Clinical Trial Protocol

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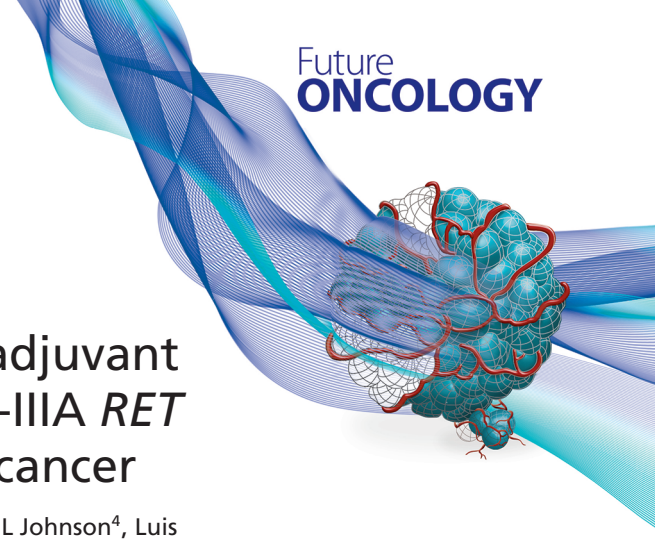

LIBRETTO-432, a phase III study of adjuvant selpercatinib or placebo in stage IB-IIIA *RET* fusion-positive non-small-cell lung cancer

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Selpercatinib, a first-in-class, highly selective and potent central nervous system-active RET kinase inhibitor demonstrated clinically meaningful activity with manageable toxicity in pretreated and treatment-naive advanced/metastatic *RET* fusion-positive non-small-cell lung cancer (NSCLC). LIBRETTO-432 is a global, randomized, double-blind, phase III trial evaluating selpercatinib versus placebo in stage IB-IIIA, *RET* fusion-positive NSCLC, previously treated with definitive surgery or radiation; participants must have undergone available anti-cancer therapy (including chemotherapy or durvalumab) or not be suitable for it, per investigator's discretion. The primary end point is investigator-assessed event-free survival (EFS) in the primary analysis population (stage II-IIIA *RET* fusion-positive NSCLC). Key secondary end points include EFS in the overall population, overall survival, and time to distant disease recurrence in the central nervous system.

Plain language summary: Selpercatinib is approved in multiple countries for the treatment of advanced or metastatic *RET*-altered lung cancers. Selpercatinib has shown promising efficacy and safety results in patients with advanced/metastatic *RET* fusion-positive NSCLC. This is a summary of the LIBRETTO-432 study which compares selpercatinib with placebo in patients with earlier stages (stage IB-IIIA) of *RET* fusion-positive NSCLC, who have already undergone surgery or radiotherapy and applicable adjuvant chemotherapy. This study is active and currently recruiting new participants. This trial will evaluate how long people live without evidence of cancer recurrence, both during and after treatment. Side effects will also be evaluated in this study.

Clinical Trial Registration: NCT04819100 (ClinicalTrials.gov)

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Lung cancer is the leading cause of cancer death worldwide, with 2 million new cases and 1.76 million deaths in 2018 [1]. The majority (80–90%) of lung cancers are non-small-cell lung cancer (NSCLC) [2], and approximately 30% of patients with NSCLC present with early-stage (IB-IIIA) disease [3]. The standard of care for these patients is definitive locoregional therapies with or without adjuvant therapy, followed by surveillance until disease progression

or recurrence [4]. The 5-year overall survival (OS) rate has been 60–74% for stage I, 47–55% for stage II and 38% for stage IIIA NSCLC [5]. Although adjuvant therapy is important for the treatment of systemic micro-metastases, the OS benefit of adjuvant chemotherapy is modest [6], and up to two-thirds of patients develop recurrence and eventually die of metastatic disease [7–10]. Thus, there is a need for therapies that can further delay disease recurrence or progression following definitive treatment and currently available adjuvant therapy.

