SELPERCATINIB (LY3527723)

RET INHIBITOR

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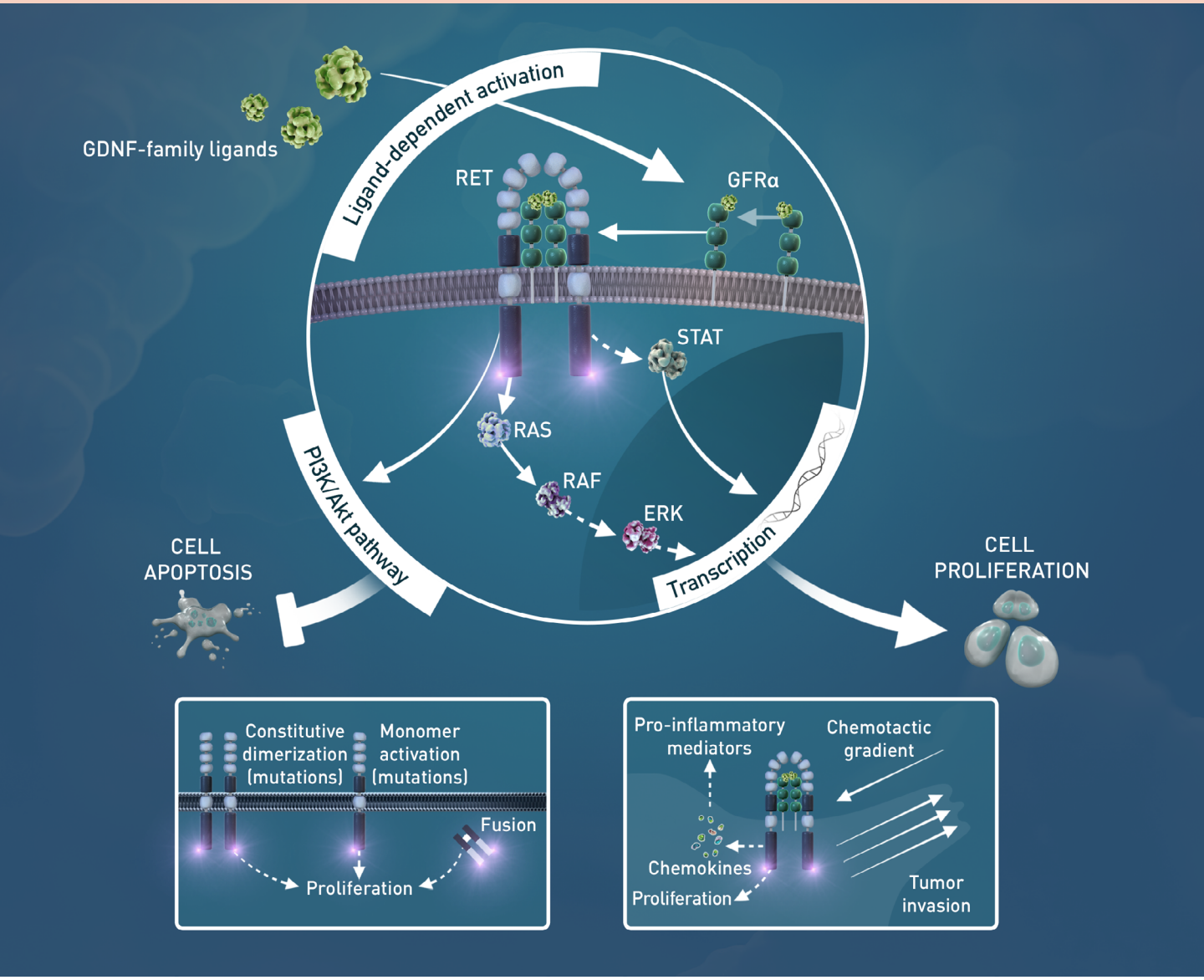
SELPERCATINIB RET INHIBITOR (LY3527723) | MECHANISM OF ACTION[1]



Mulligan LM, et al[1]

Reference: 1. Mulligan LM. *Nat Rev Cancer*. 2014;14:173-186.

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SELPERCATINIB RET INHIBITOR (LY3527723)

TARGET

Rearranged during transfection *(RET)* fusions have been identified in approximately 2% of non-small cell lung cancer,[1,2] approximately 10% of papillary thyroid cancer,[3,4] and less than 1% in other solid tumors including pancreatic and colorectal cancer.[5-7] *RET* point mutations account for approximately 60% of medullary thyroid cancer.[8-10] Cancers that harbor activating *RET* fusions or *RET* mutations depend primarily on this single constitutively activated kinase for their proliferation and survival. This dependency renders such tumors highly susceptible to small-molecule inhibitors targeting *RET*.

