Selpercatinib (Retsevmo®) for the treatment of RET-fusion positive non-small cell lung cancer, RET-fusion positive thyroid cancer and RET-mutant medullary-thyroid cancer

General information

Drug description [1]	Indication [2]
Selpercatinib (formerly known as LOXO-292) is a novel, ATP-competitive, highly selective small-molecule inhibitor of RET kinase	Selpercatinib is intended for the treatment of cancers that display rearranged during transfection (RET) gene alterations: RET-fusion positive non-small cell lung cancer (NSCLC), RET-fusion positive thyroid cancer and RET-mutant medullary-thyroid cancer (MTC).

Current treatment

NSCLC:

- 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):
  - Pembrolizumab with pemetrexed and platinum chemotherapy in combinations or pembrolizumab or chemotherapy as monotherapies.
- Patients who progress after platinum-based therapy receive:
  - Immunotherapy treatment with pembrolizumab, nivolumab or without PD-L1 expression; atezolizumab.
  - Chemotherapy with docetaxel and the multikinase inhibitor nintedanib.
  - Best supportive care [3].

Thyroid cancer and medullary-thyroid cancer:

- Currently NICE recommends the following treatment options for patients with differentiated thyroid and medullary thyroid cancer:
  - Lenvatinib and sorafenib for treating progressive, locally advanced or metastatic differentiated thyroid cancer (papillary, follicular or Hürthle cell) in adults whose disease does not respond to radioactive iodine, only if
    - they have not had a tyrosine kinase inhibitor before or
    - they have had to stop taking a tyrosine kinase inhibitor within 3 months of starting it because of toxicity (specifically, toxicity that cannot be managed by dose delay or dose modification).
  - Cabozantinib for treating progressive medullary thyroid cancer in adults with unresectable, locally advanced or metastatic disease.
- Treatment options for patients with advanced or metastatic MTC that have progressed following first-line systemic therapy are limited and consists of supportive or palliative care [4].

Regulatory status

EMA [2]

Approval status for this indication: On 10 December 2020, the CHMP adopted a positive opinion, recommending the granting of a conditional marketing authorisation for Retsevmo®.

UPDATE: Date of issue of marketing authorisation valid throughout the European Union: 11/02/2021

The full indication is:

- Selpercatinib as monotherapy is indicated for the treatment of adults with:
  - advanced RET fusion-positive NSCLC who require systemic therapy following prior treatment with immunotherapy and/or platinum-based chemotherapy
  - advanced RET fusion-positive thyroid cancer who require systemic therapy following prior treatment with sorafenib and/or lenvatinib.
- Selpercatinib as monotherapy is indicated for the treatment of adults and adolescents 12 years and older with advanced RET mutant MTC who require systemic therapy following prior treatment with cabozantinib and/or vandetanib.

Other indications: none

✓ Medicine under additional monitoring

FDA [5]

Approval status for this indication: On 8 May 2020, the FDA granted accelerated approval to selpercatinib (Retevmo™) for the following indications:

- Adult patients with metastatic RET fusion-positive NSCLC;
- Adult and paediatric patients ≥12 years of age with advanced or metastatic RET-mutant MTC who require systemic therapy;
- 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).

Other indications: none

✓ This indication is approved **under accelerated approva**l based on overall response rate and duration of response.

✓ **Medicine received a conditional marketing authorisation[1]**	

Costs

60 Retsevmo® hard capsules 80 mg = € 5,340.00 [6]

Method of administration

- Retsevmo® is for oral use.
- The capsules should be swallowed whole (patients should not open, crush, or chew the capsule before swallowing) and can be taken with or without food. Patients should take the doses at approximately the same time every day.
- Retsevmo® must be accompanied by a meal if used concomitantly with a proton pump inhibitor.
- Retsevmo® should be administered 2 hours before or 10 hours after H_2 receptor antagonists.

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®.

Special warnings and precautions for use

- **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.
- **Strong $CYP3A_4$ inducers**
  - Concomitant use of strong $CYP3A_4$ 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.

[1] 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.

❖ **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.

