


# Phase III study of selpercatinib vs chemotherapy +/- pembrolizumab in untreated *RET* positive non-small-cell lung cancer

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Selpercatinib, a novel, highly selective and potent, inhibitor of *RET*, demonstrated clinically meaningful antitumor activity with manageable toxicity in heavily pretreated and treatment-naïve *RET* fusion-positive non-small-cell lung cancer patients in a Phase I/II clinical trial. LIBRETTO-431 (NCT04194944) is a randomized, global, multicenter, open-label, Phase III trial, evaluating selpercatinib versus carboplatin or cisplatin and pemetrexed chemotherapy with or without pembrolizumab in treatment-naïve patients with locally advanced/metastatic *RET* fusion-positive nonsquamous non-small-cell lung cancer. The primary end point is progression-free survival by independent review. Key secondary end points include overall survival, response rate, duration of response and progression-free survival.

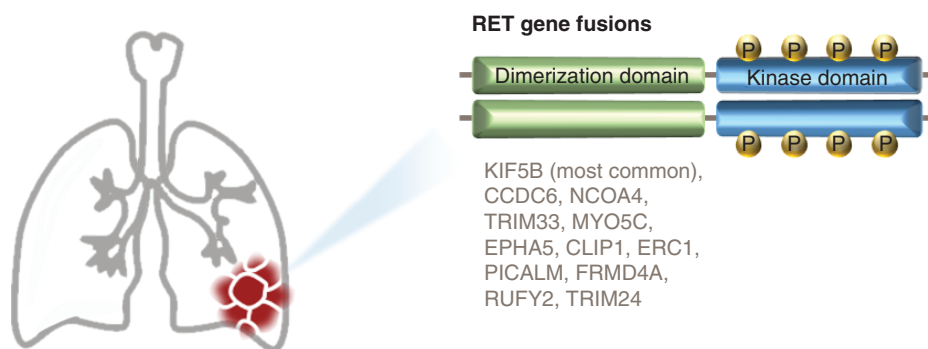
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Lung cancer is the leading cause of cancer death worldwide, accounting for 2.09 million new cases and 1.76 million deaths in 2018 [1]. The majority (80–85%) of lung cancers are classified as non-small-cell lung cancer (NSCLC), of which adenocarcinoma is the most common histologic subtype [2,3]. While outcomes for patients diagnosed with advanced disease remain poor, treatment for NSCLC has recently been revolutionized by the advent of immunotherapy, using checkpoint inhibitors as well as targeted therapies directed at actionable oncogenic drivers [4].

The standard of care (SOC) first-line treatment for patients with NSCLC has historically been platinum-based chemotherapy [5]. Recent studies have demonstrated that the addition of an immune checkpoint inhibitor (anti-PD-1 or PD-L1 antibody) to platinum-based regimens improve response rates, progression-free survival (PFS), and overall survival (OS), both for nonsquamous [6–8] and squamous NSCLC [5,7]. For patients with high PD-L1 expression (tumor proportion score of 50% or greater), monotherapy with a PD-L1 inhibitor is an option [9].



**Figure 1. Schematic illustration of *RET* gene rearrangements identified in non-small-cell lung cancer.**

Recently, the immunotherapy combination of ipilimumab and nivolumab given alone in patients with positive PD-L1 expression [10,11] or with 2 cycles of chemotherapy regardless of PD-L1 expression [12] has also been approved by the US FDA, increasing the first-line armamentarium for the treatment of patients with NSCLC.

Identification of activating genomic alterations involving specific tyrosine kinases, particularly in lung adenocarcinoma coupled with the corresponding respective tyrosine kinase inhibitors, has led to a paradigm shift in the treatment of NSCLC. Targeted therapies are now considered the preferred initial treatment for NSCLC patients with *EGFR* and *BRAF* activating mutations as well as *ALK*, *ROS1*, *NTRK*, *RET* fusions and *MET* exon14 splicing site mutations [13–15]. Molecular profiling of NSCLC tumors is recommended by international consensus guidelines as part of routine evaluation in newly diagnosed patients to identify not only *EGFR*, *ALK* and *ROS1*, but a broader panel of potentially actionable genes including *BRAF*, *MET*, *RET*, *HER2* and *KRAS* [13].

