# selpercatinib (Retevmo™)

EOCCO POLICY

## Policy Type: PA/SP  Pharmacy Coverage Policy: EOCCO192

### Description

Selpercatinib (Retevmo) is an orally administered kinase inhibitor of RET.

### Length of Authorization

- N/A

### Quantity Limits

| Product Name | Indication | Dosage Form | Quantity Limit |
|---|---|---|---|
| selpercatinib (Retevmo) | RET Fusion-Positive Non-Small Cell Lung Cancer | 40 mg capsules | 90 capsules/30 days |
| | | 80 mg capsules | 60 capsules/30 days |
| | RET-Mutant Medullary Thyroid Cancer | 40 mg tablets | 90 tablets/30 days |
| | | 80 mg tablets | 60 tablets/30 days |
| | RET Fusion-Positive Thyroid Cancer, in those that are radioactive iodine refractory | 120 mg tablets | 60 tablets/30 days |
| | RET Fusion-Positive Solid Tumors, locally advanced or metastatic | 160 mg tablets | 60 tablets/30 days |

### Initial Evaluation

I. **Selpercatinib (Retevmo)** is considered investigational when used for all indications, including but not limited to Non-Small Cell Lung Cancer, Thyroid Cancer, and other locally advanced or metastatic solid tumors with RET-fusion.

### Renewal Evaluation

I. N/A

### Supporting Evidence

I. RET, a transmembrane receptor protein, is present at the surface of several tissue types. Alterations include fusions and point mutations – both are oncogenic drivers. Selpercatinib (Retevmo) is the first FDA-approved therapy that targets RET alterations specifically.

II. Selpercatinib (Retevmo) is a kinase inhibitor of RET. It is FDA-approved for adults with metastatic RET fusion-positive non-small-cell lung cancer (NSCLC), advanced or metastatic RET-mutant medullary thyroid cancer (MTC) in patients age 12 years and older, and advanced or metastatic RET fusion-positive thyroid cancer who are radioactive iodine (RAI)-refractory in

patients age 12 years and older. As of September 2022, selpercatinib (Retevmo) also received accelerated approval for the treatment of 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.

III. RET fusion-positive NSCLC, advanced or metastatic: First-line treatment options include cabozantinib (Cometriq®) or vandetanib (Caprelsa®) (not FDA-approved for lung cancer) or combinations of platinum-based chemotherapy, anti-PD-1/PD-L1 therapy, pemetrexed, and bevacizumab. In the second-line setting, additional options include various immunotherapy and chemotherapy treatments (e.g., taxanes, gemcitabine).

IV. RET-mutant MTC, advanced or metastatic: Systemic treatment may be warranted for high volume, symptomatic or progressive MTC. General treatment options include cabozantinib (Cometriq) or vandetanib (Caprelsa).

V. RET fusion-positive thyroid cancer: In persistent/recurrent or metastatic disease, radioactive iodine (RAI) is recommended. In those not amenable to RAI, general treatment options include lenvatinib (Lenvima®) or sorafenib (Nexavar®).

VI. **Clinical Trial in the setting of NSCLC, MTC, and Thyroid Cancer:**

- Selpercatinib (Retevmo) is being evaluated in one Phase 1/2, open-label, multi-cohort, single-arm trial in patients with RET abnormal, advanced solid tumors Interim results showed potential antitumor activity, based on objective response rate (ORR), in the three FDA-approved settings. Additional outcomes: progression-free survival (PFS) and overall survival (OS) at 12 months.
- RET fusion-positive NSCLC: Patients were advanced or metastatic, progressed on platinum-based chemotherapy or were systemic treatment naïve. Over half of pretreated patients also received anti-PD1/PD-L1 therapy (n=58).
- RET-mutant MTC: 98% had metastatic disease, and patients were previously treated with cabozantinib (Cometriq) and/or vandetanib (Caprelsa) or were treatment naïve to both. Ten patients were previously treated with platinum chemotherapy or anti-PD1/PD-L1 therapy.
- RET fusion-positive TC: Patients were not amenable to RAI therapy and may have been treated with lenvatinib (Lenvima) and/or sorafenib (Nexavar), or were naïve to both.