Atezolizumab after adjuvant chemotherapy has been reported to prolong disease-free survival (DFS) in patients with resected PD-L1 positive stage II–IIIA NSCLC [11]. Additionally, in patients with resectable NSCLC, neoadjuvant nivolumab plus chemotherapy resulted in significantly longer event-free survival (EFS) and a higher percentage of patients with a pathological complete response than chemotherapy alone [12]. Although both treatment options have entered the standard of care in various countries, the benefit to patients with driver mutations is unclear. Patients with *EGFR*- or *ALK*-positive NSCLC were excluded from the aforementioned studies, and efficacy in patients with other driver tumor genomic alternations, such as *RET*, has not been reported. The efficacy of single-agent immunotherapy in patients with advanced *RET* fusion-positive NSCLC is known to be modest [13]. Therefore, there remains a need for therapies that treat driver alterations in the adjuvant setting.

While many adjuvant trials focus on participants following complete surgical resection, an unmet medical need exists for patients with early-stage disease who cannot or do not undergo resection and who instead receive definitive radiotherapy with a curative intent. For the 30–50% of stage IB–IIIA patients with NSCLC who do not undergo resection due to tumor or patient characteristics, standard treatment is definitive radiotherapy, with OS outcomes comparable to definitive surgery, but a higher rate of locoregional recurrence [9]. After definitive radiotherapy for unresected stage I and II disease, standard care is surveillance [4].

In the metastatic setting, patients with NSCLC who have driver tumor genomic alterations, such as *EGFR, ALK*, and *ROS1*, that can be matched with a targeted agent (e.g., osimertinib, alectinib and crizotinib) have demonstrated improved outcomes relative to patients who receive non-targeted therapy such as chemotherapy [14]. Recently, results from the adjuvant ADAURA trial with the EGFR tyrosine kinase inhibitor osimertinib indicated targeted therapy can improve outcomes in patients with early-stage disease. In the intent-to-treat population (stage IB-IIIA patients who had undergone complete resection with negative margins with or without adjuvant chemotherapy), osimertinib significantly improved DFS compared with placebo, with a hazard ratio of 0.20 (95% CI: 0.15–0.27) [15]. These data are consistent with the principles of oncogene addiction. Tumors with driver alterations depend on the signaling pathway of that alteration to survive and propagate, and thus may benefit from driver alteration-specific therapy, regardless of disease stage [15]. Although OS data remain immature, the degree of DFS benefit has been considered sufficient to change the standard of care. Adjuvant targeted therapy has been investigated in additional completed and ongoing clinical trials, such as the ADJUVANT-CTONG1104, EVAN, EVIDENCE, ALINA and ALCHEMIST trials [16]. Prior to LIBRETTO-432, there was no clinical study examining the use of a selective RET inhibitor as adjuvant therapy in *RET* fusion-positive NSCLC.

RET Fusion-Positive NSCLC

Activating *RET* rearrangements and mutations have been implicated in the pathogenesis of several human cancers including NSCLC, poorly differentiated thyroid cancers, and medullary thyroid cancers [17]. *RET* gene fusions have been identified in 1–2% of patients with NSCLC, of both Asian and European descent [18–20]. *RET* fusion-positive lung cancer is associated with identifiable clinicopathologic characteristics, including younger age and never-smoker status, with relatively equal sex distribution, early lymph node metastases, poor differentiation and a solid predominant subtype. *RET* alterations are established oncogenic drivers in patients with NSCLC, are generally mutually exclusive with other driver alterations (e.g., *EGFR* and *ALK* fusion), and lead to classic dependency of tumor cells on the activated oncogenic kinase [20].

Although patients with *RET* fusion-positive NSCLC have an identifiable oncogenic driver, in the adjuvant setting these patients receive the same standard of care treatments as patients with NSCLC who do not have a driver alteration. As described above, this treatment includes definitive therapy, with or without platinum-based chemotherapy, followed by surveillance until disease recurrence or progression.