Several studies have suggested that NSCLC patients with driver oncogenes may benefit less from chemotherapy-immunotherapy combinations and a recent multi-disciplinary roundtable discussion recommended that immune checkpoint inhibitors should be used after targeted therapies and chemotherapy [16]. However, it is not yet clear whether these observations extend to NSCLC patients with *RET* fusions as the reported data are variable [17–19]. Additional studies are needed to fully characterize the effect of chemotherapy-immunotherapy combinations in *RET* fusion-positive NSCLC patients.

### ***RET* gene fusions in NSCLC**

The *RET* receptor tyrosine kinase can be abnormally activated by chromosomal rearrangements producing *RET* gene fusions in 1–2% of patients with NSCLC [20–24]. *RET* rearrangements can occur with various upstream fusion partners, detailed in Figure 1. In NSCLC, the most common *RET* fusion partners are *KIF5B* (most common) and *CCDC6*. These *RET* alterations induce ligand independent *RET* kinase activity, which causes aberrant *RET* activation and drives oncogenesis [25,26].

### **Selpercatinib**

Selpercatinib (LOXO-292) is a novel, highly selective and potent, small-molecule inhibitor of *RET* signaling that was recently granted accelerated approval by the US FDA for adult patients with metastatic *RET* fusion-positive NSCLC. Selpercatinib has nanomolar potency against wild-type *RET* and other *RET* alterations, including the *KIF5B-RET* fusion and V804M gatekeeper mutation, in both enzyme and cellular assays, with minimal activity against other kinase and nonkinase targets [27,28]. A Phase I/II clinical trial LIBRETTO-001 showed that selpercatinib is clinically active in patients with *RET*-altered solid tumors (in particular *RET* rearranged NSCLC and papillary thyroid cancer and *RET* mutation positive papillary thyroid cancer), including those that have metastasized to the CNS [29,30]. Treatment with selpercatinib resulted in a 64% objective response rate (ORR) (95% CI: 54–73%) by blinded independent review in the registration dataset (n = 105) of patients with *RET* fusion-positive NSCLC who previously received platinum-based chemotherapy and an 85% ORR (95% CI: 70–94%) in treatment-naïve patients with *RET* fusion-positive NSCLC (n = 39). Although the duration of response (DOR) and PFS were not yet mature in treatment-naïve patients, in patients who previously received chemotherapy, the median DOR was 17.5 months (95% CI: 12–not estimable). Additionally, in patients previously treated with platinum-

based chemotherapy, selpercatinib demonstrated a robust CNS ORR of 91% (95% CI: 59–100%) per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 in 10 of 11 patients; all responders had a DOR of  $\geq 6$  months [29,31].

In 144 patients with *RET* fusion-positive NSCLC from the LIBRETTO-001 trial, the most common adverse reactions included diarrhea (48%), dry mouth (41%), hypertension (31%), increased aspartate aminotransferase (AST) level (30%), fatigue (29%), increased alanine transferase (ALT) level (26%), constipation (26%), nausea (26%), peripheral edema (24%), urinary tract infection (22%) and headache (21%) [29]. The majority of adverse reactions were Grade 1 or Grade 2. Grades 3–4 events occurring in  $\geq 2\%$  of patients included hypertension (14%), increased ALT level (12%), increased AST level (10%), hyponatremia (6%), lymphopenia (6%), prolonged QT corrected interval (5%), urinary tract infection (5%), diarrhea (3%), dyspnea (2%) and thrombocytopenia (2%). The safety profile was similar to the overall safety profile for all patients, regardless of tumor type, who received selpercatinib.

### The LIBRETTO-431 clinical trial

LIBRETTO-431 (also referred to as J2G-MC-JZJC) is a global, open-label, randomized, controlled Phase III trial, evaluating selpercatinib versus chemotherapy with cisplatin/carboplatin and pemetrexed treatment with or without pembrolizumab in treatment-naïve patients with locally advanced or metastatic *RET* fusion-positive non-squamous NSCLC (NCT04194944). This study is active and recruiting participants, with planned enrollment at approximately 230 sites across 26 countries.

