

LIBRETTO-531: a phase III study of selpercatinib in multikinase inhibitor-naïve *RET*-mutant medullary thyroid cancer

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Selpercatinib is a first-in-class, highly selective and potent, central nervous system-active *RET* kinase inhibitor. In the phase I/II trial, selpercatinib demonstrated clinically meaningful antitumor activity with manageable toxicity in heavily pre-treated and treatment-naïve patients with *RET*-mutant medullary thyroid cancer (MTC). LIBRETTO-531 (NCT04211337) is a multicenter, open-label, randomized, controlled, phase III trial comparing selpercatinib to cabozantinib or vandetanib in patients with advanced/metastatic *RET*-mutant MTC. The primary objective is to compare progression-free survival (per RECIST 1.1) by blinded independent central review of patients with progressive, advanced, multikinase inhibitor-naïve, *RET*-mutant MTC treated with selpercatinib versus cabozantinib or vandetanib. Key secondary objectives are to compare other efficacy outcomes (per RECIST 1.1) and tolerability of selpercatinib versus cabozantinib or vandetanib.

Plain language summary: Selpercatinib (also known by the brand name Retevmo[®]/Retsevmo[®]) is a new treatment available in multiple countries for people with advanced or metastatic *RET*-mutant medullary thyroid cancer (MTC). Thyroid cancer starts in your thyroid gland and may spread or metastasize to other parts of the body, including lungs, bones, and occasionally the brain, which means the cancer is likely to be advanced. Advanced thyroid cancer can be driven by a gene in your body, one of which is *RET*. This is a summary of the LIBRETTO-531 study which compares selpercatinib, which is a strong and selective inhibitor of *RET*, with two approved drugs, cabozantinib and vandetanib. Patients with advanced or metastatic *RET*-mutant MTC who have not already received treatment with kinase inhibitors are being enrolled. This trial will evaluate how long people during and after treatment live with the disease without it getting worse. Selpercatinib may affect both healthy cells and tumor cells, which can result in side effects, which will also be evaluated in this study. This study is active and currently recruiting new patients.

Clinical Trial Registration: NCT04211337 (ClinicalTrials.gov)

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Medullary thyroid carcinoma (MTC) is a rare neuroendocrine tumor originating from parafollicular C cells [1]. MTC occurs in hereditary (25%) and sporadic forms (75%) [2,3]. Germline mutations in the rearranged during transfection (*RET*) proto-oncogene have been identified in hereditary conditions. For example, multiple endocrine

neoplasia (MEN) 2A and MEN2B [2,3]. Germline-activating *RET* mutations are found in 95% to 98% of hereditary MTC, and somatic *RET* mutations are present in more than half the cases of sporadic MTC [4,5]. In patients with advanced and progressive MTC, the prevalence of somatic *RET* mutations was found to be up to 86% [6].

The pathogenesis of MTC is closely related to the activation of the *RET* proto-oncogene, both in hereditary [7–10] and in sporadic cases [5,11,12]. The *RET* proto-oncogene encodes a transmembrane receptor tyrosine kinase that is constitutively activated through two primary mechanisms: point mutations that directly or indirectly activate the kinase, and chromosomal rearrangements leading to the fusion of *RET* to a 5' upstream partner [4,13,14]. Codon 634 mutation (p.C634R) in exon 11 is described as the most common substitution *RET* mutation in MEN2A syndrome patients [15]. Kinase domain mutation p.M918T is described as the most common mutation in MEN2B syndrome patients and in sporadic MTC patients [15]. *RET*-mutated MTC is associated with more aggressive disease and poorer prognosis, and consequently tumors in a majority of patients with metastatic MTC harbor *RET* mutations [3,5]. National Comprehensive Cancer Network guidelines recommend germline *RET* testing for all patients diagnosed with MTC and somatic *RET* testing in patients who are *RET* germline unknown or negative [16].

The clinical course of MTC is highly heterogeneous, varying from indolent tumors that remain unchanged for many years to aggressive cancers associated with high mortality [17,18]. Initial treatment of MTC depends on its clinical presentation. Although surgery can be curative for patients who present with localized disease, approximately 50% of all patients diagnosed with MTC develop recurrent disease [19]. Metastatic MTC remains incurable.

