

## Health Technology Briefing September 2022

### Selpercatinib for previously untreated advanced RET- fusion positive thyroid cancer

Company/Developer

Eli Lilly and Company Ltd

New Active Substance

Significant Licence Extension (SLE)

NIHRIO ID: 35277

NICE ID: 11796

UKPS ID: 666913

#### Licensing and Market Availability Plans

Currently in phase I/II clinical trials.

#### Summary

Selpercatinib is in clinical development for untreated advanced RET-fusion positive thyroid cancer in adults. Thyroid cancer is a rare form of cancer that originates in the thyroid gland located in the front of the neck. RET is a type of protein called a kinase, which is involved in various cell processes. RET-fusion positive cancer is a type of cancer that is caused by the abnormal re-arrangement of the RET gene, which leads to an overactive process that causes the cancer cells to grow uncontrollably. Furthermore, thyroid cancer cases that are RET-fusion positive often result in harsher symptoms and poorer patient outcomes.

Selpercatinib is an orally administered drug designed to selectively 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 prevents the growth and spread of cancer cells. If licensed, selpercatinib will offer an additional treatment option for adult patients with advanced RET-fusion positive thyroid cancer.

#### Proposed Indication

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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Treatment of adults with untreated advanced RET-fusion positive thyroid cancer who require systemic therapy.<sup>1</sup>

## Technology

### Description

Selpercatinib (LOXO-292, LY3527723) is a novel, ATP-competitive, highly selective small-molecule inhibitor of the rearranged during transfection (RET) receptor tyrosine kinase.<sup>2,3</sup> 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 minimizing its activity against other kinases.<sup>4</sup> It blocks the activity of these abnormal proteins and prevents the growth and spread of the cancer cells.<sup>5</sup>

Selpercatinib is currently in clinical development for the treatment of adults with advanced RET-fusion positive thyroid cancer who require systemic therapy. 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.<sup>1,6</sup>

### Key Innovation

Selpercatinib is a first-in-class CNS (central nervous system) active and potent RET inhibitor.<sup>7</sup> RET fusion cancers are primarily dependent on the single activated kinase (RET) for their proliferation and survival. This dependency, often referred to as "oncogene addiction," renders such tumours highly susceptible to small molecule inhibitors targeting RET.<sup>8</sup>

Multikinase inhibitors with RET inhibitor activity have been explored in the clinic for tumours with activating RET gene alterations with modest clinical efficacy. As a result of the nonselective nature of these multikinase inhibitors, patients had off-target adverse effects, such as hypertension, rash, and diarrhoea. This resulted in a narrow therapeutic index of these drugs, limiting ability to dose for clinically effective RET inhibition. Therefore, there is need for highly potent selective RET inhibitors such as selpercatinib that have improved efficacy and a more favourable toxicity profile that can effectively alter the landscape of RET-dependent cancers.<sup>9</sup>

If licensed, selpercatinib would offer an additional treatment option for adults with advanced RET-fusion positive thyroid cancer.

### Regulatory & Development Status

Selpercatinib has Marketing Authorisation in the EU/UK for the following indications:<sup>3</sup>

- treatment of adults with advanced RET fusion-positive non-small cell lung cancer (NSCLC) who require systemic therapy following prior treatment with immunotherapy and/or platinum-based chemotherapy
- 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 Non-Small-Cell Lung Cancer.<sup>10</sup>

Selpercatinib has an orphan drug designation in the USA in 2019 for the 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.<sup>11</sup>

## Patient Group

### Disease Area and Clinical Need

Thyroid cancer is a rare type of cancer that affects the thyroid gland, a small gland at the base of the neck that produces hormones.<sup>12</sup> Rearranged during transfection (RET) is an oncogenic driver activated by either RET fusions or mutations.<sup>13</sup> RET alterations are rare in cancer overall but more common in lung and thyroid cancers. About 10%–20% of people with papillary thyroid cancer, the most common type of thyroid cancer, have tumours in which a piece of the RET gene is fused to part of another gene, known as RET fusion-positive cancer.<sup>4</sup> RET fusions in people with thyroid cancers are associated with more aggressive disease and poorer outcomes for patients.<sup>14</sup> Thyroid cancer is most common in people in their 30s and those over the age of 60. Women are two to three times more likely to develop it than men. Symptoms of thyroid cancer include: a painless lump or swelling in the front of the neck, unexplained persistent hoarseness, a sore throat or difficulty swallowing.<sup>12</sup>

Thyroid cancer is the 20th most common cancer in the UK, accounting for 1% of all new cancer cases (2016-2018). 72% of thyroid cancer cases in the UK are in females, and 28% are in males.<sup>15</sup> In England (2020-21), there were 6,040 finished consultant episodes (FCEs) and 5,802 admissions regarding malignant neoplasm of the thyroid gland (ICD-10 code C73), which resulted in 1,280 day cases and 11,144 FCE bed days.<sup>16</sup> For patients diagnosed between 2013 and 2017, followed up to 2018, the 1-year and 5-year age-standardised survival rates for stage IV (advanced) thyroid cancer were 77.1% and 64% respectively.<sup>17</sup>

### Recommended Treatment Options

People with advanced RET fusion-positive thyroid cancer are usually first offered a partial or full thyroidectomy. This is followed by radioactive iodine and then lenvatinib or sorafenib. People with advanced RET-mutant medullary thyroid cancer are usually offered a partial or full thyroidectomy, followed by cabozantinib.<sup>14</sup>

## 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

	<p><b>Phase I/II:</b> Recruiting  <b>Location(s):</b> 5 EU countries, UK, USA, Canada and other countries  <b>Primary Completion Date:</b> Mar 2024</p>
<b>Trial Design</b>	Single group assignment, open label
<b>Population</b>	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
<b>Intervention(s)</b>	Selpercatinib (oral) at the recommended dose of 160 mg twice daily, following the phase I dose escalation portion of the trial. <sup>6</sup>
<b>Comparator(s)</b>	No comparator
<b>Outcome(s)</b>	<p>Primary outcome measures:</p> <ul style="list-style-type: none"> <li>Phase 1: MTD [Time Frame: The first 28 days of treatment (Cycle 1)]</li> <li>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)]</li> <li>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]</li> </ul>
<b>Results (efficacy)</b>	-
<b>Results (safety)</b>	-

### Estimated Cost

Selpercatinib is already marketed in the UK;<sup>18</sup>

- 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. Vandetanib for treating medullary thyroid cancer (TA550). December 2018.
- NICE technology appraisal. Cabozantinib for treating medullary thyroid cancer (TA516). March 2018.
- NICE clinical guideline in development. Thyroid cancer: assessment and management (GID-NG10150). Expected December 2022.

#### NHS England (Policy/Commissioning) Guidance

- NHS England. 2013/14 NHS Standard Contract for Cancer: Head and Neck (Adult). B16/S/a.

- NHS England. 2013/14 NHS Standard Contract for Specialised Endocrinology services (adult). A03/S/a.

#### Other Guidance

- European Society for Medical Oncology. Clinical practice guidelines – Thyroid cancer. 2019.<sup>19</sup>
- Northern England Strategic Clinical Networks. Head and Neck Cancer Clinical Guidelines. 2017.<sup>20</sup>
- American Thyroid Association Management. Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer. 2015.<sup>21</sup>
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- London Cancer Alliance. Head and Neck/Thyroid Cancer Clinical Guidelines. 2014.<sup>23</sup>

#### Additional Information

#### References

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- [details/lilly-receives-fda-priority-review-selpercatinib-new-drug](#) [Accessed 8th September 2022].
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