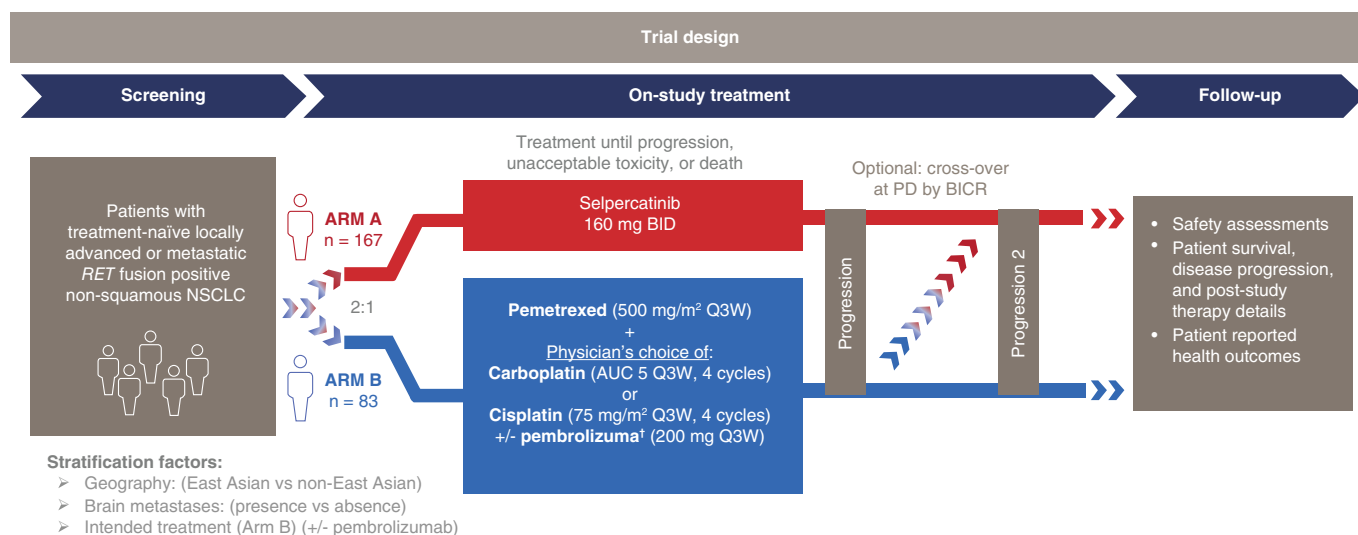
### Background & rationale

In the LIBRETTO-001 Phase I/II single arm trial, selpercatinib treatment demonstrated clinically meaningful responses and sustained antitumor activity with a manageable profile in both heavily pre-treated and treatment-naïve *RET* fusion-positive NSCLC patients [29,32]. Although the strength of the data has led to accelerated FDA approval in the US, it remains important to confirm these results in a randomized study [33] and this will be a key consideration for approval and reimbursement in many countries around the world. However, given the strength of the preliminary data it is also important to minimize the number of patients assigned to the control arm. As a result, the protocol was designed with a randomization factor of 2:1 in favor of the experimental arm and an overall sample size of 250 patients.

The control arm will consist of platinum-based therapy (cisplatin or carboplatin) with pemetrexed, with or without pembrolizumab, which is considered a SOC of nonsquamous NSCLC patients without *EGFR* mutations or *ALK* fusions. Not all patients are suitable to receive an immune checkpoint inhibitor such as pembrolizumab (e.g., patients with a history of interstitial lung disease or interstitial pneumonitis, an active autoimmune disease or requiring concurrent treatment with supraphysiologic doses of immunosuppressive agents). Additionally, there are geographical differences in frequency with which pembrolizumab is used based on individual patient characteristics (e.g., contraindications, PD-L1 expression, the potential for subsequent therapy with targeted agents whose toxicity profile may be affected by prior treatment with pembrolizumab) [34–37]. The design of LIBRETTO-431, which will allow the platinum doublet to be administered with or without pembrolizumab, provides flexibility for the investigator to select the regimen best suited for each specific patient in the control arm.