| Clinical Efficacy in Pretreated Patients | | | |
|---|---|---|---|
| **Outcome** | **RET Fusion+ NSCLC (n=105)** | **RET-Mutant MTC (n=55)** | **RET Fusion-Positive TC (n=19)** |
| **ORR (n)** | 67 (64%) | 38 (69%) | 15 (79%) |
| **CR (n)** | 2 (2%) | 5 (9%) | 1 (5%) |
| **PR (n)** | 65 (62%) | 33 (60%) | 14 (74%) |
| **PFS (months)** | 16.5 (13.7-NE) | NE | 20 (9.4-NE) |
| **OS, 12 months (%)** | 88% | 87% | NR |
| **Clinical Efficacy in Treatment-Naïve Patients** | | | |

| Outcome | RET Fusion+ NSCLC (n=39) | RET-Mutant MTC (n=88) | RET Fusion-Positive TC (n=8) |
|---|---|---|---|
| **ORR (n)** | 33 (85%) | 64 (73%) | 8 (100%) |
| **CR (n)** | 0 | 10 (11%) | 1 (12.5%) |
| **PR (n)** | 33 (85%) | 54 (61%) | 7 (87.5%) |
| **PFS (months)** | NE | 23.6 (NE-NE) | NE |
| **OS, 12 months (%)** | NR | NR | NR |

- For the treatment of RET-mutant medullary thyroid cancer and for RET-fusion positive thyroid cancer, selpercatinib (Retevmo) was FDA-approved under the accelerated approval pathway based on ORR. Continued approval may be contingent upon verification and description of clinical benefit in confirmatory trials. This therapy is being evaluated in multiple other clinical Phase 2 and Phase 3 trials. The quality of the evidence is considered low at this time given the open-label trial design and lack of comparator arm. Given the observational data, medication efficacy remains uncertain. Additionally, the medication has an unfavorable safety profile.
- As of June 2020, safety data are based on a pooled population in 702 patients, 65% were exposed for six months or greater, and 34% were exposed for over one year. Ninety-five percent of patients received 160 mg twice daily.

VII. **Clinical Trial in the setting solid tumors with RET-fusion:**

- Selpercatinib (Retevmo) was FDA-approved under the accelerated approval pathway for the treatment of 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 and FDA approval is based on an ongoing phase 1/ 2 single-arm, open-label clinical trial (basket trial, LIBRETT001). Selpercatinib (Retevmo) was administered to a tumor agnostic cohort of 41 patients with solid tumors harboring RET fusions, which consisted of following tumor types: pancreatic cancer (12), colon (10), salivary gland (4), sarcoma (3), unknown primary (3), breast (2), skin carcinoma (2), cholangiocarcinoma (2), xanthogranuloma (2), and carcinoid, ovarian, pulmonary sarcoma, rectal neuroendocrine, and small intestinal tumors (1 patient each). Majority of these patients were pre-treated and progressed after one to two lines of systemic therapies.
- At a median duration of follow-up 18.8 months, selpercatinib (Retevmo) reported a 43.9% (28.5 – 60.3) objective response rate (ORR) across all tumor types, as measured by a blinded independent committee review. When measuring the duration of response and progression-free survival outcomes, more than half of the patients were censored due to being lost to follow up. Due to the lack of causality of ORR with long-term clinically meaningful outcomes of morbidity and mortality, the quality of the current data is considered low. It is unknown if selpercatinib (Retevmo) may provide true treatment benefit if and when tested in a larger comparator-controlled trial in the setting of solid tumors with RET fusions.

- Although the adverse reaction profile for selpercatinib (Retevmo) varied across participants with different tumor types, the basket trial did not provide significant safety signals other than those previously reported during the clinical trial in the setting of NSCLC and thyroid cancer.

VIII. Warnings and precautions: hepatotoxicity, hypertension, QT interval prolongation, hemorrhagic events, hypersensitivity, impaired wound healing, and embryo-fetal toxicity. There are no contraindications. Serious adverse reactions occurred in 33% of patients. The most frequent was pneumonia. Fatal adverse reactions occurred in 3% of individuals due to sepsis (n=1), cardiac arrest (n=3), respiratory failure (N=3).

