Selpercatinib (Retsevmo®) as monotherapy for the treatment of advanced rearranged during transfection (RET) fusion-positive solid tumours

General information

Drug description [1]

Selpercatinib (Retsevmo®, LOXO-292) is a first-in-class, highly selective, and potent CNS-active RET kinase inhibitor.

Indication [2]

Selpercatinib (Retsevmo®) as monotherapy is indicated 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.

Incidence [3]

- RET is a proto-oncogene that encodes for a single-pass transmembrane glycoprotein receptor tyrosine kinase. RET plays a vital role in the embryonic development of the human enteric nervous system and genitourinary tract and is essential for the normal development of cells.
- Somatic RET gene alterations, including short variants and fusions, act as pathogenic driver alterations in approximately 2% of solid tumours.
- RET fusions occur in approximately 1% of non-small cell lung cancer (NSCLC) cases and are generally mutually exclusive to other primary driver variants and rearrangements. RET fusion-positive lung adenocarcinomas are associated with poor differentiation, solid sub-type, and smaller T stage (≤3 cm) with N2 disease. RET fusion-positive NSCLC represents a rare but clinically actionable driver alteration class of tumour.
- RET alterations play an essential role in thyroid cancer initiation and progression. RET fusions occur in approximately 10% of papillary thyroid carcinomas. While RET short variant mutations are pathognomonic of 98% hereditary and 50% of sporadic medullary thyroid cancers (MTC), they are rarely reported in other tumour types.

Current treatment [4]

- **For the treatment of stage IV NSCLC with RET translocations, Onkopedia recommends the following** [4]:
  - The RET gene encodes a receptor tyrosine kinase active in different cells. RET can fuse with different genes in NSCLC. The most common fusion partner is KIF5B, and other genes include CCDC6, NCOA, TRIM33, CUX1, KIAA1217, FRMD4A, and KIAA1468. The specific fusion partner may play a role in the disease's prognosis and the therapy's effectiveness.
  - RET gene rearrangements are associated with adenocarcinomas, younger age, and nonsmoking history.
  - Selpercatinib and pralsetinib, two highly effective, specific RET inhibitors in advanced NSCLC from first-line, are approved for use in the E.U. for divergent approvals in respective countries.
  - Pralsetinib resulted in a remission rate of 70% in 27 non-pretreated patients and a remission duration of >6 months in 80%. In 87 cisplatin-pretreated patients, the remission rate was 57%. In 69 patients without systemic pretreatment, selpercatinib achieved a response rate of 84%, primarily partial remissions. The PFS was 22 months, and the O.S. rate after 2 years was 70%.
  - Retrospective analyses debate whether chemotherapy or immunochemotherapy is the better option in first-line therapy of patients with RET translocations when molecularly targeted therapy is not used. Data from prospective studies are lacking.
  - Some multikinase inhibitors approved for other tumour entities are also effective in patients with RET gene alterations. Their use may be considered after the failure of pralsetinib or selpercatinib. These include cabozantinib, vandetanib, lenvatinib, and sunitinib.

Regulatory status

EMA [2, 5]	FDA [6, 7]
Approval status for this indication: On 21 March 2024, the CHMP adopted a positive opinion recommending changing the terms of the marketing authorisation for **Retsevmo®**. The CHMP adopted a new indication as follows: ❖ Retsevmo® as monotherapy is indicated 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. **Other indications**: Retsevmo® is indicated ❖ as monotherapy for the treatment of adults with advanced RET fusion-positive NSCLC who were not previously treated with an RET inhibitor.	**Approval status for this indication**: On 21 September 2022, the FDA granted accelerated approval to selpercatinib (**Retevmo®**), for adult patients 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. ✓ Accelerated approval ✓ Priority review ✓ Orphan drug designation **Other indications**: Retevmo® is indicated for the treatment of

❖ 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). • advanced RET-mutant MTC. ✓ **Medicine under additional monitoring** ✓ **Medicine received a conditional marketing authorisation**[1]	❖ Adult patients with locally advanced or metastatic NSCLC with a RET gene fusion, as detected by an FDA-approved test. ❖ Adult and paediatric 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. ❖ Adult and paediatric 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.