### Study design

This study will be a head-to-head comparison of selpercatinib versus an SOC regimen for the treatment of advanced or metastatic nonsquamous NSCLC, consisting of a baseline (screening) period, on-study treatment period with an optional crossover treatment phase (only Arm B patients) and poststudy follow-up period (Figure 2). During the baseline phase, patient eligibility and baseline characteristics will be determined using medical history, physical exam, clinical laboratory testing and tumor assessments. Prior to enrollment, the presence of the *RET* gene fusion must be confirmed in the tumor (by next generation sequencing and/or PCR) or in the blood (by next generation sequencing) using a sponsor enabled or locally qualified test. If available, an archived tumor sample is required for retrospective central confirmation of *RET* fusion. Patients will be stratified by geographic region (East Asian vs nonEast Asian), brain metastases per investigator assessment (presence vs absence) and intended treatment if randomized to Arm B ( $\pm$  pembrolizumab). Investigator's choice/intent of treatment regimen must be declared prior to randomization. After confirmation of eligibility, approximately 250 patients will be randomly assigned at a ratio of 2:1 into one of the 2 arms:



**Figure 2. LIBRETTO-431 study design.**

†No more than 20% of patients with intent not to receive pembrolizumab will be enrolled.

AUC: Area under the concentration versus time curve; BICR: Blinded independent central review; BID: Twice a day; ECOG PS: Eastern Cooperative Oncology Group performance status; NSCLC: Non-small-cell lung cancer; PD: Progressive disease; Q3W: Every 3 weeks.

- **Arm A:** treated with selpercatinib (160 mg twice a day [BID] continuously in 21-day cycles)
- **Arm B:** treated with pemetrexed (500 mg/m<sup>2</sup> intravenous [iv.]) every 3 weeks plus the investigator's choice of the following treatments administered every 3 weeks:
  - Four cycles of carboplatin (area under the concentration vs time curve [AUC] 5, maximum dose 750 mg iv.) or cisplatin (75 mg/m<sup>2</sup> iv.).
  - With or without pembrolizumab (200 mg iv.) up to 35 cycles.

The on-study treatment phase will begin at randomization and continue until disease progression, development of unacceptable toxicity, the start of a new anticancer therapy, withdrawal of consent, death or study completion. Patients randomly assigned to Arm B who have radiographic disease progression confirmed by blinded independent central review (BICR) will be eligible for crossover to selpercatinib. Crossover treatment will be optional at the discretion of the investigator.

The post-treatment phase will consist of a short-term follow-up period that will begin when the patient and investigator decide the patient will no longer continue study therapy, until completing a safety assessment (30 ± 7 days) after receiving the last dose of study treatment. Long-term follow-up will begin when the short-term follow-up period is complete and will continue until death, study withdrawal, the patient is lost to follow-up, or final study completion. Patients discontinuing prematurely from the study for any reason will complete adverse event and other safety assessments. Information related to patient survival, disease progression, and poststudy anticancer therapy details will be collected from the end of short-term follow-up until death or study completion. Patient-reported questionnaires will be administered to assess patient reported health outcomes including health-related quality of life, patient functioning, health status, disease symptoms and toxicities.

### Objectives & end points

The study objectives are detailed in Table 1. The primary end points of PFS (per RECIST version 1.1) as assessed by the BICR in patients intended for treatment with pembrolizumab (if assigned to control) will act as a gatekeeper for the other primary end points of PFS by independent review in the intent-to-treat (ITT) population. For ease of discussion, the 2 analysis populations will be referred to as the ITT-pembrolizumab and ITT populations, respectively. PFS in the ITT population will be tested conditionally on achieving statistical significance for PFS in the ITT-pembrolizumab population. Secondary end points include investigator assessed PFS, investigator and BICR assessed ORR/DOR, intracranial ORR/DOR, time to deterioration in pulmonary symptoms, progression after the next line of therapy, overall survival, *RET* fusion status (local vs central) and safety/tolerability.

Table 1. Study objectives.

Primary
<ul style="list-style-type: none"> <li>To compare PFS of selpercatinib with the combination of platinum-based (carboplatin or cisplatin) therapy, pemetrexed and pembrolizumab</li> <li>To compare PFS of selpercatinib with the combination of platinum-based (carboplatin or cisplatin) and pemetrexed therapy, with or without pembrolizumab</li> </ul>
Secondary
<ul style="list-style-type: none"> <li>To compare efficacy and safety/tolerability of selpercatinib with platinum-based and pemetrexed therapy with pembrolizumab</li> <li>To compare efficacy and safety/tolerability of selpercatinib with platinum-based and pemetrexed therapy with or without pembrolizumab</li> <li>To assess/evaluate performance of <i>RET</i> local laboratory tests compared with a single central test</li> </ul>
PFS: Progression-free survival.

