Selpercatinib is a first-in-class orally administered drug designed to be highly selective and specifically target RET while minimising its activity against other kinases (proteins). Selpercatinib blocks the activity of abnormal proteins produced by changes in the RET gene, and so reduces the growth and spread of cancer cells. If licensed, selpercatinib would offer a novel treatment option for patients 12 years and older with RET gene fusion advanced solid tumours.

This briefing reflects the evidence available at the time of writing and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information. A version of the briefing was sent to the company for a factual accuracy check. The company was available to comment.

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Proposed Indication

Adults and adolescents 12 years and older with advanced solid tumours including RET fusion-positive solid tumours, medullary thyroid cancer, and other tumours with RET activation.[1]

Technology

Description

Selpercatinib (LOXO-292, LY3527723) is a novel, ATP-competitive, highly selective small-molecule inhibitor of the RET receptor tyrosine kinase.[2,3] RET is a type of protein called a kinase, which is involved in various cell processes. RET gene fusions and mutations result in the production of abnormal RET proteins, which spur the growth of cancer cells. Selpercatinib was designed to selectively target RET while minimising its activity against other kinases.[4] It blocks the activity of these abnormal proteins and reduces the growth and spread of the cancer cells.[5]

Selpercatinib is currently in clinical development for the treatment of advanced RET fusion-positive solid tumours. In the phase I/II clinical trial (LIBRETTO-001; NCT03157128), following the phase I dose escalation portion of the trial, patients received selpercatinib at the recommended dose of 160 mg orally twice daily, each cycle was 28 days.[1,6]

Key Innovation

Selpercatinib is the first medicinal product to selectively target RET, which is important for the treatment of RET-altered cancers. Although other drugs have some activity against RET-altered cancers, their usefulness is limited by their side effects as they block multiple kinases, hence the likelihood of side effects is higher than it is with the selpercatinib. In a previous study, selpercatinib shrank tumours in more than half of all patients with advanced RET-altered lung and thyroid cancers, in many cases for 6 months or longer.[4] If licensed, selpercatinib would offer an additional treatment option for patients with advanced solid tumours who also have RET alterations and are intolerant to standard therapy.

Regulatory & Development Status

Selpercatinib has Marketing Authorisation in the EU/UK for the following indications:[3]

- treatment of adults with advanced RET fusion-positive non-small cell lung cancer (NSCLC) not previously treated with a RET inhibitor
- treatment of adults with advanced RET fusion-positive thyroid cancer who require systemic therapy following prior treatment with sorafenib and/or lenvatinib
- treatment of 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 in phase II and III clinical development for the following indications: [7]

- Non-small-cell lung cancer
- Thyroid cancer
- Colon cancer

Selpercatinib has the following regulatory designations:[8,9]

- an orphan drug in the USA in 2019 for treatment of RET fusion-positive or RET mutant thyroid cancers including poorly differentiated thyroid cancer, undifferentiated or anaplastic thyroid cancer, medullary thyroid cancer, and locally advanced or metastatic follicular or papillary thyroid cancer

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- a breakthrough therapy by the US FDA for adult patients with locally advanced or metastatic NSCLC with a RET gene fusion in May 2020

Patient Group

Disease Area and Clinical Need

Solid tumours are defined as abnormal masses of tissue that usually do not contain cysts or liquid areas, and may be benign or malignant. Examples of solid tumours are sarcomas, carcinomas, and lymphomas.[10] Solid tumours represent approximately 90% of adult human cancers.[11] Advanced cancer is cancer that is unlikely to be cured or controlled with treatment.[12] Cancer that spreads from where it started to a distant part of the body is called metastatic cancer.[13] Furthermore, unresectable refers to cancer that cannot be removed with surgery.[14] RET fusions occur predominantly in 2% of lung cancers and 10–20% of thyroid cancers and in low frequency in an increasing number of diverse cancers.[15] Symptoms of malignant solid tumours often include swelling or a mass that can be palpated. Other less specific signs can be weight loss, fever, or vague feelings of ill health.[16]

In England (2021-22), there were 10,125 finished consultant episodes (FCE) and 6,754 admissions for Malignant neoplasms (ICD-10 code C80.0). This resulted in 32,910 FCE bed days and 4,209 day cases.[17] RET is altered in 2.61% of all cancers with lung adenocarcinoma, colon adenocarcinoma, thyroid gland medullary carcinoma, cutaneous melanoma, and melanoma having the greatest prevalence of alterations.[18]

Recommended Treatment Options

NICE recommends the following treatment options for advanced solid tumours with RET gene fusion:[19-21]