IX. Common adverse reactions (≥25%): increase liver enzymes, laboratory abnormalities (≥25% each, glucose, leukocytes, albumin, calcium, creatinine, alkaline phosphatase, platelets, cholesterol, sodium), dry mouth, diarrhea, hypertension, fatigue, edema, rash, constipation. Permanent discontinuation due to adverse reactions occurred in 5%, dose interruptions in 42%, and dose reduction in 31% of patients.

X. Insight from oncology specialists indicate that the diagnosis of stage IV metastatic disease can include intra-pulmonary (disease contained within the lungs) and extra-pulmonary (disease spread to organs outside the lungs) metastases. Intra-pulmonary metastases are typically staged as M1a and described as one of the following situations: separate nodule in the other lung, pleural or pericardial nodules, or malignant pleural or pericardial effusions. The treatment approach for those with intra-pulmonary metastases should be individualized and include surgery and, when surgery is not feasible, standard systemic therapy.

XI. Targeted therapies in oncology have garnered interest in recent years and may be considered part of a paradigm shift in the management of solid tumors based on histology and actionable mutations. However, while initially effective, many targeted therapies have been associated with increased drug resistance after their initial use. Additionally, targeted therapy approach is also susceptible to failure due to acquired resistance and escape mutations.

XII. Ongoing research focuses on identifying potential novel biomarkers and mechanisms involved in resistance to these therapies. In this regard, conventional chemotherapy agents may remain practical and established therapeutic options for members, after progression on or after first-line therapies (e.g., platinum-based chemotherapy). Due to lack of conclusive clinical data to direct a path to curative therapies, NCCN guidelines for the treatment of majority of cancer types (e.g., NSCLC, cholangiocarcinoma, neuroendocrine, sarcoma) note that the best management for any patient with cancer is in a clinical trial setting, and participation in trial is especially encouraged. Patients participating in clinical trials receive regular care, often at leading health care facilities with experts in the field while participating in important medical research and further advancements in treatment, with close safety monitoring and follow-up. Participation in a clinical trial remains the most favorable treatment option for patients with advanced NSCLC. Despite the accelerated FDA-approval, and category 2A recommendations from NCCN, continued approval of selpercatinib (Retevmo) as a subsequent-line treatment of tumors harboring RET fusions, remains contingent upon verification of clinical benefit in confirmatory trials.

## Investigational or Not Medically Necessary Uses

I. Selpercatinib (Retevmo) has not been sufficiently studied for safety and efficacy for any condition to date.

## References

1. Retevmo [Prescribing Information]. Eli Lilly and Company. Indianapolis, IN. May 2020.
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11. National Comprehensive Cancer Network. Non-Small Cell Lung Cancer Treatment Guidelines V6.2020. June 15, 2020. Available at: https://www.nccn.org/professionals/physician_gls/default.aspx.
12. Subbiah V, Wolf J, Konda B, et al. Tumour-agnostic efficacy and safety of selpercatinib in patients with RET fusion-positive solid tumours other than lung or thyroid tumours (LIBRETTO-001): a phase 1/2, open-label, basket trial. Lancet Oncol. 2022 Oct;23(10):1261-1273.

## Related Policies

*Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.*

| Policy Name | Disease state |
|---|---|
| pralsetinib (Gavreto) | RET Fusion-Positive Non-Small Cell Lung Cancer |
| | RET-Mutant Medullary Thyroid Cancer |
| | RET Fusion-Positive Thyroid Cancer, in those that are radioactive iodine refractory |

**Policy Implementation/Update:**

| Action and Summary of Changes | Date |
|---|---|
| Add 120mg and 360mg tablets to the QL table and updated QL to 60/30. Updated QL for 40mg to 90/30 | 08/2024 |
| Added tablet variation to the QL table | 04/2024 |
| Reviewed expanded indication for Retevmo for the treatment of RET-fusion positive solid tumors; added relevant supporting evidence | 03/2023 |
| Added supporting evidence around stage IV metastatic disease and metastases. | 10/2021 |
| Policy created | 08/2020 |