Table 2. Key eligibility criteria for LIBRETTO-431.

Inclusion criteria	Exclusion criteria
<p><b>Locally advanced or metastatic NSCLC</b></p> <ul style="list-style-type: none"> <li>Histologically or cytologically confirmed Stage IIIB-IIIC or Stage IV NSCLC that is not suitable for radical surgery/radiation therapy</li> <li>Histology of the tumor must be predominantly nonsquamous</li> <li>Squamous cell and/or mixed small cell/non-small-cell histology is not permitted</li> </ul> <p><b>Patient characteristics</b></p> <ul style="list-style-type: none"> <li>Measurable disease per RECIST 1.1</li> <li>ECOG PS of 0–2</li> <li>Life expectancy of at least 3 months</li> <li>Adequate organ function</li> </ul> <p><b>RET alteration</b></p> <p>Must have a <i>RET</i> gene fusion in tumor (by PCR or NGS) or in blood (by NGS) using a qualified test</p>	<p><b>Medical conditions</b></p> <ul style="list-style-type: none"> <li>Additional known validated oncogenic drivers in NSCLC</li> <li>Symptomatic CNS involvement, carcinomatous meningitis or untreated spinal cord compression</li> <li>Patients must be neurologically stable and previous treatment must be completed at least 2 weeks prior to randomization</li> <li>Active cardiovascular disease or history of myocardial infarction <math>\leq 6</math> months prior to start of treatment or prolongation of the QT interval corrected for heart rate using QTcF <math>&gt;470</math> msec on more than 1 ECG obtained during the baseline period</li> <li>Uncontrolled, disease-related, pericardial effusion or pleural effusion</li> <li>Active, uncontrolled, systemic bacterial, viral or fungal infection that requires treatment</li> <li>Serious ongoing intercurrent illness that is not controlled, despite optimal treatment</li> <li>Clinically significant active malabsorption syndrome or other condition likely to affect gastrointestinal absorption of the study drug</li> <li>Other malignancy unless nonmelanoma skin cancer, carcinoma <i>in situ</i> of the cervix or other <i>in situ</i> cancers, or a malignancy diagnosed <math>\geq 2</math> years previously and not currently active</li> </ul> <p><b>Prior therapy</b></p> <ul style="list-style-type: none"> <li>Prior systemic therapy (chemotherapy, immunotherapy or biological therapy) for metastatic disease</li> <li>Patients who received adjuvant or neoadjuvant therapy are eligible if such therapy was completed <math>\geq 6</math> months prior to randomization</li> <li>Major surgery within 3 weeks prior to planned start of study treatment</li> <li>Palliative radiotherapy within 1 week of the first dose or any radiotherapy within 6 months prior to the first dose if <math>&gt;30</math> Gy to the lung</li> <li>Are taking a concomitant medication that is known to cause QTc prolongation</li> </ul> <p><b>Patients on pembrolizumab</b></p> <ul style="list-style-type: none"> <li>History of interstitial lung disease or interstitial pneumonitis</li> <li>Active autoimmune disease or any illness that could compromise immune system in last 2 years</li> <li>Use of escalating or chronic supraphysiologic doses of corticosteroids or immunosuppressive agents</li> </ul>

ECOG PS: Eastern Cooperative Oncology Group performance status; Gy: Gray; NGS: Next generation sequencing; NSCLC: Non-small-cell lung cancer; QTcF: QT interval corrected for heart rate using Fridericia's formula; RECIST 1.1: Response Evaluation Criteria in Solid Tumors version 1.1.

## Key eligibility criteria

Key eligibility criteria are summarized in Table 2 and below. Eligible participants must have nonsquamous Stage IIIB-IIIC not suitable for radical surgery/radiation therapy or Stage IV NSCLC, a *RET* gene fusion, measurable disease and have an Eastern Cooperative Oncology Group performance status of 0–2. Participants will be excluded from the study if any of the following criteria apply: presence of additional validated oncogenic drivers in NSCLC, received prior systemic therapy for metastatic disease, symptomatic CNS involvement, active cardiovascular disease or uncontrolled disease related pericardial effusion or pleural effusion.