Until recently, only two multikinase inhibitors (MKI), cabozantinib and vandetanib, had received regulatory approval for advanced MTC (irrespective of the presence or absence of a *RET* mutation), with tumor response rates of 28 and 45% and progression-free survival (PFS) improvements (over placebo) of 7.2 and 11.2 months, respectively [20,21]. However, the efficacy of these MKIs is ultimately limited by incomplete inhibition of *RET*, significant toxicity from more potent inhibition of other targets (e.g., KDR/VEGFR2, EGFR, MET) and poor pharmacokinetics (i.e., significant drug accumulation and long half-life contributing to toxicity but not efficacy). As a result, most patients treated with these agents experience significant toxicities requiring dose interruptions, reductions (35% with vandetanib, 79% with cabozantinib), and/or treatment cessation (12% with vandetanib, 16% with cabozantinib) [20,21]. Additionally, some *RET* disease-causing variants are non-responsive to MKI therapy, in other words, nonspecific *RET* inhibitor therapy. Thus, highly selective *RET* inhibitors have been developed to improve the efficacy and safety profile compared with MKIs. Selpercatinib [22–24] and pralsetinib [25–27] are two currently approved small molecule *RET* inhibitors.

Selpercatinib

Selpercatinib is a first-in-class highly selective and potent *RET* kinase inhibitor with nanomolar potency against wild type *RET* and *RET* alterations including M918T, MKI resistance-associated V804M, and others [28]. Selpercatinib showed robust and durable efficacy with a favorable safety profile in patients with advanced or metastatic *RET*-driven treatment-naïve and previously treated cancers, irrespective of prior therapy [22,29–31]. Based on these findings, selpercatinib is approved in multiple countries for the treatment of *RET*-altered thyroid and lung cancers [24,32].

The phase I/II LIBRETTO-001 clinical trial demonstrated the safety and efficacy of selpercatinib in patients with *RET*-mutant MTC [22,23,33]. Treatment with selpercatinib resulted in a 69% objective response rate (ORR) (95% CI: 61–77%) by blinded independent central review (BICR) in patients previously treated with cabozantinib and/or vandetanib (n = 143) [33]. At a median follow-up of 17.5 months, 76% of responses were ongoing. In cabozantinib/vandetanib-naïve patients with *RET*-mutant MTC, treatment with selpercatinib resulted in a 71% ORR (95% CI: 62–80%) by BICR (n = 112). At a median follow-up of 9.3 months, 94% of responses were ongoing.

At the updated data-cut of March 2020, the majority of adverse reactions were grade 1 or 2. Grades 3–4 events occurring in ≥2% of patients included hypertension (20%), increased ALT level (7%), increased AST level (6%), diarrhea (4%), prolonged QT corrected interval (4%), headache (2%) and abdominal pain (2%). Discontinuation rates were low with 2% of patients discontinuing due to treatment-related adverse events. The safety profile was similar to the overall safety profile for all patients who received selpercatinib, regardless of tumor type.

The LIBRETTO-531 clinical trial

LIBRETTO-531 (also referred to as J2G-MC-JZJB [JZJB]) is a multicenter, open-label, randomized, controlled, phase III trial comparing selpercatinib to cabozantinib or vandetanib in patients with advanced/metastatic *RET*-