Manufacturer

Retsevmo is manufactured by Eli Lilly.

Costs [8]

56 Retsevmo® hard capsules 40 mg = **€ 2,127.47** (ex-factory price)
56 Retsevmo hard capsules 80 mg = **€ 4,029.78** (ex-factory price)

Posology [5]

❖ The presence of a RET gene fusion should be confirmed by a validated test prior to initiation of treatment with Retsevmo®.
❖ Treatment should be continued until disease progression or unacceptable toxicity.

Warnings and precautions [5, 7]

❖ **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 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 antihypertensive 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**
- Q.T. interval prolongation was reported in patients receiving selpercatinib.
- Selpercatinib should be used with caution in patients with such conditions as congenital long Q.T. syndrome acquired long Q.T. 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.

[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.

- Hypokalaemia, hypomagnesaemia and hypocalcaemia should be corrected prior to initiating selpercatinib and during treatment. Monitor the Q.T. interval with ECGs more frequently in patients who require treatment with concomitant medicinal products known to prolong the Q.T. 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 (T_4) as selpercatinib may inhibit the conversion of levothyroxine to triiodothyronine (T_3) and supplementation with liothyronine may be needed.

❖ **Strong CYP3A4 inducers**
- Concomitant use of strong CYP_3A_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.

❖ **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 life-threatening or recurrent severe 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, and appropriate prophylaxis including hydration, should be considered.

❖ **Risk of impaired wound healing**
- Withhold selpercatinib 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 selpercatinib after resolution of wound healing complications has not been established.

Study characteristics [1, 9]

Trial name	*n*	Intervention (I)	Comparator (C)	P.E.	Median follow-up	Characteristics	Biomarker	Funding	Publication(s)
LIBRETTO-001 NCT04194944	316	selpercatinib at a dose of 160 mg twice a day[2]	-	ORR by IRC	20.3 months	**ongoing**[3], open-label, single-arm, phase I/II trial	RET	Loxo Oncology (a subsidiary of Eli Lilly and Company)	LIBRETTO-001 [1]

Inclusion criteria[4]	Exclusion criteria	Patient characteristics at baseline:

[2] Selpercatinib was orally administered in a continuous 28-day cycle until disease progression, death, unacceptable toxic effects, or withdrawal of consent. Patients enrolled in the phase I dose escalation portion received 20 mg once daily or 20-240 mg twice a day of selpercatinib. All patients in phase II received the recommended phase II dose of 160 mg twice a day.
[3] The LIBRETTO-001 trial is currently ongoing; the estimated study completion date is 02/2026.
[4] For detailed in- and exclusion criteria, please see trial protocol.