## Planned sample size

The planned sample size is approximately 250 patients who will be randomized at a ratio of 2:1 to selpercatinib or control arms (i.e., 167 and 83 patients, respectively). To ensure adequate power for the test of treatment effect in the ITT-pembrolizumab population, no more than 20% of patients with the intent to not receive pembrolizumab if randomized to the control arm will be enrolled (e.g., no more than 50 patients with intent not to receive



Table 3. Doses &amp; dosing schedule.

Arm A (selpercatinib)	Arm B (Investigator's discretion of carboplatin or cisplatin + pemetrexed ± pembrolizumab)				
	Selpercatinib	Carboplatin	Cisplatin	Pemetrexed	Pembrolizumab (investigator's choice)
<b>Dose</b>	160 mg	AUC 5 (maximum dose 750 mg)	75 mg/m <sup>2</sup>	500 mg/m <sup>2</sup> (with vitamin supplementation)	200 mg
<b>Schedule</b>	BID continuously in 21-day cycles	Day 1 Q3W for 4 cycles	Day 1 Q3W for 4 cycles	Day 1 Q3W	Day 1 Q3W up to 35 cycles
<b>Route</b>	Oral	iv.	iv.	iv.	iv.

AUC: Area under the concentration vs time curve; BID: Twice a day; iv.: Intravenous; Q3W: Every 3 weeks.

pembrolizumab). The study was started in March 2020 and the estimated primary and study completion dates are December 2023 and April 2026, respectively.

### Dose & schedule of therapy

Patients in Arm A will receive selpercatinib (160 mg BID, oral) administered in continuous 21-day cycles. Patients in Arm B will receive pemetrexed (500 mg/m<sup>2</sup>, iv.) administered every 3 weeks plus the investigator's choice of carboplatin (AUC 5, maximum dose 750 mg, iv.) or cisplatin (75 mg/m<sup>2</sup>, iv.) administered every 3 weeks for 4 cycles. For patients in Arm B, at the investigator's discretion, pembrolizumab (200 mg, iv.) may also be given for up to 35 cycles. After the completion of 4 cycles of chemotherapy without progressive disease, patients assigned to Arm B may receive maintenance therapy with pemetrexed (500 mg/m<sup>2</sup>) with or without pembrolizumab (200 mg) every 3 weeks. Treatment will continue until radiographic disease progression confirmed by BICR, unacceptable toxicity, withdrawal of consent or death. Dosing and treatment durations for all intervention groups are outlined in Table 3.

### Efficacy evaluations

To evaluate PFS, radiographic tumor assessments will be performed per RECIST 1.1. Scans should be obtained within 28 days of baseline and then during the study treatment at approximately 6, 12, 21, 30, 39 and 48 weeks after the start of dosing, then every 12 weeks thereafter until progression, the start of a new anticancer therapy, death or study completion. Response assessments, will be evaluated by the BICR. These data will constitute the primary assessment for PFS and ORR analyses.

### Safety evaluations

Safety evaluations including electrocardiogram, physical examination with vital signs, clinical laboratory testing (hematology, clinical chemistry, coagulation and urinalysis) and hepatic safety monitoring will be assessed at scheduled intervals. Adverse events will be assessed continuously throughout the study duration.

### Statistical analyses

Patient demographics, baseline disease characteristics, prior anticancer therapies, historical illness and pre-existing conditions will be summarized. Descriptive statistics (i.e., number of patients, mean, median, standard deviation, minimum and maximum) will be used for continuous variables. Categorical variables will be reported by frequency and the corresponding percentage. The primary end points of BICR PFS will be estimated using the Kaplan–Meier method and comparison between treatment arms will be assessed using the Cox proportional hazard regression and log-rank test, stratified by the randomization strata. Under the current statistical assumptions, the study will deliver approximately 90% power at a 2-sided type alpha level of 0.05. The study will be considered positive if a statistically significant improvement in PFS in the ITT-pembrolizumab population is observed. ORR will be summarized for each treatment arm. ORR and CNS ORR will be compared between Arm A and Arm B using a Cochran–Mantel–Haenszel test stratified by the randomization strata. DOR according to both BICR and investigator assessed best overall response (BOR) will be evaluated.