Selpercatinib

Selpercatinib is a first-in-class, highly selective and potent RET kinase inhibitor with central nervous system (CNS) activity [21,22]. Selpercatinib has been approved in multiple countries for the treatment of advanced or metastatic *RET*-altered lung cancers.

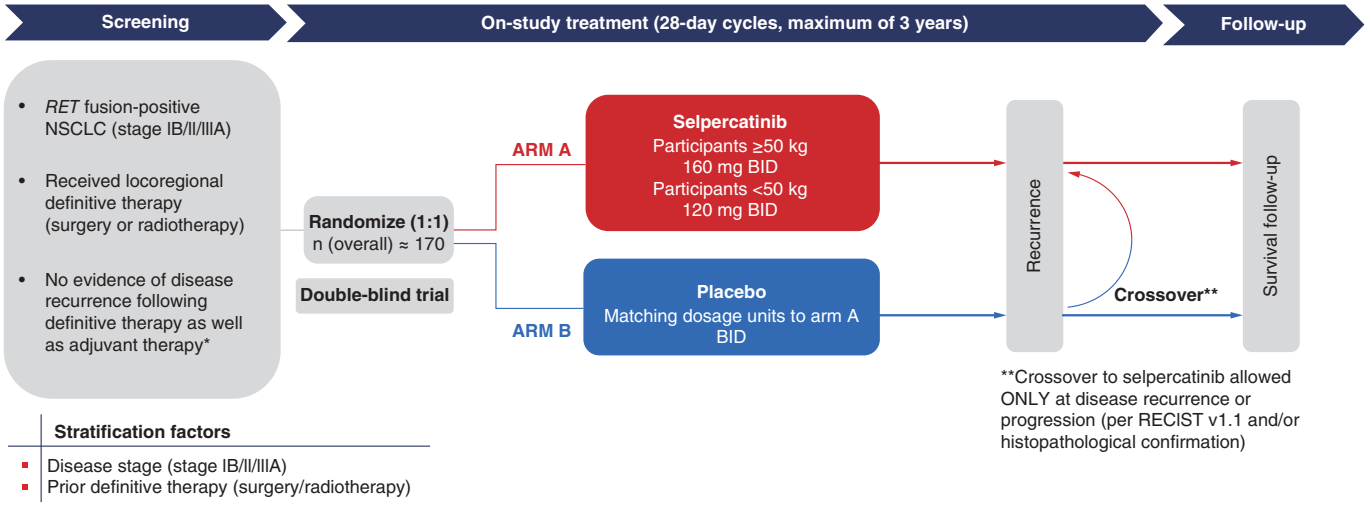

Figure 1. LIBRETTO-432 study design.
*Participants must have undergone available anti-cancer therapy (including chemotherapy or durvalumab) or not be suitable for it, based on the investigator's discretion.
BID: Twice daily; N: Number of participant; NSCLC: Non-small-cell lung cancer; RECIST v1.1: Response Evaluation Criteria in Solid Tumors Version 1.1.

There is compelling activity of selpercatinib in patients with metastatic *RET* fusion-positive NSCLC, a manageable safety profile that supports a long duration of therapy [23], and a growing body of evidence suggesting targeting the underlying driver of disease can improve outcomes regardless of disease stage [24–26]. Given its activity in the metastatic setting, it is hypothesized treatment with selpercatinib will also improve outcomes in patients with early stage (i.e., stage IB-IIIA) *RET* fusion-positive NSCLC following completion of therapies with a curative intent (e.g., definitive locoregional therapy, surgery, radiotherapy) and applicable adjuvant chemotherapy, as determined by the investigator.

