The safety and efficacy of the agents under investigation have not been established. There is no guarantee that the agents will receive regulatory approval and become commercially available for the uses being investigated.
Rearranged during transfection (RET) fusions have been identified in approximately 2% of non-small cell lung cancer, 10% to 20% of papillary thyroid cancer, and a subset of colon and other cancers. RET point mutations account for approximately 60% of medullary thyroid cancer. 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 highly 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 high selectivity for RET, with limited activity against other tyrosine kinases.

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 cancer, and other advanced solid tumors.

References:
13. Drilon A, et al. ASCO Annual Meeting; June 1-5, 2018; Chicago, IL.

The safety and efficacy of the agents under investigation have not been established. There is no guarantee that the agents will receive regulatory approval and become commercially available for the uses being investigated.
# A Multicenter, Randomized, Open-Label, Phase 3 Trial Comparing Selpercatinib to Platinum-Based and Pemetrexed Therapy With or Without Pembrolizumab as Initial Treatment of Advanced or Metastatic RET Fusion-Positive Non-small Cell Lung Cancer*

The safety and efficacy of the agents under investigation have not been established. There is no guarantee that the agents will receive regulatory approval and become commercially available for the uses being investigated.

## KEY INCLUSION CRITERIA

- Stage IIB-IIIC or stage IV nonsquamous non-small cell lung cancer (NSCLC) not suitable for radical surgery or radiation therapy
- A RET gene fusion in tumor and/or blood from a qualified laboratory
- Eastern Cooperative Oncology Group (ECOG) performance status of 0-2
- Adequate organ function
- Patients with reproductive potential must use a highly effective contraceptive method for the duration of treatment and for 6 months after
- Able to swallow capsules

## KEY EXCLUSION CRITERIA

- Stage IIIB-IIIC or stage IV nonsquamous non-small cell lung cancer (NSCLC) not suitable for radical surgery or radiation therapy
- A RET gene fusion in tumor and/or blood from a qualified laboratory
- Eastern Cooperative Oncology Group (ECOG) performance status of 0-2
- Adequate organ function
- Patients with reproductive potential must use a highly effective contraceptive method for the duration of treatment and for 6 months after
- Able to swallow capsules

- Participants may continue treatment until disease progression, unacceptable toxicity, or death from any cause.

* This clinical trial is being conducted globally.
† Selpercatinib 160 mg is administered PO BID.
‡ Carboplatin AUC 5 mg·min/mL is administered intravenously (IV) Q3W.
§ Cisplatin 75 mg/m² is administered IV Q3W.
¶ Pembrolizumab 200 mg is administered IV Q2W.
# The primary endpoints are PFS in patients receiving pembrolizumab and PFS in all patients.

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- Stage IIB-IIIC or stage IV nonsquamous non-small cell lung cancer (NSCLC) not suitable for radical surgery or radiation therapy
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- Able to swallow capsules

## KEY EXCLUSION CRITERIA

- Additional validated oncogenic drivers in NSCLC, if known.
- Previously received systemic therapy for metastatic disease
- Treatment (chemotherapy, immunotherapy, or biological therapy) in the adjuvant/neoadjuvant setting is permitted if completed at least 6 months prior to randomization
- Major surgery within 3 weeks prior to planned start of treatment
- Radiotherapy for palliation within 1 week of the first dose of study treatment or within 6 months prior to the first dose of study treatment if more than 30 Gy to the lung
- Symptomatic central nervous system 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 treatment
- Prolongation of the QTcF interval of >470 ms
- Other malignancy unless nonmelanoma skin cancer, carcinoma in situ of the cervix, or malignancy diagnosed ≥2 years previously and not currently active
- Uncontrolled, disease-related pericardial effusion or pleural effusion
- Receiving pembrolizumab and have a history of interstitial lung disease or interstitial pneumonitis, or have an active autoimmune disease or any illness or treatment that could compromise the immune system
- Active, uncontrolled systemic bacterial, viral, or fungal infections, or serious ongoing intercurrent illness such as hypertension or diabetes, despite optimal treatment

Please visit www.clinicaltrials.gov for more information on this clinical trial [NCT04194944].
The safety and efficacy of the agents under investigation have not been established. There is no guarantee that the agents will receive regulatory approval and become commercially available for the uses being investigated.

