# Selpercatinib (Retsevmo®) as monotherapy is indicated for the treatment of adults and adolescents with advanced RET fusion-positive thyroid cancer

## General information

### Drug description [1]

Selpercatinib (Retsevmo®, LOXO-292) is an inhibitor of the rearranged during transfection (RET) receptor tyrosine kinase.

### Indication [2]

Selpercatinib (Retsevmo®) as monotherapy is indicated for the treatment of adults and adolescents 12 years and older with advanced RET fusion-positive thyroid cancer who are radioactive iodine-refractory (if radioactive iodine is appropriate).

## Incidence

In Austria, in 2022, the age-standardised incidence rate[1] of thyroid cancer was 9.7/100,000 in men and 6.2/100,000 in women.
In total, 906 persons were newly diagnosed with thyroid cancer [3].
RET fusions are found in ~6–10% of papillary thyroid cancer (PTC), 6% of poorly differentiated thyroid cancer and are less frequently in anaplastic thyroid cancer (ATC). The prevalence of RET fusions is higher (approximately 60–80%) in radiation-induced thyroid cancer as evidenced after the Chernobyl nuclear accident and the atomic bomb in Japan. RET fusions are seen more often in children and young adults diagnosed with thyroid cancers [4].

## Current treatment[2]

**For the management of advanced/metastatic disease, the ESMO recommends the following [5]:**

- **Differentiated thyroid cancer (DTC), including poorly differentiated cancer**
  - Radioactive iodine therapy
    - Patients with distant metastases should receive 100–200 mCi (3.7–7.4 GBq) of 131I after TSH stimulation.
    - Non-radioactive iodine-avid lesions and those that lose their ability to concentrate radioactive iodine or progress despite radioactive iodine avidity should be considered radioactive iodine-refractory.
    - Between treatments, suppressive doses of levothyroxine are given to maintain serum TSH levels <0.1 l IU/ml (unless there are specific contraindications).
  - Locoregional therapy
    - Single lesions that are symptomatic or progressive may be eligible for locoregional treatments (e.g. palliative surgery, EBRT, percutaneous therapies)
    - Bone resorption inhibitors (bisphosphonates and denosumab) can be used alone or combined with locoregional treatments in the management of thyroid cancer-related bone metastases.
    - There is limited evidence that conservative techniques (RFA, cryotherapy) are effective for treating thyroid cancer-related bone lesions.
    - Metastasectomy is not the standard approach for lung metastases, but it may be considered for oligometastasis in patients with good PS.
    - RFA is a possibility for solitary lung lesions or those causing a specific symptom due to their volume and location.
    - Invasion of the upper aerodigestive tract should always be excluded in thyroid cancer patients with locoregional disease.
  - Systemic therapy and personalised medicine
    - TSH suppression (serum level <0.1 l IU/mL) is recommended for all thyroid cancer patients with persistent structural disease in the absence of specific contraindications.
    - Decisions on whether or not to use MKIs must always be based on patient preference after a careful discussion with the managing physician of the expected benefits and risks associated with specific drugs.
    - Lenvatinib and sorafenib should be considered the standard first-line systemic therapy for radioactive iodine-refractory DTC.
- **ATC**
  - Systemic therapy and personalised medicine

[1] European Standard Population 2013.
[2] Currently, there is no Onkopedia Guideline available for the treatment of thyroid cancer.

- Clinical trial enrolment should be encouraged for patients with good clinical PS.
- Patients with BRAF V600E-positive malignancies should be treated with the BRAF inhibitor dabrafenib (150 mg twice daily) plus the MEK inhibitor trametinib (2 mg once daily) if they are available.

❖ **Medullary thyroid cancer (MTC)**

- Systemic therapy and personalised medicine
  - Cabozantinib and vandetanib are the first-line systemic therapy for patients with progressive, metastatic MTC.
  - In patients with RETM918T or RAS-mutant MTCs, cabozantinib offers significant PFS and OS advantages over wild-type MTCs.
  - There is little evidence to support the use of either chemotherapy or radionuclide therapy in patients with MTC, although either might be considered when MKIs are contraindicated.

