Selpercatinib (Retsevmo®) as monotherapy for the treatment of advanced RET fusion positive non-small cell lung cancer (NSCLC)

General information

Drug description	Indication [1]
Selpercatinib (Retsevmo®) is a kinase inhibitor.	Selpercatinib (Retsevmo®) as monotherapy is indicated for the treatment of adults with advanced RET fusion positive NSCLC not previously treated with a RET inhibitor.

Current treatment [2]

- ❖ 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.

Regulatory status

EMA [1, 3]

Approval status for this indication: On 22 April 2022, the CHMP adopted a positive opinion recommending a change to the terms of the marketing authorisation for Retsevmo®.

The CHMP adopted an extension to an existing indication as follows:

- ❖ Retsevmo® as monotherapy is indicated for the treatment of adults with advanced RET fusion positive NSCLC not previously treated with a RET inhibitor.

Other indications: Retsevmo® as monotherapy is indicated

- ❖ for the treatment of adults with advanced RET fusion-positive thyroid cancer who require systemic therapy following prior treatment with sorafenib and/or lenvatinib.
- ❖ for the treatment of adults and adolescents 12 years and older with advanced RET-mutant medullary thyroid cancer (MTC)

✓ **Medicine under additional monitoring**
✓ **Medicine received a conditional marketing authorisation[1]**

FDA [4, 5]

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

- ❖ Adult patients with locally advanced or metastatic NSCLC with a RET gene fusion, as detected by an FDA-approved test

✓ Accelerated approval based on overall response rate and response duration
✓ Priority review
✓ Breakthrough therapy designation
✓ Orphan drug designation

Other indications: Retevmo™ is indicated for the treatment of :

- ❖ Adult and pediatric patients 12 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 based on overall response rate and duration of response).
- ❖ Adult and pediatric patients 12 years of age and older with advanced or metastatic thyroid cancer with a RET gene fusion, as detected by an FDA-approved test, who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate); (this indication is approved under accelerated approval based on overall response rate and duration of response).
- ❖ Adult patients with locally advanced or metastatic solid tumors 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 based on overall response rate and duration of response).

Costs

56 Retsevmo® hard capsules 40 mg = **€2,524.02** (ex-factory price) [6].

Warnings and precautions [3, 4]

[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.

- ❖ Hepatotoxicity
  - Monitor ALT and AST prior to initiating Retevmo™, every 2 weeks during the first 3 months, then monthly thereafter and as clinically indicated.
  - Withhold, reduce dose, or permanently discontinue Retevmo™ based on severity.
- ❖ Interstitial Lung Disease/pneumonitis
  - Monitor for new or worsening pulmonary symptoms.
  - Withhold, reduce the dose or permanently discontinue Retevmo™ based on severity.
- ❖ Hypertension
  - Do not initiate Retevmo™ in patients with uncontrolled hypertension.
  - Optimize blood pressure prior to initiating Retevmo™.
  - Monitor blood pressure after 1 week, at least monthly thereafter and as clinically indicated.
  - Withhold, reduce dose, or permanently discontinue Retevmo™ based on severity.
- ❖ QT interval prolongation
  - Monitor patients who are at significant risk of developing QTc prolongation.
  - Assess QT interval, electrolytes and TSH at baseline and periodically during treatment.
  - Monitor QT interval more frequently when Retevmo™ is concomitantly administered with strong and moderate CYP3A inhibitors or drugs known to prolong QTc interval.
  - Withhold and dose reduce or permanently discontinue Retevmo™ based on severity.
- ❖ Haemorrhagic events
  - Permanently discontinue Retevmo™ in patients with severe or life-threatening haemorrhage.
- ❖ Hypersensitivity
  - Withhold Retevmo™ and initiate corticosteroids. Upon resolution, resume at a reduced dose and increase dose by 1 dose level each week until reaching the dose taken prior to onset of hypersensitivity. Continue steroids until patient reaches target dose and then taper.
- ❖ Tumour lysis syndrome
  - Closely monitor patients at risk and treat as clinically indicated.
- ❖ Risk of impaired wound healing
  - Withhold Retevmo™ for at least 7 days prior to elective surgery.
  - Do not administer for at least 2 weeks following major surgery and until adequate wound healing.
  - The safety of resumption of Retevmo™ after resolution of wound healing complications has not been established.
- ❖ Embryo-foetal toxicity
  - Can cause foetal harm. Advise females of reproductive potential of the possible risk to the foetus and to use effective contraception.
- ❖ Strong CYP3A4 inducers
  - Concomitant use of strong CYP3A4 inducers should be avoided due to the risk of decreased efficacy 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.