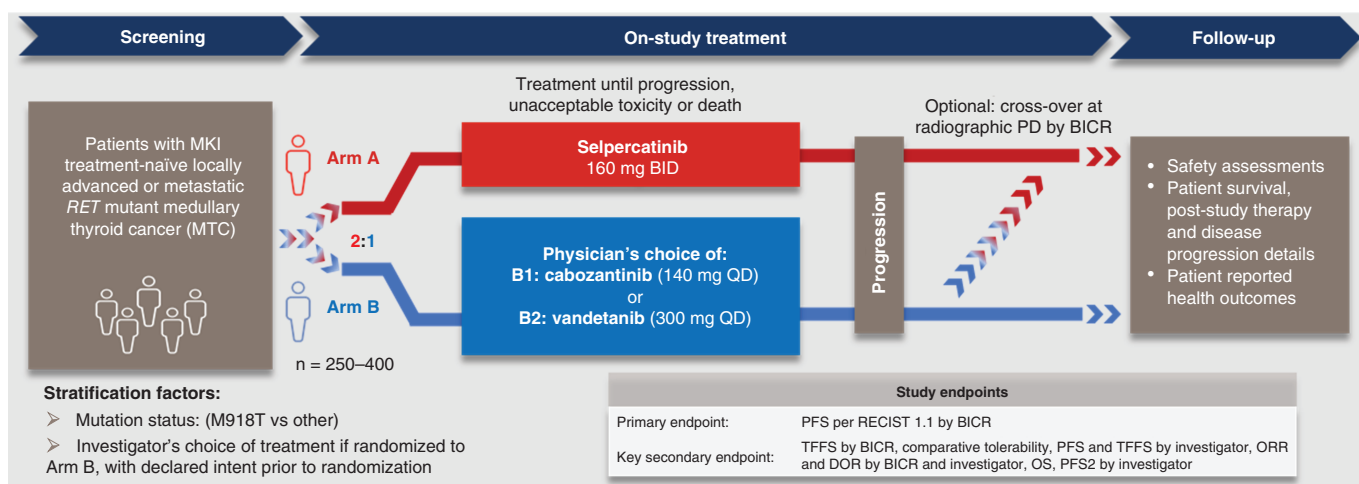


Figure 1. LIBRETTO-531 study design.

BICR: Blinded independent committee review; BID: Twice daily; DOR: Duration of response; MKI: Multikinase inhibitor; ORR: Objective response rate; OS: Overall survival; PD: Progressive disease; PFS: Progression-free survival; PFS2: Progression after the next line of therapy; QD: Once daily; RECIST 1.1: Response Evaluation Criteria in Solid Tumors version 1.1; TFFS: Treatment failure free survival, which incorporates radiographic PD, unacceptable toxicity (predefined by protocol) or death.

mutant MTC (NCT04211337), naïve to any prior kinase inhibitor therapy. This study is active and recruiting participants, with initial planned enrollment of 250 patients at approximately 160 sites in 21 countries. Sample size re-estimation based on comparative data will be conducted at the interim efficacy analysis. The total number of patients could be increased from 250 up to a maximum of approximately 400, depending on the results of the interim efficacy analysis.

Although the LIBRETTO-001 phase I/II trial demonstrated that selpercatinib can produce high rates of objective responses that are durable in both MKI pretreated and MKI-naïve MTC patients, it remains important to confirm these results and better understand the benefit of selpercatinib in the context of other available first-line treatments for advanced/metastatic MTC. This will be a key consideration for approval and reimbursement in many countries around the world. Furthermore, the study evaluates key secondary end points, including treatment failure-free survival (TFFS) and comparative tolerability, which could further characterize the potential benefits of selpercatinib relative to the current standard of care MKI inhibitors [34].

Study design

This phase III study is a head-to-head comparison of selpercatinib versus physician's choice of cabozantinib or vandetanib in patients with advanced or metastatic MTC. The study includes a screening phase, an on-study treatment phase with an optional crossover treatment phase (only arm B patients), and a post-treatment follow-up phase (Figure 1). During the screening phase, baseline patient characteristics and eligibility criteria will be assessed using medical history, physical exam, clinical labs and tumor evaluations. Prior to enrollment, the presence of the *RET* gene alteration must be confirmed in a tumor, germline DNA or blood sample. An unstained, archived tumor tissue sample in a quantity sufficient to allow for retrospective central analysis confirmation of *RET* mutation status is required. Patients will be stratified by *RET* mutation (M918T vs other) and intended treatment if randomized to arm B (cabozantinib vs vandetanib). The selection of cabozantinib or vandetanib for each eligible patient is required by the investigator prior to randomization. Treatment will continue until disease progression, development of unacceptable toxicity, the start of a new anticancer therapy, withdrawal of patient consent, death, or completion of the study. Patients who were randomized to arm B who have radiographic disease progression confirmed by BICR may be eligible for crossover to selpercatinib if they meet the eligibility criteria.

The post-treatment phase includes a short-term follow-up period that begins once the patient and investigator decide the patient will end study therapy. Long-term follow-up begins when the patient completes the (30 ± 7 days) short-term follow-up period and ends with the patient's death, upon study withdrawal, upon loss to follow-up, or