## Regulatory status

| EMA [1, 2] | FDA |
|---|---|
| **Approval status for this indication**: On 25 January 2024, the CHMP adopted a positive opinion recommending a change to the terms of the marketing authorisation for **Retsevmo®**.<br><br>The CHMP adopted a new indication:<br><br>❖ Retsevmo® as monotherapy is indicated for the treatment of adults and adolescents 12 years and older with advanced RET fusion-positive thyroid cancer who are radioactive iodine-refractory (if radioactive iodine is appropriate).<br><br>**Other indications**: Retsevmo® as monotherapy is indicated<br>❖ for the treatment of adults with advanced RET fusion-positive non-small cell lung cancer (NSCLC) not previously treated with a RET inhibitor.<br>❖ for the treatment of adults and adolescents 12 years and older with advanced RET-mutant medullary thyroid cancer (MTC).<br>❖ for the treatment of adults with advanced RET fusion-positive solid tumours, when treatment options not targeting RET provide limited clinical benefit or have been exhausted.<br><br>✓ **Medicine under additional monitoring**<br>✓ **Medicine received a conditional marketing authorisation**[3] | **Approval status for this indication**: On 8 May 2020, the FDA granted accelerated approval to selpercatinib (**Retevmo®**) for the treatment of adult and paediatric patients ≥12 years of age with advanced or metastatic RET fusion-positive thyroid cancer who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate) [6].<br><br>On 12 June 2024, the FDA granted traditional approval to selpercatinib (Retevmo®) for adult and paediatric patients 2 years of age and older with advanced or metastatic RET fusion-positive thyroid cancer who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate) [7].<br><br>**Other indications**: Retevmo® is indicated for the treatment of [8]:<br>❖ Adult patients with locally advanced or metastatic NSCLC with a RET gene fusion, as detected by an FDA-approved test.<br>❖ Adult and paediatric patients 2 years of age and older with advanced or metastatic MTC with a RET mutation, as detected by an FDA-approved test, who require systemic therapy (this indication is approved under accelerated approval).<br>❖ Adult and paediatric patients 2 years of age and older with locally advanced or metastatic solid tumours with a RET gene fusion that have progressed on or following prior systemic treatment or who have no satisfactory alternative treatment options (this indication is approved under accelerated approval) [9]. |

## Manufacturer

Retsevmo® is manufactured by Eli Lilly.

## Costs [10]

56 Retsevmo® hard capsules 80 mg = **€ 4,029.00** (ex-factory price)

[3] The approval of a medicine that address unmet medical needs of patients on the basis of less comprehensive data than normally required. The available data must indicate that the medicine's benefits outweigh its risks and the applicant should be in a position to provide the comprehensive clinical data in the future.

## Posology [1]

- **RET testing**
  - 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 Retsevmo®.