MOLECULE

Selpercatinib is a selective, potent, CNS-active small-molecule inhibitor of RET. Selpercatinib possesses nanomolar potency against diverse *RET* alterations, including *RET* fusions, activating *RET* point mutations, and acquired resistance mutations. Selpercatinib has been shown *in vitro* and *in vivo* to exhibit specificity for RET, with limited activity against other tyrosine kinases.[11,12]

CLINICAL DEVELOPMENT

Selpercatinib is being investigated in clinical trials in patients with RET-associated medullary thyroid cancer, non-small cell lung cancer, papillary thyroid carcinoma, pediatric cancers, and other solid tumors.

References: 1. Lipson D, et al. *Nat Med*. 2012;18(3):382-384. **2.** Takeuchi K, et al. *Nat Med*. 2012;18(3):378-381. **3.** Drilon A, et al. *Nat Rev Clin Oncol*. 2018;15(3):151-167. **4.** Parimi V, et al. *NPJ Precis Oncol*. 2023;7(1):10. **5.** Yang SR, et al. *Clin Cancer Res*. 2021;27(5):1316-1328. **6.** Kohno T, et al. *Carcinogenesis*. 2020;41(2):123-129. **7.** Li AY, et al. *Cancer Treat Rev*. 2019;81:101911. **8.** Hofstra RM, et al. *Nature*. 1994;367(6461):375-376. **9.** Agrawal N, et al. *J Clin Endocrinol Metab*. 2013;98(2):E364-E369. **10.** Taccaliti A, et al. *Curr Genomics*. 2011;12(8):618-625. **11.** Subbiah V, et al. *Ann Oncol*. 2018;29:1869-1876. **12.** Drilon A, et al. LIBRETTO-001: A phase 1 study of LOXO-292, a potent and highly selective RET inhibitor, in patients with *RET*-altered cancers. Presented at: ASCO Annual Meeting; June 1-5, 2018; Chicago, IL.

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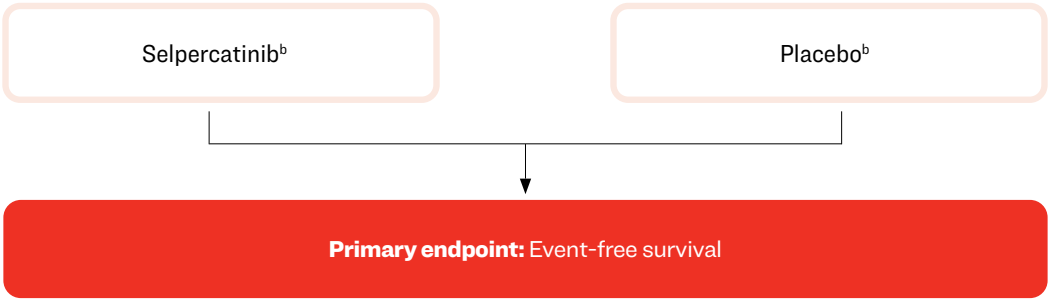
SELPERCATINIB RET INHIBITOR (LY3527723)

LIBRETTO-432

A Placebo-Controlled, Double-Blinded, Randomized, Phase 3 Study of Adjuvant Selpercatinib Following Definitive Locoregional Treatment in Participants With Stage IB-IIIA *RET* Fusion-Positive NSCLC[a]



[a]This clinical trial is being conducted globally. [b]Selpercatinib or placebo equivalent is administered PO.

Please visit clinicaltrials.gov for more information on this clinical trial [NCT04819100].

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LIBRETTO-432

A Placebo-Controlled, Double-Blinded, Randomized, Phase 3 Study of Adjuvant Selpercatinib Following Definitive Locoregional Treatment in Participants With Stage IB-IIIA *RET* Fusion-Positive NSCLC (cont.)