Study characteristics [7-10]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
LIBRETTO-001 NCT03157128	105	phase 1 (dose-escalation) selpercatinib	-	objective response (complete or partial response) as	ongoing[2], open-label phase 1–2 trial	RET	Loxo Oncology and others	[9]

[2] The LIBRETTO-001 trial is currently ongoing; estimated study completion date is 11/2023.

		at doses ranging from 20 mg once daily to 240 mg twice daily **phase 2** selpercatinib at a dose of 160 mg twice daily		determined by an independent review committee				
Efficacy							**Safety**	
Patients who had previously received platinum-based chemotherapy **Objective response (by the independent review committee)**: 64% (95% CI 54-73) **Complete response**: 2% **Partial response**: 62% **Stable disease**: 29% **Progressive disease**: 4%, **Could not be evaluated**: 4% **Median duration of response**: 17.5 months (95% CI 12.0-NE) **Ongoing responses 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) Patients with an **objective intracranial response**: 10/11 (91%, 95% CI 59-100); including 3 complete responses (in 27%), 7 partial responses (in 64%), and 1 stable disease. **Median CNS duration of response**: 10.1 months (95% CI, 6.7-NE) **Patients with a response** (according to **investigator assessment)**: 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%; 71% of the patients with a response continued to receive treatment (treatment was administered beyond RECIST progression in some patients because of ongoing clinical benefit). **Longest response**: ongoing at 26.0 months **PFS at 1 year**: 68% **Previously untreated patients (n=39)** **Patients with a response (**according to **independent review**): 85% (95% CI 70-94) **Patients with a response** (according to **investigator assessment**): 90% (95% C, 76-97) **Ongoing responses at 6 months**: 90% **Median duration of response**: NR (at a median follow-up of 7.4 months) **Median PFS**: NR (at a median follow-up of 9.2 months)							**AEs in 144 patients with RET fusion–positive NSCLC who received selpercatinib** **Any AEs (regardless of attribution) grade 3:** 69/144 (48%) **Any AEs (regardless of attribution) grade 4:** 14/144 (10%) **Any treatment-related AEs grade 3:** 39/144 (27%) **Any treatment-related AEs grade 4:** 2/144 (1%) **AEs in all selpercatinib treated patients (n=531)** **Dose reduction due to treatment-related AEs:** 160/531 (30%) **Discontinuation due to treatment-related AEs:** 12/531 (2%)[3]	

[3] Most common were an increase in the alanine aminotransferase level (n=2) and drug hypersensitivity (n=2).

UPDATE: Data cutoff-date 15 June 2021[3]

Treatment-naive RET fusion-positive NSCLC (n=69)

Objective response (CR + PR): 84.1% (95% CI, 73.3-91.8)
Complete response: 5.8%
Partial response: 78.3%
Median duration of response: 20.21 months (95% CI,13.0-NE)
Duration of response ≥ 6 months: 87.7% (95% CI, 75.9-93.9)
Duration of response ≥ 12 months: 66.1% (95% CI, 51.6-77.3)

Previously treated RET fusion-positive NSCLC (n=247)

Objective response (CR + PR): 61.1% (95% CI, 54.7-67.2)
Complete response: 7.3%
Partial response: 53.8%
Median duration of response: 28.58 months (95% CI 20.4-NE)
Duration of response ≥ 6 months: 86.9% (95% CI, 80.3-91.5)
Duration of response ≥ 12 months: 73.1% (95% CI, 64.9-79.7)

ESMO-MCBS version 1.1 [11]

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	NC	3	-	ORR: 64%	-	ORR (CR+PR) ≥ 60%	3	-	-	-	3

The adapted version is not applicable for single-arm studies.