The LIBRETTO-432 clinical trial

LIBRETTO-432 (also referred to as J2G-MC-JZJX [JZJX]) is a global, multicenter, randomized (1:1), double-blind, phase III study (NCT04819100) comparing the efficacy and safety of selpercatinib to placebo in participants with *RET* fusion-positive, stage IB-IIIA NSCLC following completion of therapies with a curative intent (e.g., definitive locoregional treatment, such as surgery or radiotherapy, and applicable adjuvant chemotherapy, as determined by the investigator). This study is active and recruiting participants, with planned enrollment at approximately 170 sites and 30 countries.

Based on the efficacy, safety and tolerability of selpercatinib in patients with metastatic *RET* fusion-positive NSCLC, this study aims to demonstrate safety and efficacy of selpercatinib in participants with earlier stages of *RET* fusion-positive NSCLC. A placebo-controlled trial is appropriate given the patients who are being enrolled will have completed all standard of care treatments and will be in a surveillance period; of note, participants randomized to the placebo arm may be eligible to receive open-label selpercatinib should the cancer recur or progress. Regardless of treatment assignment, study participants will receive regularly scheduled clinical and laboratory assessments to detect and manage treatment-emergent adverse events while receiving study intervention, including those receiving crossover treatment. Multiple patient-focused outcomes will be collected in all participants to contextualize adverse events and participant experience. As described in earlier sections, the potential benefit of adjuvant selpercatinib is expected regardless of the modality of prior definitive therapy being surgery or radiotherapy and regardless of prior immunotherapy exposure.

Study design

Approximately 170 participants with stage IB-IIIA NSCLC will be randomized (1:1) to receive either selpercatinib (arm A) or placebo (arm B) (Figure 1). Study participants must have an activating *RET* gene fusion in tumor based on PCR or next-generation sequencing. Results in blood based on next-generation sequencing are also acceptable. Only patients known to have *RET* fusion-positive NSCLC proceed with screening for the study. The

Box 1. Study objectives.

Primary
- To compare EFS of participants in the primary analysis population with stage II-IIIA *RET* fusion-positive NSCLC treated with selpercatinib versus placebo.

Secondary
- To compare EFS of participants in the overall population with stage IB-IIIA *RET* fusion-positive NSCLC treated with selpercatinib versus placebo.
- To compare other efficacy outcomes achieved with selpercatinib versus placebo in the primary analysis and overall populations.
- To evaluate the safety and tolerability of selpercatinib versus placebo in the primary analysis and overall populations.
- To assess/evaluate performance of *RET* tests from investigator-identified laboratories compared with a single Lilly-designated *RET* test.
- To compare onset or worsening of NSCLC symptoms in participants treated with selpercatinib versus placebo.
- To compare physical functioning in participants treated with selpercatinib versus placebo.

EFS: Event-free survival; Lilly: Eli Lilly and Company; NSCLC: Non-small-cell lung cancer.

RET gene fusion result should be generated by a Lilly designated laboratory using the Oncomine™ Dx Target Test or from an investigator-identified laboratory with certification that meets local regulations (as conducted before screening). Study participants will be stratified by disease stage (stage IB/II/IIIA) and prior definitive therapy (surgery/radiotherapy). The on-study treatment phase will begin at randomization and continue until disease progression, development of unacceptable toxicity, start of a new anticancer therapy, withdrawal of consent, death, or study completion, for a maximum of 3 years. Participants randomly assigned to arm B who discontinue treatment for disease recurrence or progression will be eligible for crossover to selpercatinib. Crossover treatment will be optional at the discretion of the investigator and the consent of the participant. The post-treatment phase will consist of short-term follow-up that will begin when the patient and investigator decide the patient will no longer continue study therapy, until completing a safety assessment (28 ± 7 days) after receiving the last dose of study treatment. Long-term follow-up begins when short-term follow-up is complete, and will continue until death, study withdrawal, the patient is lost to follow-up, or final study completion. Information related to patient survival, post-study anticancer therapy, and disease progression will be collected until death or study completion.

Objectives & end points

The study objectives are detailed in Box 1. The primary analysis population is defined as participants with stage II-IIIA *RET* fusion-positive NSCLC. The overall population is defined as participants with stage IB-IIIA *RET* fusion-positive NSCLC. The primary end point is investigator-assessed EFS in the primary analysis population.