### Conclusion

The LIBRETTO-431 Phase III trial outlined here will evaluate selpercatinib in comparison to chemotherapy with carboplatin or cisplatin and pemetrexed with or without pembrolizumab in treatment-naïve patients with

advanced or metastatic *RET* fusion-positive nonsquamous NSCLC. The findings of this study will help define the benefit of selpercatinib used as first-line therapy in patients with *RET* fusion-positive NSCLC. It is also expected to demonstrate the importance of upfront broad-based genomic testing of newly diagnosed patients with NSCLC for molecular alterations including *RET* fusions and will define the optimal therapy for this population.

### Executive summary

#### Background

- Lung cancer is the leading cause of cancer death worldwide, with non-small-cell lung cancer (NSCLC) accounting for approximately 80–85% of all lung cancers.
- Standard-of-care first-line treatment, platinum-based chemotherapy ± an immune checkpoint inhibitor, is not specific in targeting the primary driver alteration in patients with *RET* fusion-positive NSCLC.
- The identification of mutually exclusive, activating genetic alterations in specific tyrosine kinases has led to a new classification of NSCLC based on molecular genotype rather than histology. Patients with *RET* fusion-positive NSCLC represent a population with a high unmet need.

#### Selpercatinib

- Selpercatinib (LOXO-292) is a highly potent and specific small-molecule inhibitor of the RET kinase, with minimal inhibition of other kinase and nonkinase targets.
- Selpercatinib was designed to inhibit RET signaling as well as anticipated acquired resistance mechanisms that could otherwise limit the activity of this therapeutic approach.
- In the LIBRETTO-001 Phase I/II trial, selpercatinib treatment demonstrated clinically meaningful responses and sustained antitumor activity with a manageable toxicity profile in both heavily pretreated and treatment-naïve patients, including patients with brain metastases, with *RET* fusion-positive NSCLC.

#### LIBRETTO-431 study

- The global, open-label, randomized, controlled, Phase III LIBRETTO-431 trial, will evaluate selpercatinib versus platinum-based and pemetrexed treatment with or without pembrolizumab in treatment-naïve patients with locally advanced or metastatic *RET* fusion-positive nonsquamous NSCLC (NCT04194944).
- First ever randomized Phase III clinical trial in treatment-naïve *RET* fusion-positive NSCLC.

#### Conclusion

- The results of this important trial will help further define the role of selpercatinib as a front-line treatment for people living with advanced or metastatic *RET* fusion-positive NSCLC.

### Supplementary data

An infographic accompanies this paper and is included at the end of the references section in the PDF version. To view or download this infographic in your browser please click here: [www.futuremedicine.com/doi/10.2217/fon-2020-0935](http://www.futuremedicine.com/doi/10.2217/fon-2020-0935)

### Author contributions

All authors were involved in the conception, design or planning of the study and critically reviewed and revised the manuscript for intellectual content as well as read and approved the final version to be published.

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### Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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# The LIBRETTO-431 Trial

NCT04194944

A Phase III study 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

## Objectives

**The primary endpoint of PFS per RECIST v1.1 by BICR in patients with intent to receive pembrolizumab will act as a gatekeeper for the endpoint of PFS by independent review in the intent-to-treat population**

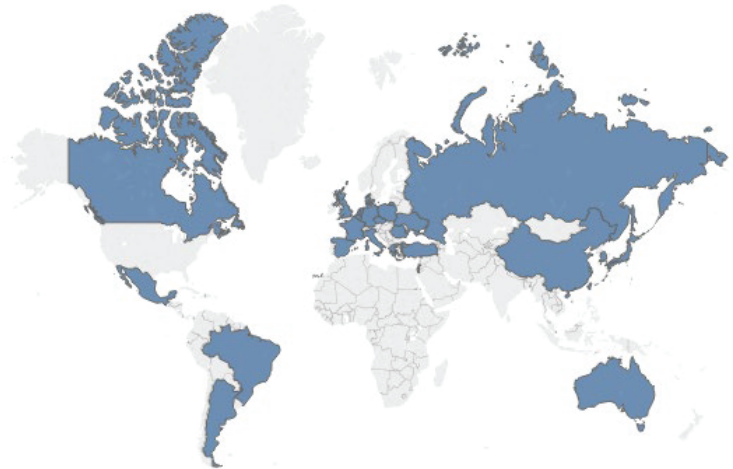
- Secondary endpoints include:
- Investigator-assessed PFS
  - ORR/DOR
  - intracranial ORR/DOR
  - time to deterioration in pulmonary symptoms
  - PFS2
  - OS
  - RET* fusion status: local vs central
  - safety/tolerability