## Warnings and precautions [1]

- **Interstitial Lung Disease (ILD)/Pneumonitis**
  - Severe, life-threatening, or fatal cases of ILD/pneumonitis have been reported in patients treated with selpercatinib. Patients should be monitored for pulmonary symptoms indicative of ILD/pneumonitis. Selpercatinib should be withheld, and patients should be promptly investigated for ILD if they present with acute or worsening of respiratory symptoms which may be indicative of ILD (e.g., dyspnoea, cough, and fever), and treated as medically appropriate. Based on the severity of ILD/pneumonitis, the dose of selpercatinib should be interrupted, reduced, or permanently discontinued.
- **Increased alanine aminotransferase (ALT)/ aspartate aminotransferase (AST)**
  - Grade ≥3 increased ALT and Grade ≥3 increased AST were reported in patients receiving selpercatinib. ALT and AST should be monitored prior to the start of selpercatinib therapy, every 2 weeks during the first 3 months of treatment, monthly for the next 3 months of treatment, and otherwise as clinically indicated. Based on the level of ALT or AST elevations, selpercatinib may require dose modification.
- **Hypertension**
  - Hypertension was reported in patients receiving selpercatinib. Patient blood pressure should be controlled before starting selpercatinib treatment, monitored during selpercatinib treatment and treated as needed with standard anti-hypertensive therapy. Based on the level of increased blood pressure, selpercatinib may require dose modification.
  - Selpercatinib should be discontinued permanently if medically significant hypertension cannot be controlled with antihypertensive therapy.
- **QT interval prolongation**
  - QT interval prolongation was reported in patients receiving selpercatinib. Selpercatinib should be used with caution in patients with such conditions as congenital long QT syndrome or acquired long QT syndrome or other clinical conditions that predispose to arrhythmias. Patients should have a QTcF interval of ≤470 ms and serum electrolytes within normal range before starting selpercatinib treatment. Electrocardiograms and serum electrolytes should be monitored in all patients after 1 week of selpercatinib treatment, at least monthly for the first 6 months and otherwise, as clinically indicated, adjusting frequency based upon risk factors including diarrhoea, vomiting, and/or nausea. Hypokalaemia, hypomagnesaemia and hypocalcaemia should be corrected prior to initiating selpercatinib and during treatment. Monitor the QT interval with ECGs more frequently in patients who require treatment with concomitant medications known to prolong the QT interval. Selpercatinib may require dose interruption or modification.
- **Hypothyroidism**
  - Hypothyroidism has been reported in patients receiving selpercatinib. Baseline laboratory measurement of thyroid function is recommended in all patients. Patients with pre-existing hypothyroidism should be treated as per standard medical practice prior to the start of selpercatinib treatment. All patients should be observed closely for signs and symptoms of thyroid dysfunction during selpercatinib treatment. Thyroid function should be monitored periodically throughout treatment with selpercatinib. Patients who develop thyroid dysfunction should be treated as per standard medical practice, however patients could have an insufficient response to substitution with levothyroxine (T4) as selpercatinib may inhibit the conversion of levothyroxine to liothyronine (T3) and supplementation with liothyronine may be needed.
- **Strong CYP3A4 inducers**
  - Concomitant use of strong CYP3A4 inducers should be avoided due to the risk of decreased efficacy of selpercatinib.
- **Women of childbearing potential/Contraception in females and males**
  - Women of childbearing potential must use highly effective contraception during treatment and for at least one week after the last dose of selpercatinib. Men with female partners of childbearing potential should use effective contraception during treatment and for at least one week after the last dose of selpercatinib.
- **Fertility**
  - Based on nonclinical safety findings, male and female fertility may be compromised by treatment with Retsevmo®. Both men and women should seek advice on fertility preservation before treatment.
- **Hypersensitivity**

- Hypersensitivity was reported in patients receiving selpercatinib with a majority of events observed in patients with NSCLC previously treated with anti-PD-1/PD-L1 immunotherapy. Signs and symptoms of hypersensitivity included fever, rash and arthralgias or myalgias with concurrent decreased platelets or elevated aminotransferases. Suspend selpercatinib if hypersensitivity occurs and begin steroid treatment. Based on the grade of hypersensitivity reactions, selpercatinib may require dose modification. Steroids should be continued until patient reaches target dose and then tapered. Permanently discontinue selpercatinib for recurrent hypersensitivity.

❖ **Haemorrhages**

- Serious including fatal haemorrhagic events were reported in patients receiving selpercatinib. Permanently discontinue selpercatinib in patients with severe or life-threatening haemorrhage.

❖ **Tumour lysis syndrome (TLS)**

- Cases of TLS have been observed in patients treated with selpercatinib. Risk factors for TLS include high tumour burden, pre-existing chronic renal insufficiency, oliguria, dehydration, hypotension, and acidic urine. These patients should be monitored closely and treated as clinically indicated, inappropriate prophylaxis including hydration should be considered.

**Study characteristics [11-14]**

| Trial name | *n* | Intervention (I) | Comparator (C) | PE | Median follow-up | Characteristics | Biomarker | Funding | Publication(s) |
|---|---|---|---|---|---|---|---|---|---|
| LIBRETTO-001 NCT03157128 | 162[4] | selpercatinib 160 mg twice daily[5] | - | ORR (CR or PR) by IRC | 7.8 months | **ongoing**[6], single-arm, multicentre, multi-cohort, open-label, phase 1–2 trial | RET | Loxo Oncology and others | LIBRETTO-001 [14] |