KEY INCLUSION CRITERIA

- Stage IB, II, or IIIA non-small cell lung cancer (NSCLC)
- Activating *RET* gene fusion in tumor based on polymerase chain reaction (PCR) or next-generation sequencing (NGS)
- Prior definitive locoregional therapy with curative intent (surgery or radiotherapy) for stage IB, II, or IIIA NSCLC
  - Participants must have undergone the available anticancer therapy (including chemotherapy or durvalumab) or not be suitable for it, based on the investigator's discretion
- Complete recovery from definitive therapy (surgery or radiotherapy) as well as adjuvant therapy at the time of randomization
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
- Adequate hematologic, hepatic, and renal function
- Patients with reproductive potential must use conventional and highly effective birth control for the duration of the treatment

KEY EXCLUSION CRITERIA

- Additional oncogenic drivers in NSCLC, if known
- Evidence of small cell lung cancer
- Clinical or radiologic evidence of disease recurrence or progression following definitive therapy
- Known or suspected interstitial fibrosis or interstitial lung disease, or history of (noninfectious) pneumonitis that required steroids
- Clinically significant active cardiovascular disease or history of myocardial infarction within 6 months prior to planned start of selpercatinib or prolongation of the QT interval corrected for heart rate using Fridericia's formula (QTcF) greater than 470 ms
- Uncontrolled HIV infection or active hepatitis B or C
- Active uncontrolled systemic bacterial, viral, or fungal infection or serious ongoing intercurrent illness, such as hypertension or diabetes, despite optimal treatment
- Major surgery within 4 weeks prior to planned start of selpercatinib
- Clinically significant active malabsorption syndrome or other condition likely to affect gastrointestinal absorption of the study drug
- Other malignancy unless nonmelanoma skin cancer, carcinoma in situ of the cervix, or other *in situ* cancers or a malignancy diagnosed ≥2 years previously and not currently active
- Pregnancy or lactation
- Prior treatment with a selective RET inhibitor (eg, selpercatinib or pralsetinib)

Please visit clinicaltrials.gov for more information on this clinical trial [NCT04819100].

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SELPERCATINIB RET INHIBITOR (LY3527723)

LIBRETTO-001

A Phase 1/2 Study of Oral Selpercatinib in Patients With Advanced Solid Tumors, Including RET Fusion-Positive Solid Tumors, Medullary Thyroid Cancer, and Other Tumors With RET Activation[a]

Phase 1/Dose Escalation

Selpercatinib[b]

↓

Primary endpoint: Maximum tolerated dose and recommended phase 2 dose

Phase 2/Dose Expansion

Cohort 1: Selpercatinib[b] in participants with an advanced *RET* fusion-positive solid tumor, other than NSCLC or thyroid cancer, who have progressed on or are intolerant to first-line therapy

Cohort 2: Selpercatinib[b] in treatment-naïve participants with an advanced *RET* fusion-positive solid tumor, other than NSCLC or thyroid cancer

Cohort 3: Selpercatinib[b] in participants with advanced *RET*-mutant MTC who have progressed on or are intolerant to first-line therapy [closed]

Cohort 4: Selpercatinib[b] in treatment-naïve participants with advanced *RET*-mutant MTC [closed]

Cohort 5: Selpercatinib[b] in participants with an advanced *RET*-altered solid tumor who are otherwise ineligible for cohorts 1-4

Cohort 6: Selpercatinib[b] in participants otherwise eligible for cohorts 1-5, who have discontinued another RET inhibitor due to intolerance, may be eligible with prior sponsor approval [closed]

Cohort 7: Selpercatinib[b] in participants with *RET* fusion-positive early-stage NSCLC who are candidates for definitive surgery. Participants will receive Selpercatinib[b] in a neoadjuvant or adjuvant setting and will be followed for disease recurrence for up to 5 years from date of surgery [closed]

↓

Primary endpoint: Objective response rate

[a]This clinical trial is being conducted globally. [b]Selpercatinib is administered PO.

Please visit clinicaltrials.gov for more information on this clinical trial [NCT03157128].

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SELPERCATINIB RET INHIBITOR (LY3527723)

LIBRETTO-001

A Phase 1/2 Study of Oral Selpercatinib in Patients With Advanced Solid Tumors, Including RET Fusion-Positive Solid Tumors, Medullary Thyroid Cancer, and Other Tumors With RET Activation (cont.)

KEY INCLUSION CRITERIA

Phase 1

- Participants with a locally advanced or metastatic solid tumor who:
  - Progressed on or are 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 PK exposure is achieved, evidence of *RET* gene alteration in tumor and/or blood is required as identified through molecular assays, as performed for clinical evaluation
- Measurable or nonmeasurable disease as defined by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 or Response Assessment in Neuro-Oncology (RANO) as appropriate to tumor type
- Eastern Cooperative Oncology Group (ECOG) performance status of 0-2 or Lansky Performance Score (LPS) ≥40% (age <16 years) with no sudden deterioration 2 weeks prior to the first dose of study treatment
- ≥12 years of age
- Adequate hematologic, hepatic, and renal function
- Life expectancy of ≥3 months