- Pralsetinib for RET fusion-positive advanced non-small-cell lung cancer
- Selpercatinib for previously treated RET fusion-positive advanced non-small-cell lung cancer
- Selpercatinib for advanced thyroid cancer with RET alterations

Clinical Trial Information

Trial	**LIBRETTO-001**, NCT03157128, 2017-000800-59; A Phase 1/2 Study of Oral Selpercatinib (LOXO-292) in Patients With Advanced Solid Tumours, Including RET Fusion-Positive Solid Tumours, Medullary Thyroid Cancer, and Other Tumours With RET Activation **Phase I/II:** Recruiting **Location(s):** 5 EU countries, UK, USA, Canada and other countries **Primary Completion Date:** Mar 2024
Trial Design	Single group assignment, open label
Population	N=875 (estimated); aged 12 years and older; Participants with a locally advanced or metastatic solid tumour that has progressed on or is intolerant to standard therapy
Intervention(s)	Selpercatinib (oral) at the recommended dose of 160 mg twice daily, following the phase I dose escalation portion of the trial.[6]
Comparator(s)	No comparator
Outcome(s)	Primary outcome measures: • Phase 1: MTD [Time Frame: The first 28 days of treatment (Cycle 1)]

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	• Phase 1: RP2D [Time Frame: The first 28 days of treatment (Cycle 1) and every cycle (28 days) for approximately 12 months (or earlier if the participant discontinues from the study)] • Phase 2: Objective Response Rate [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 participants who have not progressed]
Results (efficacy)	The objective response rate per independent review committee and investigator assessment was 43·9% (95% CI 28·5–60·3; 18 of 41 patients). As per both the independent review committee and investigator, a complete response was attained in two (5%) of 41 patients. The median duration of response was 24·5 months (95% CI 9·2–not evaluable [NE]) as per the independent review committee and 18·4 months (9·2–NE) as per the investigator. The median progression-free survival was 13·2 months (95% CI 7·4–26·2) as per the independent review committee and 11·1 months (5·6–19·1) as per investigator assessment. The estimated proportion of patients who were alive and progression-free at 1 year was 53·1% (95% CI 34·1–68·8) by independent review committee assessment and 43·1% (25·5–59·6) by investigator assessment. The median overall survival was 18·0 months (95% CI 10·7–NE); the estimated proportion of patients alive at 18 months was 51·7% (95% CI 32·9–67·6).[22]
Results (safety)	At the time of data analysis, 18 (44%) of 41 patients remained on selpercatinib treatment. The median duration of treatment was 11·0 months (95% CI 3·7–NE). Overall, 11 (27%) of 41 patients received selpercatinib treatment beyond progression on the basis of continued clinical benefit. In the RET fusion-positive tumour-agnostic safety population (n=45), the safety profile was consistent with that of previous reports, with no new safety signals identified compared to the full safety population. Dose reductions occurred in 14 (31%) of 45 patients. Treatment-related adverse events leading to permanent selpercatinib discontinuation were observed in one (2%) patient (increased alanine aminotransferase, increased aspartate aminotransferase, increased blood bilirubin, and drug-induced liver injury).[22]

Estimated Cost

Selpercatinib is already marketed in the UK:[23]

- a pack of 56 x 40mg capsules costs £2,184
- a pack of 168 x 40mg capsules costs £6,552
- a pack of 56 x 80mg capsules costs £4,368
- a pack of 112 x 80mg capsules cost £8,736

Relevant Guidance

NICE Guidance

- NICE technology appraisal. Pralsetinib for treating RET fusion-positive advanced non-small-cell lung cancer (TA812). August 2022.
- NICE technology appraisal. Selpercatinib for previously treated RET fusion-positive advanced non-small-cell lung cancer (TA760). January 2022.

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- NICE technology appraisal. Selpercatinib for treating advanced thyroid cancer with RET alterations (TA742). November 2021.

NHS England (Policy/Commissioning) Guidance

- NHS England. 2013/14 Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.
- NHS England. 2013/14 Standard Contract for Cancer: Chemotherapy (Children, Teenagers and Young Adults). B15/S/b.
- NHS England. 2013/14 Standard Contract for Cancer: Teenagers & Young Adults. B17/S/a.
- NHS England. Standard Contract for Paediatric Medicine: Palliative Care. E03/S/h.

Other Guidance

- European Society for Medical Oncology. ESMO Clinical Practice Guideline update on the use of systemic therapy in advanced thyroid cancer. 2022.[24]

Additional Information

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NB: This briefing presents independent research funded by the National Institute for Health and Care Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.

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