| Inclusion criteria[7,8] | Exclusion criteria | Patient characteristics at baseline in patients with previously treated RET fusion–positive thyroid cancer (n=19) |
|---|---|---|
| ❖ Adult patients with a locally advanced or metastatic solid tumour with evidence of a RET gene alteration in tumour and/or blood (e.g., gene rearrangement and/or mutation, excluding synonymous, frameshift and nonsense mutations), as determined with prior molecular assays as performed in a CLIA-certified or equivalent laboratory.<br>❖ For MTC: have PD within the previous 14 months as defined by RECIST 1.1.<br>❖ Any number of prior TKIs with anti-RET activity are allowed.<br>❖ At least one measurable lesion as defined by RECIST 1.1 or RANO, as appropriate to tumour type, not previously irradiated and not chosen for biopsy during the screening period. Patients | ❖ For NSCLC patients, a targetable mutation in EGFR, or targetable rearrangement involving ALK or ROS1.<br>❖ Investigational agent or anticancer therapy within 2 weeks (14 days) prior to planned start of LOXO-292. In addition, no concurrent investigational therapy is permitted.<br>❖ Major surgery (excluding placement of vascular access) within 4 weeks prior to planned start of LOXO-292.<br>❖ Radiotherapy with a limited field of radiation for palliation within 1 week of the first dose of study treatment, except for patients receiving radiation to more than 30% of the bone marrow or with a wide | ❖ Median age (range): 54 (25–88) years<br>❖ Male sex: 47%<br>❖ Race:<br>• White: 74%<br>• Asian: 11%<br>• Black: 5%<br>• Other: 11%<br>❖ ECOG PS score:<br>• 0: 26%<br>• 1: 63%<br>• 2: 11%<br>❖ Histologic type of thyroid cancer |

[4] 55 patients with RET-mutant medullary thyroid cancer previously treated with vandetanib, cabozantinib, or both; 88 patients with RET-mutant medullary thyroid cancer not previously treated with vandetanib or cabozantinib; and **19 patients with RET fusion–positive previously treated thyroid cancer**.

[5] 82% of the cohort previously treated with vandetanib, cabozantinib, or both received selpercatinib at the recommended dose of 160 mg twice daily. Almost all the patients with RET-mutant medullary thyroid cancer not previously treated with vandetanib or cabozantinib and those with RET fusion–positive thyroid cancer received selpercatinib at a dose of 160 mg twice daily (98% and 95%, respectively).

[6] The LIBRETOO-001 trial is currently ongoing; estimated study completion date is 02/2026.

[7] Since 95% of the patients received selpercatinib at the recommended dose of 160 mg twice daily, inclusion criteria for the dose expansion cohort are listed herein. For inclusion criteria for the dose escalation group, please see trial protocol.

[8] For detailed in- and exclusion criteria, please see trial protocol.

without RECIST 1.1 or RANO measurable disease will be eligible for enrolment to Cohort 5.

- ❖ At least 18 years of age.
- ❖ ECOG PS score of 0, 1, or 2 with no sudden deterioration 2 weeks prior to the first dose of study treatment.
- ❖ Life expectancy of at least 3 months.
- ❖ Archived tumour tissue sample available or lesion that can be safely biopsied if the archived sample is not available.
- ❖ Adequate hematologic status, defined as:
  - ANC ≥1.5x$10^9$/L not requiring growth factor support for at least 7 days prior to screening, and
  - Platelet count ≥100x$10^9$/L not requiring transfusion support for at least 7 days prior to screening, and
  - Hb ≥10 mg/dL not requiring transfusion support for at least 7 days prior to Screening.
- ❖ Adequate hepatic function, defined as:
  - ALT and AST ≤2.5x ULN or ≤5x ULN with documented liver involvement (such as liver metastasis or a primary biliary tumour) and
  - Total bilirubin ≤1.5x ULN (patients with Gilbert's Disease may be enrolled with Sponsor approval).
- ❖ Serum calcium level between 8.0 mg/dL and the institutional ULN.
- ❖ Serum TSH level ≤10 U/mL.
- ❖ Adequate renal function, with estimated glomerular filtration rate ≥30 mL/minute.
- ❖ Ability to swallow capsules and comply with outpatient treatment, laboratory monitoring, and required clinic visits for the duration of study participation.
- ❖ Willingness of men and women of reproductive potential to observe conventional and effective birth control for the duration of treatment and for 3 months following the last dose of study treatment.

field of radiation, which must be completed at least 4 weeks prior to the first dose of study treatment.