The study will be considered positive if a statistically significant improvement in PFS in the ITT-pembrolizumab population is observed

~250 patients

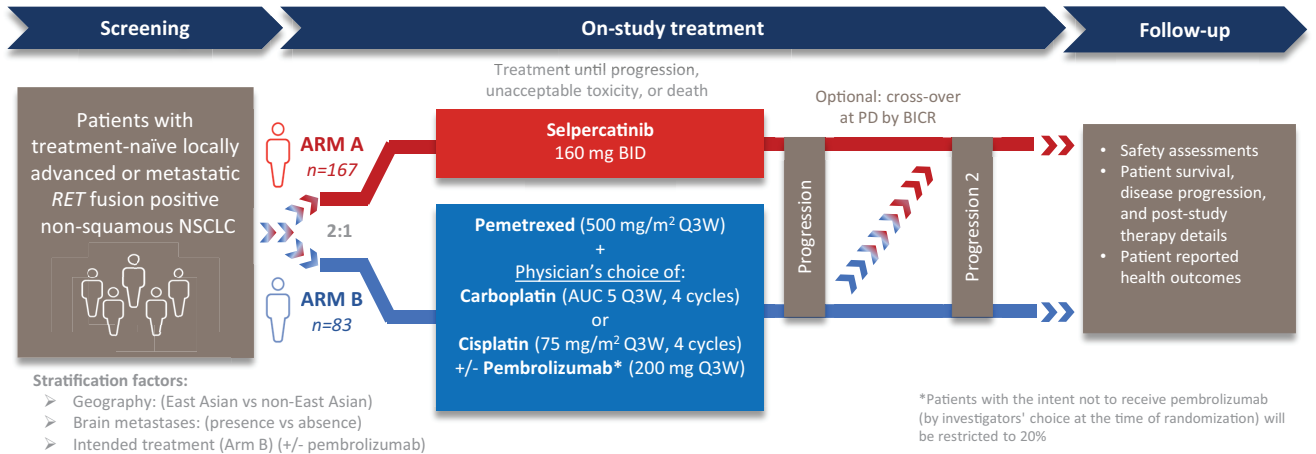
~230 sites

26 countries



This study is active and recruiting participants, with planned enrollment at approximately 230 sites across 26 countries. Approximately 250 patients will be randomly assigned at a ratio of 2:1 to the selpercatinib or control arm, respectively

## Trial design



## Key eligibility criteria

<p><b>Non-squamous NSCLC</b></p> <p>Stage IIIB-IIIC not suitable for radical surgery/radiation therapy or Stage IV non-small cell lung cancer</p>	<p><b>RET fusion positive</b></p> <p>RET fusion positive identified by PCR or NGS (tumor) or NGS (blood)</p>	<p><b>Treatment-naïve</b></p> <p>Received no prior systemic therapy (chemotherapy, immunotherapy or biological therapy) for metastatic disease</p>	<p><b>≥ 18 years old</b></p> <p>Have measurable disease by RECIST 1.1; an ECOG PS of 0-2; a life expectancy ≥ 3 months; adequate organ function</p>	<p><b>Key exclusion criteria:</b></p> <ul style="list-style-type: none"> <li>presence of other oncogenic drivers</li> <li>symptomatic CNS involvement</li> <li>active cardiovascular disease</li> </ul> <p><i>Additional screening criteria will be assessed prior to trial enrollment</i></p>
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**Glossary:** AUC: Area under the concentration versus time curve; BICR: Blinded independent review committee; BID: Twice a day; CNS: Central nervous system; DOR: Duration of response; ECOG PS: Eastern Cooperative Oncology Group performance status; NSCLC: Non-small cell lung cancer; ORR: Objective response rate; OS: Overall survival; PD: Progressive disease; PFS: Progression free survival; PFS2: Progression after the next line of therapy; Q3W: Every 3 weeks; RECIST 1.1 = Response Evaluation Criteria In Solid Tumours version 1.1