Study characteristics [1, 7-12]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
LIBRETTO-001 NCT03157128 Patients with RET fusion-positive **NSCLC** who received **previous platinum chemotherapy** (n=105) and who were **previously untreated** (n=39)	105 + 39	<u>phase 1 dose-escalation portion:</u> Selpercatinib orally at doses ranging from **20 mg once daily to 240 mg twice daily** <u>phase 2 portion:</u> Selpercatinib orally **160 mg twice daily**	-	objective response (complete or partial response)[2]	open-label, multicenter, phase 1–2 trial	RET	Loxo Oncology and others	[1]
LIBRETTO-001 NCT03157128 Patients with *RET*-mutant **MTC previously treated** with vandetanib, cabozantinib, or both (n=55); patients with *RET*-mutant **MTC not previously treated** with vandetanib or cabozantinib (n=88); and patients with *RET* fusion–positive **previously treated thyroid cancer** (n=19)	162	<u>phase 1 dose-escalation portion:</u> Selpercatinib orally at doses ranging from **20 mg once daily to 240 mg twice daily** <u>phase 2 portion:</u> Selpercatinib orally **160 mg twice daily**		objective response (complete response or partial response)[3]	open-label, multicenter, phase 1–2 trial	RET	Loxo Oncology and others	[12]

Efficacy/ NSCLC

<u>**Patients with previous platinum chemotherapy/independent review:**</u>

Objective response: 64% (95% CI, 54-73); **CR**: n=2/105 (2%); **PR**: n=65/105 (62%); **Stable disease**: n=30/105 (29%); **Progressive disease**: n=4/105 (4%); **Not evaluated**: n=4 (4%); **Median duration of response**: 17.5 months (95% CI, 12.0-NE); **Responses ongoing** at a median follow-up of 12.1 months: 63%

PFS at 1 year: 66% (95% CI, 55-74)

Median PFS: 16.5 months (95% CI, 13.7-NE).

<u>**Patients with previous platinum chemotherapy/investigator assessment:**</u>

Patients with a response: 70% (95% CI, 60-78); **Median time to response**: 1.8 months; **Median duration of response**: 20.3 months (95% CI, 15.6-24.0); **Ongoing responses** at a median follow-up of 14.8 months: 58%

PFS at 1 year: 68%

Median PFS: 18.4 months (95% CI, 16.4-24.8)

Among 38 of 105 patients who had previously received platinum-based chemotherapy and who had investigator-assessed CNS metastasis at baseline, 11 patients were deemed to have measurable lesions according to RECIST, version 1.1, by independent review. Among these 11 patients, the percentage with an **objective intracranial**

Safety/NSCLC

Grade 3 AEs: n=69/144 (48%)
Grade 4 AEs: n=14/144 (10%)
Treatment-related grade 3 AEs: n=39/144 (27%)
Treatment-related grade 4 AEs: n=2/144 (1%)
Grade 5 AEs[4]: n=6/144 (4%)
Discontinuation[5]: n=12/144 (2%)

[2] as determined by an independent review committee of expert radiologists, according to the RECIST, version 1.1.14
[3] as determined by an independent review committee of expert radiologists, according to the RECIST, version 1.1.14
[4] Including sepsis (in 2 patients) and cardiac arrest, multiple organ dysfunction syndrome, pneumonia, and respiratory failure (in 1 patient each). These events were deemed by the investigators to be unrelated to selpercatinib.
[5] Discontinuation due to treatment-related AE(s)

response was 91% (10 of 11 patients; 95% CI, 59-100) according to independent review, including 3 complete responses (in 27%), 7 partial responses (in 64%), and 1 stable disease. The median CNS duration of response was 10.1 months (95% CI, 6.7-NE).

Previously untreated patients:

Patients with a response: 85% (95% CI, 70-94), according to independent review) and 90% (95% CI, 76-97, according to investigator assessment) **Ongoing responses at 6 months**: 90%

Median duration of response/ median PFS: not reached at a median follow-up of 7.4 and 9.2 months, respectively.

PROs (preliminary interim analysis) [13]:

- As of the database lock, 184 patients with NSCLC completed a baseline assessment; adherence was >85% at each scheduled visit.
- Baseline physical, emotional, cognitive and social subscales were >70 points.
- The mean baseline global health status was 61.5 (standard deviation, SD=23.6).
- The highest mean baseline symptom scores were fatigue (37.9, SD=26.0) and insomnia (28.1, SD=30.9).
- Mean post-baseline subscale scores reached CMD improvements among >30% of patients for physical function and 45% or more of patients for global health status and fatigue.
- Conclusion: The proportion of patients reaching a CMD suggests a subset of patients with NSCLC who may have improvements on some PROs during therapy with selpercatinib.