		Treatment-naïve patients (n=69); patients who received previous platinum chemotherapy (n=247)
For Phase 1: ❖ Participants with a locally advanced or metastatic solid tumour that: • Has progressed on or is intolerant to standard therapy or • For which no standard therapy exists, or in the opinion of the Investigator, are not candidates for or would be unlikely to tolerate or derive significant clinical benefit from standard therapy or • Decline standard therapy. ❖ Prior multikinase inhibitors (MKIs) with anti-RET activity are allowed. ❖ A RET gene alteration is not required initially. Once adequate P.K. exposure is achieved, evidence of RET gene alteration in tumour and/or blood is required as identified through molecular assays, as performed for clinical evaluation. ❖ Measurable or non-measurable disease as determined by RECIST 1.1 or RANO as appropriate to tumour type. ❖ ECOG score of 0, 1, or 2 or LPS ≥ 40 % (age < 16 years) with no sudden deterioration 2 weeks prior to the first dose of study treatment. ❖ Adequate hematologic, hepatic and renal function. ❖ Life expectancy of at least 3 months. **For Phase 2: As for phase 1 with the following modifications:** ❖ For Cohort 1[5]: Participants must have received prior standard therapy appropriate for their tumour type and stage of disease, or in the opinion of the Investigator, would be unlikely to tolerate or derive clinical benefit from appropriate standard of care therapy. ❖ Cohorts 1 and 2: • Enrolment will be restricted to participants with evidence of a RET gene alteration in the tumour. • At least one measurable lesion, as defined by RECIST 1.1 or RANO, is appropriate to the tumour type and has not been previously irradiated. ❖ Cohorts 3 and 4: Enrolment closed ❖ Cohort 5: • Cohorts 1-4 without measurable disease. • MCT not meeting the requirements for Cohorts 3 or 4. • MTC syndrome spectrum cancers, cancers with neuroendocrine features/differentiation, or poorly differentiated thyroid cancers with other RET	**Phase 1 and Phase 2:** ❖ Phase 2 Cohorts 1 and 2: an additional known oncogenic driver. ❖ Cohorts 3 and 4: Enrolment closed ❖ Cohorts 1, 2 and 5: prior treatment with a selective RET inhibitor. ❖ Investigational agent or anti-cancer therapy within 5 half-lives or 2 weeks (whichever is shorter) prior to planned start of selpercatinib. ❖ Major surgery (excluding placement of vascular access) within 2 weeks prior to planned start of selpercatinib. ❖ Radiotherapy with a limited field of radiation for palliation within 1 week of planned start of selpercatinib, with the exception of participants receiving radiation to more than 30% of the bone marrow or with a wide 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. ❖ Symptomatic primary CNS tumour, metastases, leptomeningeal carcinomatosis, or untreated spinal cord compression. ❖ Clinically significant active cardiovascular disease or history of myocardial infarction within 6 months prior to planned start of selpercatinib or prolongation of the Q.T. interval corrected >470 msec. • Participants with implanted pacemakers may enter the study without meeting QTc criteria due to nonevaluable measurement if it is possible to monitor for Q.T. changes. • Participants with bundle branch block may be considered for study entry if QTc is appropriate by a formula other than Fridericia's and if it is possible to monitor for Q.T. changes.	❖ Median age (range): 63.0 (23-92); 61.0 (23-81) ❖ Female sex: 62.3%; 56.7% ❖ Race: • White: 69.6%; 43.7% • Asian: 18.8%; 47.8% • Black: 5.8%; 4.9% • Others: 5.8%; 2.8% • Missing: 0; 0.8% ❖ Smoking status • Never smoker: 69.6%; 66.8% • Former smoker: 27.5%; 31.6% • Current smoker: 2.9%; 1.6% ❖ ECOG PS score: • 0: 36.2%; 36.4% • 1: 58.0%; 60.7% • 2: 5.8%; 2.8% ❖ NSCLC histologic subtype: • Adenocarcinoma: 89.9%; 89.5% • Large cell neuroendocrine carcinoma: 0; 1.2% • Squamous cell carcinoma: 0; 0.4% • NSCLC-NOS: 10.1%; 8.9% ❖ Median previous systemic lines: • Number/range: 0; 2 (1-15) • 1-2: 0; 56.7% • ≥3: 0; 43.3% ❖ Previous regimen: • Platinum-based chemotherapy: NA; 100% • Anti–PD-1 or anti–PD-L1 therapy: NA; 58.3% • Multikinase inhibitor: NA; 34.4% • Others: NA; 39.3% ❖ RET fusion: • KIF5B-RET: 69.6%; 61.9% • CCDC6-RET: 14.5%; 21.5% • NCOA4-RET: 1.4%; 2.0% • Others: 14.5%; 15.4% ❖ CNS metastases at baseline: 23.2%; 31.2%

[5] Cohort 1: RET-fusion NSCLC and previous treatment with kinase inhibitor(s) with anti-RET activity; Cohort 2: RET-fusion NSCLC with no prior treatment with kinase inhibitor(s) with anti-RET activity; Cohort 3: RET-mutant MTC and previous treatment with kinase inhibitor(s) with anti-RET activity; Cohort 4: RET-mutant MTC with no prior treatment with kinase inhibitor(s) with anti-RET activity; Cohort 5: Evaluable but non-measurable disease, other tumour type (not NSCLC or MTC), other RET gene alteration (excluding synonymous, frameshift or nonsense mutations) or other evidence of increased RET activity, circulating free DNA positive for a RET gene alteration with tumour discordant or unknown and not further evaluable, RET mutation-negative MTC.