Table 1. Study objectives.	
Objectives	End points
Primary	
To compare PFS of patients with progressive, advanced, kinase inhibitor-naive, <i>RET</i> -mutant MTC treated with selpercatinib vs cabozantinib or vandetanib	<ul style="list-style-type: none"> • PFS by BICR
Secondary	
To compare other efficacy outcomes, based on RECIST 1.1 criteria, observed in patients with progressive, advanced, kinase inhibitor-naive, <i>RET</i> -mutant MTC treated with selpercatinib vs cabozantinib or vandetanib	<ul style="list-style-type: none"> • TFFS by BICR • TFFS by investigator • PFS by investigator • ORR by investigator and BICR • DOR by investigator and BICR • OS • PFS2 by investigator
To evaluate the safety and tolerability of selpercatinib compared with cabozantinib or vandetanib	<ul style="list-style-type: none"> • Safety per CTCAE v5.0 (including but not limited to): incidence and severity of TEAEs, SAEs, deaths, and clinical laboratory abnormalities
To compare the tolerability of selpercatinib vs cabozantinib or vandetanib	<ul style="list-style-type: none"> • Proportion of time with high side-effect bother based on FACT-GP5
To assess/evaluate performance of local <i>RET</i> laboratory tests compared with a single, central test	<ul style="list-style-type: none"> • <i>RET</i> mutation status
To assess the pharmacokinetics of selpercatinib in patients receiving selpercatinib	<ul style="list-style-type: none"> • Predose plasma concentrations at Day 8 of Cycle 1, and at Day 1 of Cycles 2 through 6
<p>BICR: Blinded independent committee review; DOR: Duration of response; FACT-GP5: Functional Assessment of Cancer Therapy general scale to assess overall side effect burden; MTC: Medullary thyroid cancer; ORR: Objective response rate; OS: Overall survival; PFS: Progression-free survival; PFS2: Progression after the next line of therapy; SAE: Serious adverse event; TEAE: Treatment-emergent adverse event; TFFS: Treatment failure free survival, which incorporates radiographic disease progression, unacceptable toxicity (predefined by protocol) or death.</p>	

upon study completion. To evaluate patient reported health outcomes (quality of life, patient functioning, health status, disease symptoms and toxicities) patient-reported surveys will be administered.

Objectives & end points

The study objectives are detailed in Table 1. The primary objective is to compare PFS (per RECIST 1.1) by BICR. PFS by BICR will act as a gatekeeper for the key secondary end point of TFFS by BICR, in other words, this key secondary end point will be tested conditionally on achieving a statistical significance for the primary end point. TFFS incorporates radiographic progressive disease, unacceptable toxicity (predefined by protocol) or death, of patients with progressive, advanced, kinase inhibitor naive, *RET*-mutant MTC treated with selpercatinib versus cabozantinib or vandetanib. TFFS was selected as this end point takes into account potential improvement in both efficacy and toxicity profile relative to comparator agents. Additional secondary end points are comparative tolerability, investigator-assessed PFS, investigator-assessed TFFS, investigator- and BICR-assessed ORR/duration of response, overall survival, investigator-assessed progression after the next line of therapy, safety/tolerability and pharmacokinetics of selpercatinib.

Key eligibility criteria

Key eligibility criteria are summarized in Table 2 and below. To be eligible for the trial, participants must have histologically or cytologically confirmed unresectable, locally advanced/metastatic MTC, a *RET* gene alteration, documented RECIST 1.1 progression within 14 months by BICR, measurable disease per RECIST 1.1, an Eastern Cooperative Oncology Group performance status of 0 to 2, a life expectancy of at least 3 months, adequate organ function, and the ability to swallow capsules. Exclusion criteria include: presence of additional validated oncogenic drivers in MTC, having received prior systemic treatment with kinase inhibitor(s), taking a concomitant medication that is known to cause QTc prolongation, or having symptomatic central nervous system involvement, or active cardiovascular disease.

Dose & schedule of therapy

Patients in Arm A will receive selpercatinib at a starting dose of 160 mg twice daily. Patients in Arm B will receive cabozantinib at a starting dose of 140 mg once daily (QD) or vandetanib at a starting dose of 300 mg QD. All treatments are administered orally, and a cycle is defined as 28 days in length, regardless of treatment arm assignment. Treatment will continue until radiographic disease progression, unacceptable toxicity, withdrawal of consent or death. Dosing and treatment durations for all intervention groups are outlined in Table 3.

Table 2. Key eligibility criteria for LIBRETTO-531.