Phase 2

- Phase 1 criteria with the following modifications:
- Cohort 1: Participants must have received prior standard therapy appropriate for their tumor 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:
  - Enrollment will be restricted to participants with evidence of a *RET* gene alteration in tumor
  - At least one measurable lesion as defined by RECIST 1.1 or RANO, as appropriate to tumor type and not previously irradiated
- Cohorts 3 and 4: Enrollment closed
- Cohort 5:
  - Without measurable disease but otherwise meet criteria for cohorts 1 and 2
  - Medullary thyroid cancer (MTC) syndrome spectrum cancers (eg, MTC, pheochromocytoma), cancers with neuroendocrine features/differentiation, or poorly differentiated thyroid cancers with other *RET* alteration/activation may be allowed with prior sponsor approval
  - Cell-free DNA (cfDNA) positive for a *RET* gene alteration not known to be present in a tumor sample
- Cohort 6: Participants who otherwise are eligible for cohorts 1, 2, or 5, who discontinued another RET inhibitor due to intolerance, may be eligible with prior sponsor approval (closed)
- Cohort 7: Participants must have a histologically confirmed stage IB-IIIA non-small cell lung cancer (NSCLC) by the American Joint Committee on Cancer (AJCC) version 8. The tumor must have been deemed resectable by a thoracic surgeon, the participant must be determined to be medically operable based on the determination of a thoracic surgeon, and the participant must not have received prior systemic therapy, including prior radiation therapy, for NSCLC (closed)

Please visit clinicaltrials.gov for more information on this clinical trial [NCT03157128].

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LIBRETTO-001

A Phase 1/2 Study of Oral Selpercatinib in Patients With Advanced Solid Tumors, Including *RET* Fusion-Positive Solid Tumors, Medullary Thyroid Cancer, and Other Tumors With RET Activation (cont.)

KEY EXCLUSION CRITERIA

Phase 1 and 2

- Cohorts 1 and 2 (phase 2): An additional known oncogenic driver
- Cohorts 3 and 4 (phase 2): Enrollment closed
- Cohorts 1, 2, and 5 (phase 2): Prior treatment with a selective RET inhibitor. **Note:** Participants otherwise eligible for cohorts 1, 2, and 5, who discontinued another selective RET inhibitor, may be eligible for cohort 6 (phase 2) with prior sponsor approval
- Investigational agent or anticancer therapy (including chemotherapy, biologic therapy, immunotherapy, anticancer Chinese medicine, or other anticancer herbal remedy) within 5 half-lives or 2 weeks (whichever is shorter) prior to planned start of selpercatinib. In addition, no concurrent investigational anticancer therapy is permitted.
  Note: Potential exception for this exclusion criterion will require a valid scientific justification and approval from the sponsor
- Major surgery (excluding placement of vascular access) within 4 weeks prior to planned start of selpercatinib
- Radiotherapy with a limited field of radiation for palliation within 1 week of planned start of selpercatinib, except for 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 > grade 1 toxicities as defined by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0 attributed to prior therapy (other than alopecia and grade 2, prior platinum-therapy related neuropathy) at the start of study treatment
- Symptomatic primary central nervous system (CNS) tumor, metastases, leptomeningeal carcinomatosis, or untreated spinal cord compression. Participants are eligible if neurological symptoms and CNS imaging are stable and steroid dose is stable for 14 days prior to the first dose of selpercatinib and no CNS surgery or radiation has been performed for 28 days, 14 days if stereotactic radiosurgery (SRS)
- Clinically significant active cardiovascular disease or history of myocardial infarction within 6 months prior to planned start of selpercatinib or prolongation of the QTc interval of >470 ms using Fridericia's formula
- Required treatment with certain strong cytochrome P450 3A4 (CYP3A4) inhibitors or inducers and certain prohibited concomitant medications

Please visit clinicaltrials.gov for more information on this clinical trial [NCT03157128].