- ❖ Any unresolved toxicities from prior therapy greater than CTCAE Grade 1 at the time of starting study treatment except for alopecia and Grade 2, prior platinum-therapy related neuropathy.
- ❖ Symptomatic primary CNS tumour or metastases; symptomatic leptomeningeal carcinomatosis; untreated spinal cord compression.
- ❖ For MTC patients, clinically significant involvement in the trachea, oesophagus or complete encasement of great vessels (e.g., aorta or pulmonary artery) that in the opinion of the Investigator, could result in life-threatening complications due to rapid tumour regression.
- ❖ Clinically significant active cardiovascular disease or history of myocardial infarction within 6 months prior to planned start of LOXO-292 or prolongation of the QT interval corrected for heart rate (QTcF) >470 msec on at least 2/3 consecutive ECGs, and mean QTcF >470 msec on all 3 ECGs, during screening. Correction of suspected drug-induced QTcF prolongation may be attempted at the Investigator's discretion if clinically safe to do so.
- ❖ Active uncontrolled systemic bacterial, viral, or fungal infection, which in the opinion of the Investigator makes it undesirable for the patient to participate in the trial. Screening for chronic conditions is not required.
- ❖ Clinically significant active malabsorption syndrome or other condition likely to affect gastrointestinal absorption of the study agent.
- ❖ Current treatment with certain strong CYP3A4 inhibitors or inducers.
- ❖ Current treatment with proton pump inhibitors (PPIs).
- ❖ Pregnancy or lactation.

  - Medullary: 0
  - Papillary: 68%
  - Poorly differentiated: 16%
  - Hürthle cell: 5%
  - Anaplastic: 11%
- ❖ Median no. of previous systemic regimens (range): 4 (1–7)
- ❖ Previous regimen
  - Cabozantinib, vandetanib, or both: 0
  - Radioiodine: 84%
  - Sorafenib, lenvatinib, or both: 68%
  - Multitargeted kinase inhibitor therapy:
    - o 1: 37%
    - o ≥2: 42%
  - Therapy other than multitargeted kinase inhibitor therapy: 74%
- ❖ Brain metastases: 32%
- ❖ RET alteration:
  - RET M918T mutation: 0
  - RET V804 M/L mutation: 0
  - RET extracellular cysteine mutation: 0
  - Other mutations: 0
  - CCDC6-RET fusion: 47%
  - NCOA4-RET fusion: 32%
  - Other RET fusion: 21%

| Efficacy | Safety in patients with RET-mutant MTC or RET fusion–positive thyroid cancer who received selpercatinib (n=162) |
|---|---|
| **Patients with RET fusion–positive previously treated thyroid cancer (n=19), primary analysis:**<br>**ORR by IRC**: 79% (95% CI, 54 to 94). | **AE of any grade:** 100%<br>**AE of grade ≥3:** 66%<br>**TRAE of any grade:** 94% |

| | |
|---|---|
| Of 2 patients with anaplastic thyroid cancer who were treated, 1 had a response for 18 months, with the response ongoing.<br>**Ongoing responses at 1 year**: 71% (95% CI, 39-88)<br>**Progression-free at 1 year**: 64% (95% CI, 37-82) | **TRAE of grade 3**: 28%<br>**TRAE of grade 4**: 2% |