Risk of bias - study level (case series) [12]

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	yes	yes	yes	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	yes	yes	yes	unclear	yes

Overall risk of bias: moderate

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Abbreviations: AE=adverse event, AJ=adjustment, ALT=alanine transaminase, AST=aspartate aminotransferase, C=comparator, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CR=complete response, 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, MG=median gain, n=number of patients, NICE=National Institute for Health and Care Excellence, NSCLC=non small-cell lung cancer, OR=objective response rate, OS=overall survival, PD-L1=programmed death-ligand 1, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, PR=partial response, QoL=quality of life, RET=rearranged during transfection, SAE=serious adverse event, ST=standard treatment, TSH=thyroid stimulating hormone.

1. European Medicines Agency (EMA). Medicines. Retsevmo. [Available from: https://www.ema.europa.eu/en/medicines/human/summaries-opinion/retsevmo-0].
2. National Institute for Health Research (NIHR). Selpercatinib for metastatic RET fusionpositive non-small cell lung cancer. [Available from: https://www.io.nihr.ac.uk/wp-content/uploads/2022/01/27907-TSID_10287-Selpercatinib-for-NSCLC-v1.0-DEC2019-NONCONF.pdf].
3. European Medicines Agency (EMA). Retsevmo: EPAR - Product Information. [Available from: https://www.ema.europa.eu/en/documents/product-information/retsevmo-epar-product-information_en.pdf].
4. U.S. Food and Drug Administration (FDA). Retevmo. Label Information. [Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/213246s008lbl.pdf].
5. U.S. Food and Drug Administration (FDA). FDA approves selpercatinib for lung and thyroid cancers with RET gene mutations or fusions. [Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-selpercatinib-lung-and-thyroid-cancers-ret-gene-mutations-or-fusions].
6. Österreichischer Apotheker-Verlag. Warenverzeichnis Online. [Available from: https://warenverzeichnis.apoverlag.at/].
7. Protocol for: Drilon A, Oxnard GR, Tan DSW, et al. Efficacy of selpercatinib in RET fusion–positive non–small cell lung cancer. N Engl J Med 2020;383:813-24. .
8. Supplement to: Drilon A, Oxnard GR, Tan DSW, et al. Efficacy of selpercatinib in RET fusion–positive non–smallcell lung cancer. N Engl J Med 2020;383:813-24.
9. Drilon A, Oxnard G, Tan D, et al. Efficacy of Selpercatinib in RET Fusion–Positive Non–Small-Cell Lung Cancer. N Engl J Med 2020;383:813-24. . [Available from: https://www.nejm.org/doi/full/10.1056/NEJMoa2005653].
10. U.S. National Library of Medicine, ClinicalTrials.gov. A Study of Selpercatinib (LOXO-292) in Participants With Advanced Solid Tumors, RET Fusion-Positive Solid Tumors, and Medullary Thyroid Cancer (LIBRETTO-001). [Available from: https://clinicaltrials.gov/ct2/show/NCT03157128].
11. Cherny NI, Dafni U, Bogaerts J., et al. ESMO-Magnitude of Clinical Benefit Scale version 1.1. Annals of Oncology 28: 2340–2366, 2017.
12. Institute of Health Economics (IHE). Quality Appraisal of Case Series Studies Checklist. Edmonton (AB): Institute of Health Economics; 2014. [Available from: http://www.ihe.ca/research-programs/rmd/cssqac/cssqac-about].