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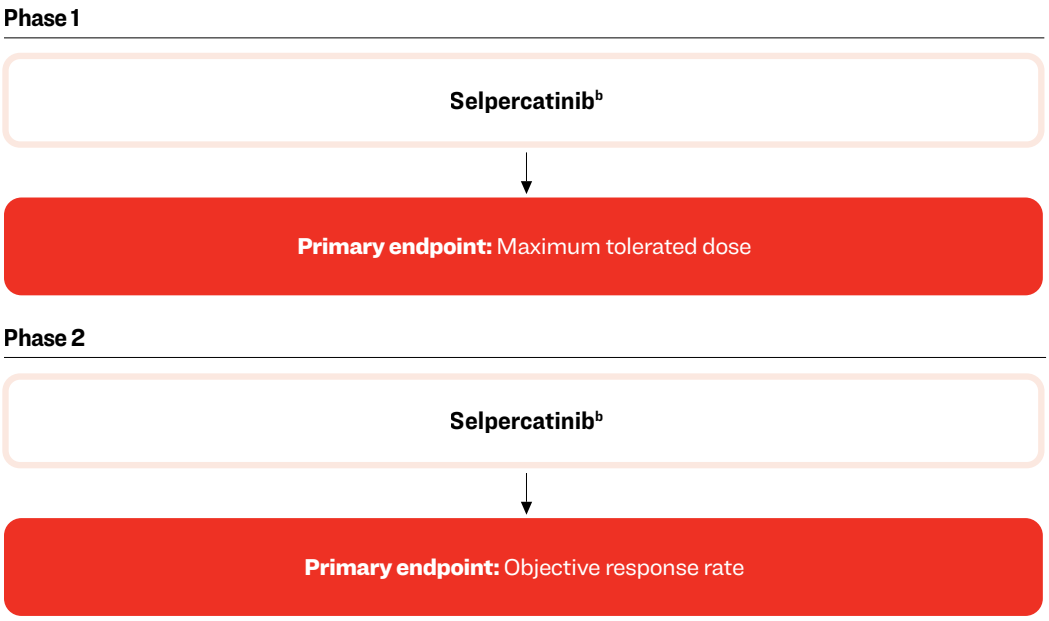
SELPERCATINIB RET INHIBITOR (LY3527723)

LIBRETTO-121

A Phase 1/2 Study of the Oral RET Inhibitor Selpercatinib in Pediatric Patients With Advanced *RET*-Altered Solid or Primary Central Nervous System Tumors[a]



[a]This clinical trial is being conducted globally. [b]Selpercatinib is administered PO.

Please visit clinicaltrials.gov for more information on this clinical trial [NCT03899792].

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SELPERCATINIB RET INHIBITOR (LY3527723)

LIBRETTO-121

A Phase 1/2 Study of the Oral RET Inhibitor Selpercatinib in Pediatric Patients With Advanced *RET*-Altered Solid or Primary Central Nervous System Tumors (cont.)

KEY INCLUSION CRITERIA

- Pediatric patients aged 6 months to 21 years with advanced or metastatic solid or primary central nervous system (CNS) tumors and have failed standard-of-care therapies
- Evidence of an activating *RET* gene alteration in the tumor and/or blood
- Measurable or evaluable disease
- Karnofsky (patients ≥16 years of age) or Lansky (patients <16 years of age) performance score of at least 50
- Patients with primary CNS tumors or cerebral metastases must be neurologically stable for 7 days prior to start of treatment and must not have required increasing doses of steroids within the last 7 days
- Adequate hematologic, hepatic, and renal function
- Able to receive study drug therapy orally or via gastric access
- Males and females of reproductive potential must be willing to use conventional and effective birth control

KEY EXCLUSION CRITERIA

- Major surgery within 14 days prior to planned start of selpercatinib
- Clinically significant, uncontrolled cardiac or cardiovascular disease, or history of myocardial infarction within 6 months prior to planned start of selpercatinib
- Active uncontrolled systemic bacterial, viral, fungal, or parasitic infection
- Clinically significant active malabsorption syndrome
- Pregnant or breastfeeding
- Uncontrolled symptomatic hyperthyroidism or hypothyroidism
- Uncontrolled symptomatic hypercalcemia or hypocalcemia
- For patients who will be receiving selpercatinib suspension: Known hypersensitivity to any of the components of the investigational agent or Ora-Sweet® and Ora-Plus®
- Prior treatment with a selective RET inhibitor(s), including investigational

Please visit clinicaltrials.gov for more information on this clinical trial [NCT03899792].

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ACTIVE TRIALS CURRENTLY NOT ENROLLING

[NCT04194944] Lung Cancer
LIBRETTO-431: A Study of Selpercatinib (LY3527723) in Participants With Advanced or Metastatic *RET* Fusion-Positive Non-small Cell Lung Cancer

[NCT04211337] Thyroid Cancer
LIBRETTO-531: A Study of Selpercatinib (LY3527723) in Participants With *RET*-Mutant Medullary Thyroid Cancer

[NCT04280081] Thyroid Cancer
LIBRETTO-321: A Study of Selpercatinib (LY3527723) in Participants With Advanced Solid Tumors Including *RET* Fusion-positive Solid Tumors, Medullary Thyroid Cancer and Other Tumors With *RET* Activation

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Pipeline information is current through August 20, 2024.