Inclusion criteria	Exclusion criteria
<p>Locally advanced or metastatic MTC</p> <ul style="list-style-type: none"> Histologically confirmed, unresectable locally advanced or metastatic disease and no prior history of treatment with kinase inhibitors for advanced/metastatic disease <p>Patient characteristics</p> <ul style="list-style-type: none"> Age ≥ 12, where allowed Documented RECIST 1.1 progression within 14 months by BICR Measurable disease by RECIST 1.1 ECOG performance status of 0–2 Adequate organ function Able to swallow capsules Not pregnant/agreeable to highly effective birth control/no breastfeeding <p><i>RET</i> alteration</p> <ul style="list-style-type: none"> <i>RET</i> mutation identified via local NGS or PCR testing on germline DNA, tumor or blood Sufficient tissue for central analysis of <i>RET</i> mutation 	<p>Medical conditions</p> <ul style="list-style-type: none"> An additional validated oncogenic driver in MTC Symptomatic CNS 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 study treatment or prolongation of the QT interval corrected for heart rate using Fridericia's formula (QTcF) >470 msec on more than one ECG during screening Active uncontrolled systemic bacterial, viral or fungal infection or serious ongoing intercurrent illness, such as hypertension or diabetes, despite optimal treatment (screening for chronic conditions is not required) Clinically significant active malabsorption syndrome or other condition likely to affect gastrointestinal absorption of the study drug. Active hemorrhage or at significant risk for hemorrhage <p>Prior/Concomitant Therapy</p> <ul style="list-style-type: none"> Prior systemic treatment with kinase inhibitor(s) Are taking a concomitant medication that is known to cause QTc prolongation <p>Prior/Concurrent Clinical Study Experience</p> <ul style="list-style-type: none"> Have participated, within the last 30 days (4 months for studies conducted in Japan; 3 months for studies conducted in the UK), in a clinical study involving an investigational product
<p>BICR: Blinded independent committee review; CNS: Central nervous system; ECOG: Eastern Cooperative Oncology Group; MTC: Medullary thyroid cancer; NGS: Next-generation sequencing; PCR: Polymerase chain reaction; RECIST 1.1: Response Evaluation Criteria in Solid Tumors version 1.1.</p>	

Table 3. Doses and dosing schedule.

Intervention	Arm A (selpercatinib)	Arm B (investigator's discretion of B1: cabozantinib or B2: vandetanib)	
	Selpercatinib	Cabozantinib	Vandetanib [†]
Dose	160 mg	140 mg	300 mg
Schedule	BID continuously in 28-day cycles	QD continuously in 28-day cycles	QD continuously in 28-day cycles
Route	Oral	Oral	Oral
<p>[†] Starting dose of vandetanib for patients with creatinine clearance <50 ml/min is 200 mg QD. BID: Twice daily; QD: Once daily.</p>			

Efficacy evaluations

All patients are required to undergo imaging at baseline and subsequent serial imaging at disease assessment time points. Scans should be obtained within 28 days of baseline and every 8 weeks after treatment initiation through week 24, and every 12 weeks thereafter until progression, the start of a new anticancer therapy, death, or study completion. The BICR will conduct assessment of tumor response by RECIST 1.1.

Safety evaluations

For each patient, safety assessments including physical examination, vital signs, electrocardiogram and clinical laboratory tests will be evaluated at predefined intervals. Adverse events will be continuously evaluated throughout the duration of the study.

Conclusion

The LIBRETTO-531 phase III trial outlined here will evaluate selpercatinib versus cabozantinib or vandetanib in patients with advanced/metastatic *RET*-mutant MTC. The findings of this study will help further define the benefit of selpercatinib used as first-line therapy in patients with *RET*-mutant MTC, naive to prior kinase inhibitor therapy.

Executive summary

Background

- Medullary thyroid carcinoma (MTC) is a rare malignancy of the thyroid that accounts for 5–10% of all thyroid malignancies.
- Germline-activating *RET* mutations are found in 95–98% of hereditary MTC, and somatic *RET* mutations are present in >50% of the cases of sporadic MTC.
- Multikinase inhibitors (MKI) with anti-*RET* activity have limited efficacy due to incomplete inhibition and significant toxicity.

Selpercatinib

- Selpercatinib, a first-in-class highly selective and potent *RET* kinase inhibitor, is approved in multiple countries for the treatment of *RET*-altered lung or thyroid cancers.
- Selpercatinib has nanomolar potency against wild type *RET* and *RET* alterations including M918T, MKI resistance-associated V804M, and others.
- 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 pre-treated and treatment-naive patients with *RET*-mutant MTC.

LIBRETTO-531 study

- The global, multicenter, open-label, randomized, controlled, phase III LIBRETTO-531 trial, will evaluate selpercatinib versus cabozantinib or vandetanib in patients with MKI-naive locally advanced or metastatic *RET*-mutant MTC (NCT04211337).
- First ever randomized Phase III clinical trial in patients with MKI treatment naive *RET*-mutant MTC.

Conclusion

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

Supplementary data

An infographic accompanies this paper. To view or download this infographic in your browser please click here: <https://www.futuremedicine.com/doi/suppl/10.2217/fon-2022-0657>

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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