**KEY INCLUSION CRITERIA**

- Patients ≥12 years of age
- Unresectable, locally advanced and/or metastatic medullary thyroid cancer (MTC) and no prior treatment with kinase inhibitors for advanced/metastatic disease
- Radiographic progressive, evaluable disease at screening
- A defined RET gene alteration identified in a tumor, germline DNA, or blood sample
  - Tumor tissue in sufficient quantity to allow for retrospective central analysis of RET mutation status
- Eastern Cooperative Oncology Group (ECOG) performance status of 0-2
- Adequate organ function
- Patients with reproductive potential must use a highly effective contraceptive method for the duration of treatment and for 4 months after
- Able to swallow capsules
- An additional validated oncogenic driver in MTC, if known, that could cause resistance to selpercatinib treatment
- Symptomatic central nervous system metastases, leptomeningeal carcinomatosis, or untreated spinal cord compression
- Clinically significant active cardiovascular disease or history of myocardial infarction within 6 months
- History of torsades de pointes
- Prolongation of the QTc interval of >470 ms using Fridericia’s formula on more than one electrocardiogram during screening
  - Participants intended to receive vandetanib if QTc is >450 ms
- Active bacterial, viral, or fungal infection, or serious uncontrolled and ongoing illness
- Active or at significant risk for hemorrhage
- Other malignancy unless nonmelanoma skin cancer, carcinoma in situ, or malignancy diagnosed ≥2 years previously and not currently active
  - Participants with multiple endocrine neoplasia type 2 (MEN2) associated phaeochromocytoma may be eligible

**KEY EXCLUSION CRITERIA**

- An additional validated oncogenic driver in MTC, if known, that could cause resistance to selpercatinib treatment
- Symptomatic central nervous system metastases, leptomeningeal carcinomatosis, or untreated spinal cord compression
- Clinically significant active cardiovascular disease or history of myocardial infarction within 6 months
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- Other malignancy unless nonmelanoma skin cancer, carcinoma in situ, or malignancy diagnosed ≥2 years previously and not currently active
  - Participants with multiple endocrine neoplasia type 2 (MEN2) associated phaeochromocytoma may be eligible

**A Multicenter, Randomized, Open-Label, Phase 3 Trial Comparing Selpercatinib to Physician’s Choice of Cabozantinib or Vandetanib in Patients With Progressive, Advanced, Kinase Inhibitor-Naïve, RET-Mutant Medullary Thyroid Cancer**

- The trial is being conducted globally.
- Selpercatinib 160 mg is administered PO BID.
- Cabozantinib 140 mg is administered PO QD.
- Vandetanib 300 mg is administered PO QD.

**Primary endpoint: Treatment failure-free survival**

Participants may continue treatment until disease progression, unacceptable toxicity, or death from any cause.

**Please visit www.clinicaltrials.gov for more information on this clinical trial [NCT04211337].**
The safety and efficacy of the agents under investigation have not been established. There is no guarantee that the agents will receive regulatory approval and become commercially available for the uses being investigated.

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*  

* This clinical trial is being conducted globally.

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)
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

The safety and efficacy of the agents under investigation have not been established. There is no guarantee that the agents will receive regulatory approval and become commercially available for the uses being investigated.

Phase 1

Dose escalation of selpercatinib†

Primary endpoints:
Maximum tolerated dose and recommended phase 2 dose

Phase 2

Cohort 1: Dose expansion of selpercatinib† in participants with an advanced RET fusion-positive solid tumor who have progressed on or are intolerant to first-line therapy

Cohort 2: Dose expansion of selpercatinib† in treatment-naïve participants with an advanced RET fusion-positive solid tumor

Cohort 3: Dose expansion of selpercatinib† in participants with advanced RET-mutant MTC who have progressed on or are intolerant to first-line therapy (closed)

Cohort 4: Dose expansion of selpercatinib† in treatment-naïve participants with advanced RET-mutant MTC (closed)

Cohort 5: Dose expansion of selpercatinib† in participants with an advanced RET-altered solid tumor who are otherwise ineligible for cohorts 1-4

Cohort 6: Dose expansion of selpercatinib† in participants otherwise eligible for cohorts 1-5, who have discontinued another RET inhibitor due to intolerance, may be eligible with prior sponsor approval

Cohort 7: Dose expansion of selpercatinib† in participants with RET fusion-positive early-stage NSCLC who are candidates for definitive surgery. Participants will receive selpercatinib† in a neoadjuvant or adjuvant setting and will be followed for disease recurrence for up to 5 years from the date of surgery

Primary endpoint: Objective response rate

† Selpercatinib is administered PO.