## Patient-reported outcomes (interim analysis results) [15]

- Instrument completion time points were baseline (cycle 1, day 1) and approximately every other 28-day cycle until cycle 13 (every 12 weeks thereafter) for the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30, and baseline, weekly during cycle 1, and day 1 of every cycle for the modified Systemic Therapy–Induced Diarrhoea Assessment Tool (mSTIDAT).
- A ≥10-point change from baseline in domain score was considered clinically meaningful. PROs were summarized through cycle 13 in all patients and by subgroups with or without prior exposure to MKIs vandetanib and/or cabozantinib (V/C).
- Among the overall MTC population (n = 226), 88 (39%) and 124 (55%) patients comprised the V/C-naïve and previous V/C subgroups, respectively. Compliance was >85% for both instruments at each time point. Most patients maintained/improved in all HRQoL subscales throughout treatment.
- Improvements in diarrhoea were clinically meaningful in 43.5% of patients overall and in 36.8% and 51.3% of V/C-naïve and previous V/C subgroups, respectively. At baseline, 80.4% of all patients reported diarrhoea on mSTIDAT. The percentage of patients who reported diarrhoea was reduced to less than half of all patients (range: 33.3%–48.3%) after cycle 2.

## ESMO-MCBS version 1.1 [16]

| Scale | Int. | Form | MG ST | MG | HR (95% CI) | Score calculation | PM | Toxicity | QoL | AJ | FM |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Original | NC | 3 | - | ORR: 79% | - | ORR (PR+CR) ≥60% | 3 | - | stable | - | 3 |

The adapted scale was not applied due to the low level of evidence (single arm).

## Risk of bias - study level (case series) [17]

| 1. | 2. | 3. | 4. | 5. | 6. | 7. | 8. | 9. |
|---|---|---|---|---|---|---|---|---|
| Was the hypothesis/ aim/ objective of the study clearly stated? | Were the cases collected in more than one centre? | Were patients recruited consecutively? | Were the eligibility criteria (inclusion and exclusion criteria) for entry into the study clearly stated? | Did participants enter the study at similar point in the disease? | Was the intervention clearly described? | Were additional interventions (co-interventions) clearly described? | Were relevant outcome measures established a priori? | Were outcome assessors blinded to the intervention that patients received? |
| yes | yes | yes | yes | no[9] | yes | yes[10] | yes | no |
| 10. | 11. | 12. | 13. | 14. | 15. | 16. | 17. | 18. |
| Were the relevant outcomes measured using appropriate objective/ subjective methods? | Were the relevant outcomes measured before and after intervention? | Were the statistical tests used to assess the relevant outcomes appropriate? | Was the length of follow-up reported? | Was the loss to follow-up reported? | Did the study provide estimates of random variability in the data analysis of relevant outcomes? | Were adverse events reported? | Were the conclusions of the study supported by results? | Were both competing interest and source of support for the study reported? |
| yes | yes | yes | yes | no[11] | yes | yes | partial[12] | yes |
| **Overall risk of bias: moderate** | | | | | | | | |

## Ongoing trials [18]

[9] Different baseline characteristics.
[10] No additional interventions conducted.
[11] No information available.
[12] No final analysis data available; the trial is currently ongoing.

| NCT number/trial name | Description | Estimated study completion date |
|---|---|---|
| NCT03157128/LIBRETTO-001 | Please see above. | 02/2026 |
| NCT05668962 | Restoration of Radioiodine uptake with selpercatinib in RET fusion-positive Radioiodine-refractory thyroid cancer: A phase 2 study performed in collaboration with the International Thyroid Oncology Group. | 01/2025 |
| NCT04280081/LIBRETTO-321 | A phase 2 study of oral selpercatinib (LOXO-292) in patients with advanced solid tumours, including rearranged in RET fusion-positive solid tumours, MTC and other tumours with RET activation. | 11/2025 |

## Available assessments

- In October 2021, NICE published a final appraisal document "Selpercatinib for treating advanced thyroid cancer with RET alterations" [19].
- In July 2022, a reimbursement recommendation was published by CADTH [20].
- IQWIG assessed "Selpercatinib (RET-mutiertes medulläres Schilddrüsenkarzinom, Erstlinie)" in December 2022 [21].
- NIHR published a Health Technology Briefing "Selpercatinib for previously untreated advanced RET-fusion positive thyroid cancer" in September 2022 [22].
- No assessment was found via ICER.