Efficacy (MTC/Thyroid cancer, by independent review)

RET-mutant MTC/previously treated

Objective response: 69% (95% CI, 55-81); **CR**: n=5/55 (9%); **PR:** n=33/55 (60%); **Stable disease**: n=14/55 (25%); **Progressive disease**: n=1/55 (2%); **Could not be evaluated**: n=2/55 (4%); **Ongoing responses at 1 year**: 86%

PFS at 1 year: 82% (95% CI, 69-90)

Patients with a **biochemical response**: 91% (95% CI, 80-97); **Median time to calcitonin response**: 0.5 months (range, 0.4-1.9); **Median time to CEA response**: 1.8 months (range, 0.4-18.8)

RET-mutant MTC not previously treated:

Objective response: 73% (95% CI, 62-82); **CR**: n=10/88 (11%); **PR**: n=54/88 (61%); **Stable disease**: n=20/88 (23%); **Progressive disease**: n=2/88 (2%); **Could not be evaluated**: n=2/88 (2%); **Ongoing responses at 1 year**: 91% (95% CI, 72-97)

PFS at 1 year: 92% (95% CI, 82-97)

RET Fusion–Positive Thyroid Cancer:

Objective response: 79% (95% CI, 54-94); **CR**: n=1/19 (5%); **PR:** n=14/19 (74%); **Stable disease:** n=4/19 (21%); **Ongoing responses at 1 year**: 71%

PFS at 1 year: 64% (95% CI, 37-82)

Safety (MTC/Thyroid cancer)

Grade 3 AEs: n=95/162 (59%)
Grade 4 AEs: n=11/162 (7%)
Treatment-related grade 3 AEs: n=45/162 (28%)
Treatment-related grade 4 AEs: n=3/162 (2%)
Grade 5 AEs[6]**:** n=5/162 (3%)
Discontinuation[7]: n=12/162 (2%)

ESMO-MCBS version 1.1 [14]

Indication	Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
NSCLC	Original	NC	3	-	ORR: 64%	95% CI, 54-73	ORR (PR+CR) ≥ 60%	3	-	-	-	3
Thyroid cancer	Original	NC	3	-	ORR: 69%	95% CI 55-81	ORR (PR+CR) ≥ 60%	3	-	-	-	3
Due to the low level of evidence (single-arm study design) the adapted scale was not applied.												

Risk of bias (study level) [15][8]

[6] Hemoptysis, postprocedure hemorrhage, sepsis, cardiac arrest, and cardiac failure were observed, all deemed by the investigators to be unrelated to selpercatinib.

[7] Discontinuation due to treatment-related AEs

8 Since both indications were assessed in the same trial a joint risk of bias assessment was conducted.

Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Other aspects which increase the risk of bias	**Risk of bias**
no	no	no, open-label	unclear[9]	yes[10]	unclear
				First published: 12/2020 **Last updated**: 05/2021	

Abbreviations: AE=adverse event, AJ=adjustment, ALT=alanine aminotransferase, AST=aspartate aminotransferase, ATP=adenosine triphosphate, C=comparator, CEA=carcino-embryonic antigen, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CMD=clinical meaningful difference, CR=complete response, ECG=electrocardiogram, 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, HR=hazard ratio, I=intervention, Int.=intention, n=number, MG=median gain, MTC= medullary-thyroid cancer, n=number of patients, NICE=National Institute for Health and Care Excellence, NSCLC=non-small cell lung cancer, ORR=overall response rate, OS=overall survival, PD-L1= Programmed cell death 1 ligand 1, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, PR=partial response, PROs=patient-reported outcomes, QoL=quality of life, RECIST=Response Evaluation Criteria in Solid Tumors, RET=rearranged during transfection, SAE=serious adverse event, ST=standard treatment

References:

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[9] Primary analysis data presented; the LIBRETTO-001 trial is ongoing until 05/2022

[10] This trial was designed jointly by the sponsor and the investigators. The sponsor collected, analyzed, and interpreted the trial data in collaboration with the authors. The first draft of the manuscript was written by the first author and last author in collaboration with the sponsor. A medical writer paid by the sponsor provided writing assistance.