* This clinical trial is being conducted globally.

Please visit www.clinicaltrials.gov for more information on this clinical trial [NCT03157128].
KEY EXCLUSION 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 molecular inhibitors (MKIs) with anti-RET activity are allowed
• A RET gene alteration is not required initially. Once adequate PK
  exposure is achieved, evidence of a 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 determined 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
• Participants with a locally advanced or metastatic solid tumor who:
  - Cell-free DNA (cfDNA) positive for a RET gene alteration not known to be
    present in a tumor sample
  - Without measurable disease but otherwise meet criteria for cohorts 1 and 2
  - Medullary thyroid cancer (MTC), pheochromocytoma, cancers with neuroendocrine features/differentiation, cancers with neuroendocrine features/differentiation,
  or poorly differentiated thyroid cancers with other
  - At least one measurable lesion as defined by RECIST 1.1 or RANO, as
    appropriate to tumor type and not previously irradiated
  - At least one measurable lesion as defined by RECIST 1.1 or RANO, as
    appropriate to tumor type and not previously irradiated
  - Enrollment will be restricted to participants with evidence of a RET gene
    alteration in tumors
  - Cohorts 3 and 4: Enrollment closed
  - Cohort 5:
    - Without measurable disease but otherwise meet criteria for cohorts 1 and 2
    - At least one measurable lesion as defined by RECIST 1.1 or RANO, as
      appropriate to tumor type and not previously irradiated
    - If patients will have received prior systemic therapy (other than
      alopecia and grade 2, prior platinum-therapy related neuropathy) at the start of study treatment
    - Major surgery (excluding placement of vascular access) within 6 weeks prior to the first dose of selpercatinib
    - Participants are otherwise eligible for cohorts 1, 2, and 5, who discontinued another RET inhibitor due to intolerance, may be eligible with prior sponsor approval
  - Major surgery (excluding placement of vascular access) within 6 weeks prior to the first dose of selpercatinib
  - Cell-free DNA (cfDNA) positive for a RET gene alteration not known to be
    present in a tumor sample
  - Investigational agent or anticancer therapy (including chemotherapy, biologic therapy, immunotherapy, anti-Cancer 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
  - 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 6 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, which
    are not resolved or are not fully resolved prior to the planned start of selpercatinib
  - At least one measurable lesion as defined by RECIST 1.1 or RANO, as
    appropriate to tumor type and not previously irradiated
  - Cell-free DNA (cfDNA) positive for a RET gene alteration not known to be
    present in a tumor sample
  - Prior treatment with a selective RET inhibitor, may be eligible for cohort 6 (phase 2) with prior sponsor approval
  - Enrollment will be restricted to participants with evidence of a RET gene
    alteration in tumors
  - Cohorts 3 and 4: Enrollment closed
  - Cohort 5:
    - With or without measurable disease but otherwise meet criteria for cohorts 1 and 2
    - If patients will have received prior systemic therapy (other than
      alopecia and grade 2, prior platinum-therapy related neuropathy) at the start of study treatment
  - Major surgery (excluding placement of vascular access) within 6 weeks prior to the first dose of selpercatinib
  - Cell-free DNA (cfDNA) positive for a RET gene alteration not known to be
    present in a tumor sample
  - At least one measurable lesion as defined by RECIST 1.1 or RANO, as
    appropriate to tumor type and not previously irradiated
  - Cell-free DNA (cfDNA) positive for a RET gene alteration not known to be
    present in a tumor sample
  - Prior treatment with a selective RET inhibitor, may be eligible for cohort 6 (phase 2) with prior sponsor approval
  - 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 have received prior systemic therapy, including prior radiation therapy, for
    NSCLC.
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*

The safety and efficacy of the agents under investigation have not been established. There is no guarantee that the agents will receive regulatory approval and become commercially available for the uses being investigated.

**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 www.clinicaltrials.gov for more information on this clinical trial [NCT03899792].

* This clinical trial is being conducted globally.
† Selpercatinib is administered PO. 

**Primary endpoint:**

- Phase 1: Selpercatinib
  - Maximum tolerated dose
- Phase 2: Selpercatinib
  - Objective response rate