alteration/activation may be allowed with prior Sponsor approval. • cfDNA positive for a RET gene alteration not known to be present in a tumour sample. ❖ Cohort 6: Participants who otherwise are eligible for Cohorts 1, 2 or 5 who discontinued another RET inhibitor may be eligible with prior sponsor approval. ❖ Cohort 7: Participants with a histologically confirmed stage IB-IIIA NSCLC and a RET fusion; determined to be medically operable and tumour deemed resectable by a thoracic surgical oncologist, without prior systemic treatment for NSCLC.	❖ Required treatment with certain strong cytochrome P450 3A4 (CYP3A4) inhibitors or inducers and certain prohibited concomitant medications. ❖ Phase 2 Cohort 7 (neoadjuvant treatment): Participant must not have received prior systemic therapy for NSCLC.	

Efficacy	Safety (full safety population: n=796)
Treatment-Naive Patients (n=69): **ORR by IRC**: 84% (95% CI, 73-92) **C.R.**: 6% of patients **Median DoR by IRC**: 20.2 months (95%CI, 13.0-NE), with 40% of responses ongoing **Median time to response**: 1.8 months (range, 0.7-10.8) **Median PFS**: 22.0 months (95%CI,13.8-NE) **Estimated proportion of patients who were alive and progression-free at 1 and 2 years**: 70.6% (95% CI, 57.8-80.2) and 41.6% (95% CI, 26.8-55.8), respectively **Median O.S. at a median follow-up of 25.2 months**: not estimable (71% censoring rate) **Estimated proportion of patients alive at 2 years**: 69% (95% CI, 55-80) **Chemotherapy Pretreated Patients (n=247)** **ORR by IRC**: 61% (95% CI, 55-67) **C.R.**: 7% **Median DoR by IRC**: 28.6 months (95% CI, 20.4-NE), with 49% of responses ongoing **Median time to response**: 1.9 months (range, 0.7-21.9) **Median PFS:** 24.9 months (95% CI, 19.3-NE) **Estimated proportion of patients who were alive and progression-free at 1 and 2 years**: 70.5% (95% CI, 64.1-76.0) and 51.4% (95% CI, 44.3-58.1), respectively **Median O.S. at median follow-up of 26.4 months**: not estimable (68% censoring rate) **Estimated proportion of patients alive at 2 years**: 69% (95% CI, 62-75) **Median duration of treatment:** 24.9 months (95% CI, 20.5-32.2) **Patients With CNS Metastases (n=106)** **Median intracranial PFS**: 19.4 months (95% CI, 13.8-NE) **Intracranial ORR by IRC In patients with measurable CNS metastasis at baseline (n=26):** 85% (95% CI, 65-96), including 27% intracranial C.R.s **Median duration of CNS response in 22 responders with measurable CNS metastases**: 9.4 months (95% CI, 7.4-15.3) **Estimated probability of observing intracranial progression at 2 years in patients with baseline confirmation that no CNS metastasis was present (n=178)**: 0.7%	**Patients with ≥1 TRAEs of any grade**: 95.0% **Patients with ≥1 TRAEs of grade ≥3:** 38.6% **Treatment-related hypertension grade ≥3**: 13.2% **Treatment-related AST/ALT elevations grade ≥3**: 6.3%/9.0% **Treatment-emergent SAEs:** 44% (including 11% related to selpercatinib) **Fatal A.E.:** n=1 (considered related to selpercatinib per the investigator in a patient with RET-mutant MTC who died because of acute respiratory failure) **Treatment discontinuation due to A.E.s:** 8% (with 3% considered by the investigator to be related to selpercatinib).

Patient-reported outcomes
The assessment of patient-reported outcomes is not provided in the LIBRETTO-001 trial.

ESMO-MCBS version 1.1 [10]

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	A.J.	FM
Original	NC	3	-	ORR by IRC: 84%	-	ORR ≥60%	3	-	Not available	-	3

Due to the low level of evidence (single-arm study design) the adapted scale was not applied.