Investigator-assessed EFS in the overall population (stage IB-IIIA) is a gated (alpha-controlled) secondary end point. The other gated secondary end point is OS. The non-gated secondary efficacy end points include blinded independent central review (BICR)-assessed EFS, time to distant disease recurrence in the CNS assessed by investigator and BICR, and progression-free survival on the next line of treatment (PFS2).

Key eligibility criteria

Key eligibility criteria are summarized in Table 1. Eligible participants must have histologically confirmed stage IB, II, or IIIA NSCLC with staging according to the Tumor, Node, Metastasis staging system for lung cancer (8th edition), and have an Eastern Cooperative Oncology Group Performance Status of 0–1. Participants are excluded from the study for the following criteria: presence of additional validated oncogenic drivers in NSCLC, evidence of small cell lung cancer, or clinical or radiologic evidence of disease recurrence, or progression following definitive therapy. Of note, prior immunotherapy, either in the neoadjuvant or adjuvant setting, is not excluded by this study.

Dose & schedule of therapy

Participants in arm A weighing ≥50 kg will receive oral selpercatinib 160 mg twice daily (BID). Participants weighing <50 kg will receive oral selpercatinib 120 mg BID. Participants in arm B will receive matching placebo BID. Dosing will last for up to 3 years in continuous 28-day cycles. Participants randomly assigned to arm B who discontinue treatment due to disease recurrence or progression may be eligible for crossover to selpercatinib.

Table 1. Key eligibility criteria for LIBRETTO-432.

Inclusion criteria	Exclusion criteria
Stage IB-IIIA *RET* fusion-positive NSCLC • Histologically confirmed stage IB, II, or IIIA NSCLC, staging according to the Tumor, Node, Metastasis staging system for lung cancer (8th edition) • Received definitive locoregional therapy with curative intent (surgery or radiotherapy) for stage IB, II, or IIIA NSCLC • Participants must have undergone the available anti-cancer therapy (including chemotherapy or durvalumab) or not be suitable for it, based on the investigator's discretion **Patient characteristics** • Adequate organ function • ECOG performance status score of 0 or 1 ***RET* alteration** • Activating *RET* gene fusion in tumor based on PCR or NGS	**Medical conditions** • Additional oncogenic driver mutations of NSCLC (e.g., *ALK* fusion, or activating mutations of *EGFR*) • 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 (non-infectious) pneumonitis that required steroids • Clinically significant active cardiovascular disease or history of myocardial infarction within 6 months prior to planned start of study treatment or prolongation of the QT interval corrected for heart rate using QTcF >470 msec on more than 1 ECG obtained during the baseline period • Active, uncontrolled, systemic bacterial, viral or fungal infection that requires treatment or have serious ongoing intercurrent illness that is not controlled, despite optimal treatment • 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 **Prior/Concomitant Therapy** • Prior treatment with a selective RET inhibitor (e.g., selpercatinib or pralsetinib) • Taking a concomitant therapy • Known to cause QTc prolongation • Systemic anti-cancer therapy (in addition to study treatment)

ECG: Electrocardiogram; ECOG: Eastern Cooperative Oncology Group; NGS: Next-generation sequencing; NSCLC: Non-small-cell lung cancer; QTcF: Corrected QT interval using the Fridericia's formula.

Efficacy evaluations

To evaluate EFS, radiographic tumor assessments will be performed per Response Criteria in Solid Tumors version 1.1 (RECIST 1.1). Computed tomography scans of the chest and abdomen will be obtained beginning at Week 12 and magnetic resonance imaging scans of the brain beginning at Week 24, with imaging continuing every 24 weeks until Year 5, at which time imaging will be performed annually. EFS is defined as the time from randomization until either: locoregional disease recurrence/progression with histopathological confirmation, distant disease recurrence/progression per RECIST 1.1 or histopathological confirmation, or death from any cause. Local or regional recurrence or progression is defined as recurrence or progression in the area of the tumor bed, hilum, or mediastinal lymph nodes. Loco-regional recurrence progression of the disease is required to be cytologically/histologically confirmed. Distant recurrence or progression must be diagnosed by radiological examination or histopathological confirmation when the metastatic lesion is easily accessible for biopsy.