## Other aspects and conclusions

- In January 2024, the **CHMP adopted a new indication** for **Retsevmo®** as monotherapy for the treatment of adults and adolescents 12 years and older with advanced RET fusion-positive thyroid cancer who are radioactive iodine-refractory (if radioactive iodine is appropriate). In May 2020, the **FDA granted accelerated approval** to selpercatinib **(Retevmo®)** for the treatment of adult and paediatric patients ≥12 years of age with advanced or metastatic RET fusion-positive thyroid cancer who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate).
- **LIBRETTO-001** (NCT03157128) is an **ongoing**, open-label, multi-cohort, **single-arm phase 1–2 trial** assessing the efficacy and safety of selpercatinib in patients with RET-altered thyroid cancers. Eligible patients were ≥12 years and had RET-mutant medullary thyroid cancer or RET fusion–positive thyroid cancer of any histologic type. Other inclusion criteria included an ECOG PS score of 0-2, adequate organ function, and a QT interval corrected for heart rate of 470 msec or less. Exclusion criteria included the administration of investigational agent or anticancer therapy within 2 weeks prior to planned start of LOXO-292; major surgery within 4 weeks prior to planned start of LOXO-292; radiotherapy with a limited field of radiation for palliation within 1 week of the first dose of study treatment, and symptomatic primary CNS tumour or metastases.
- The primary end point of LIBRETTO-001 was **objective response** (CR or PR), as determined by an IRC. In 19 patients with previously treated RET fusion–positive thyroid cancer, ORR was 79% (95% CI, 54-94).
- The evaluation of **patient-reported outcomes** was an exploratory endpoint of the trial; however, results are **not available** (yet).
- The original and adapted **ESMO-MCBS** was applied, resulting in a **final adjusted magnitude of clinical benefit of 3** with the original scale. The adapted scale was not applied due to the low level of evidence (single-arm).
- The **risk of bias** of LIBRETTO-001 was considered **moderate**, it is increased by the ongoing status of the trial and the lack of reporting if patients were lost to follow-up.
- Beside the LIBRETTO-001 trial, two further ongoing phase 2 trials, investigating selpercatinib in RET fusion-positive tumour, were identified.
- In conclusion, it must be stated that the **available evidence** for selpercatinib treatment in patients with RET-fusion positive thyroid cancer is **rare** and patient-reported outcome data is completely **lacking**. LIBRETTO-trial´s primary analysis set showed results of **19 patients** with a wide range in age, who had different histologic types of thyroid cancer and received different types of previous treatments. Due to these facts, an **applicability of the results is currently not feasible**. Final analysis data, completed by patient-reported outcomes and phase 3 data, is urgently required to ensure efficacy and safety of this treatment.

**First published:** 02/2024
**Last updated**: 09/2024

Abbreviations: AE=adverse event, AJ=adjustment, ALT=alanine aminotransferase, ANC=absolute neutrophil count, AST=aspartate aminotransferase, ATC=anaplastic thyroid cancer, C=comparator, CADTH=Canada´s Drug and Health Technology Agency, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CLIA=Clinical Laboratory Improvement Amendments, CR=complete response, DTC=differentiated thyroid cancer, EBRT=external beam radiotherapy, EMA=European Medicines Agency, ESMO-MCBS=European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, G-BA=Gemeinsamer Bundesausschuss, Hb=haemoglobin, HR=hazard ratio, HRQoL=health-related quality of life, I=intervention, ICER=Institute for Clinical and Economic Review, ILD=interstitial lung disease, Int.=intention, IRC=independent review committee, MG=median gain, MKI=multikinase inhibitor, mSTIDAT=modified Systemic Therapy–Induced Diarrhoea Assessment Tool, MTC=medullary thyroid cancer, n=number of

patients, NICE=National Institute for Health Care Excellence, NSCLC=non-small cell lung cancer, ORR=objective response rate, OS=overall survival, PD=progressive disease, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, PR=partial response, PTC=papillary thyroid cancer, QoL=quality of life, QTcF=QT interval corrected for heart rate, RANO=Response Assessment in Neuro-Oncology, RECIST=Response Criteria for Solid Tumors, RET=rearranged during transfection, RFA=Radiofrequency ablation, SAE=serious adverse event, ST=standard treatment, TLS=tumuor lysis syndrome, TRAE=treatment-related adverse event, TSH=thyroid stimulating hormone, ULN=upper limit of normal, V/C=vandetanib and/or cabozantinib

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