Risk of bias - study level (case series) [11]

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[6]	yes	unclear[7]	yes	partial[8]
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	unclear[9]	yes	yes	unclear[10]	yes

Overall risk of bias: moderate

Ongoing trials [12]

NCT number/trial name	Description	Estimated study completion date
NCT04194944/ LIBRETTO-001	Please see above.	02/2026
NCT04280081/ LIBRETTO-321	A phase 2 study of selpercatinib in participants with advanced solid tumours including RET fusion-positive solid tumours, MTC and other tumours with RET activation.	11/2025
NCT04320888/ MATCH	Selpercatinib for the treatment of advanced solid tumours, lymphomas, or histiocytic disorders with activating RET gene alterations, a paediatric MATCH treatment trial.	09/2027

Available assessments

- No assessments were identified via NICE, CADTH, ICER, NIHR and G-BA

Other aspects and conclusions

- In March 2024, the **CHMP adopted a new indication** for **Retsevmo®** as monotherapy 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. In September 2022, the **FDA granted accelerated approval** to selpercatinib (**Retevmo®**) for adult patients with locally advanced or metastatic solid tumours with a RET gene fusion that have progressed on or following prior systemic treatment or have no satisfactory alternative treatment options.
- **LIBRETTO-001** (NCT04194944) is an **ongoing, phase I/II, single-arm, open-label study** of selpercatinib in patients with RET-altered cancers. Eligible patients were aged≥18 years or ≥12 years, if permitted by regulatory authorities, with measurable disease per RECIST Version 1.1. Patients were required to have an ECOG PS of 0-2 and adequate organ function. Patients with known brain metastases, either asymptomatic or neurologically stable for ≥2 weeks, were eligible. Patients with an additional known oncogenic driver, prior treatment with a selective RET inhibitor, who received an investigational agent or anti-cancer therapy within 5 half-lives or 2 weeks (whichever is shorter) or a concurrent investigational anti-cancer therapy were excluded.
- **The primary endpoint is ORR**. In treatment-naive patients, the **ORR was 84%** (95% CI, 73-92); in platinum-based chemotherapy pretreated patients, the **ORR was 61%** (95% CI, 55-67).

[6] Differences in number and type of previous treatment, different ECOG PS scores.
[7] No information available.
[8] The phase II primary end point (ORR) was assessed by the IRC.
[9] Currently no information available; the trial is ongoing.
[10] Due to the ongoing status of the trial, this issue was considered unclear.

- There is no information available regarding the assessment of patient-reported outcomes.
- The **original ESMO-MCBS** was applied, resulting in a final adjusted magnitude of clinical benefit **3**. Due to the low level of evidence (single-arm study design), the adapted scale was not applied.
- The **risk of bias** of LIBRETTO-001 was considered **moderate**; however, it is increased by differences in the number and type of previous treatment and different ECOG PS scores.
- Besides LIBRETTO-001, two further ongoing phase 2 trials, aiming to evaluate selpercatinib for the treatment of advanced solid tumours with activating RET gene alterations (one of them in a paediatric patient population), were identified via ClinicalTrials.gov.
- Final analysis data and patient-reported outcomes from LIBRETTO-001, as well as **robust phase 3** data, are required to determine the role of selpercatinib in patients with advanced RET fusion-positive solid tumours when treatment options not targeting RET provide limited clinical benefit or have been exhausted.

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Abbreviations: AE=adverse event, AJ=adjustment, ALT=alanine aminotransferase, AST=aspartate aminotransferase, C=comparator, CADTH=Canada's Drug and Health Technology Agency, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CNS=central nervous system, CTCAE=Common Terminology Criteria for Adverse Events, DoR=duration of response, ECG=electrocardiogram, ECOG=Eastern Cooperative Oncology Group, 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, HR=hazard ratio, I=intervention, ICER=Institute for Clinical and Economic Review, ILD=interstitial lung disease, Int.=intention, IRC=independent review committee, LPS=Lansky Performance Score, MG=median gain, MKIs=multikinase inhibitors, MTC=medullary thyroid cancer, n=number of patients, NA=not applicable, NE=could not be evaluated, NICE=National Institute for Health Care Excellence, ORR=objective response rate, OS=overall survival, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, QoL=quality of life, RANO=Response Assessment in Neuro-Oncology, RECIST=Response Evaluation Criteria in Solid Tumours, RET=rearranged in transfection, SAE=serious adverse event, ST=standard treatment, TLS=tumour lysis syndrome, TRAE=treatment-related adverse event

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