Safety evaluations

Safety evaluations including electrocardiogram and physical examination with vital signs will be assessed on Days 1 and 8 of Cycle 1, Day 1 of Cycles 2–6, and as clinically indicated after Cycle 6; clinical laboratory testing including hematology, clinical chemistry, and hepatic safety monitoring will be assessed at minimum on Day 1 of each cycle, and as clinically indicated. Adverse events will be assessed continuously throughout the study duration.

Statistical analyses

Baseline characteristics, including patient demographics, baseline disease characteristics, prior anticancer therapies and pre-existing conditions will be summarized using descriptive statistics (i.e. number of participants, mean, median, standard deviation, minimum, and maximum) for continuous variables and frequencies (percentages) for categorical variables.

The primary end point is investigator-assessed EFS in the primary analysis population (participants with stage II-IIIA). EFS will be described using Kaplan–Meier method and comparison between treatment arms will be assessed using the stratified Cox regression model and log-rank test. Investigator-assessed EFS in the overall population (patients with stage IB-IIIA), OS, BICR-assessed EFS, distant disease recurrence in the CNS, and PFS2 will be evaluated with stratified Cox regression models and log-rank tests to compare between treatment arms.

Conclusion

The LIBRETTO-432 phase III trial outlined here will evaluate the efficacy and safety of adjuvant selpercatinib versus placebo in participants with *RET* fusion-positive, stage IB-IIIA NSCLC following completion of definitive

radiotherapy or surgery with a curative intent, and other adjuvant therapy if indicated. The findings of this study will help define the benefit of selpercatinib used as adjuvant therapy in patients with *RET* fusion-positive NSCLC. Given the compelling activity of selpercatinib in patients with metastatic, *RET* fusion-positive NSCLC, a manageable safety profile, and a growing body of evidence that targeting the underlying driver of disease can improve outcomes regardless of stage of disease [24–26], it is hypothesized that treatment with selpercatinib during the surveillance period following completion of therapies with a curative intent and applicable adjuvant chemotherapy will improve outcomes for patients with stage IB-IIIA *RET* fusion-positive NSCLC.

Executive summary

Background

- Non-small-cell lung cancer (NSCLC) accounts for approximately 80% to 90% of all lung cancers.
- Standard of care treatment, definitive locoregional therapies with or without adjuvant therapy, followed by surveillance until disease progression or recurrence, does not prevent recurrence in two-thirds of patients with *RET* fusion-positive, stage IB-IIIA NSCLC.
- Patients with stage IB-IIIA *RET* fusion-positive NSCLC represent a population with a high unmet need of a new treatment.

Selpercatinib

- Selpercatinib is a highly selective and potent RET inhibitor with CNS activity.
- Selpercatinib is approved in multiple countries for the treatment of metastatic *RET* fusion-positive NSCLC.
- In the LIBRETTO-001 phase 1/2 trial, selpercatinib treatment demonstrated clinically meaningful responses and sustained antitumor activity with a manageable toxicity profile as a selective inhibitor of activating *RET* aberrations, including *RET* fusions.

LIBRETTO-432 study

- This global, randomized, double-blind, phase III LIBRETTO-432 trial, will evaluate selpercatinib versus placebo in participants with *RET* fusion-positive stage IB-IIIA NSCLC following completion of therapies with a curative intent (NCT04819100).

Conclusion

- The results of this important trial will determine whether selpercatinib will improve outcomes in patients with stage IB-IIIA *RET* fusion-positive NSCLC.

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 and 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 all participants involved.

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