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CADTH Reimbursement Recommendation

Selpercatinib (Retevmo)

Indication: Adult patients with rearranged during transfection (*RET*) fusion-positive differentiated thyroid carcinoma with advanced or metastatic disease (not amenable to surgery or radioactive iodine therapy) following prior treatment with sorafenib and/or lenvatinib

Sponsor: Eli Lilly Canada Inc.

Final recommendation: Reimburse with conditions

CADTH

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Redactions: Confidential information in this document may be redacted at the request of the sponsor in accordance with the *CADTH Drug Reimbursement Review Confidentiality Guidelines.*

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Summary

CADTH

What Is the CADTH Reimbursement Recommendation for Retevmo?

CADTH recommends that Retevmo be reimbursed by public drug plans for the treatment of adults with advanced or metastatic rearranged during transfection (*RET*) fusion-positive differentiated thyroid cancer (DTC) if certain conditions are met.

Which Patients Are Eligible for Coverage?

Retevmo should only be covered to treat patients who have advanced or metastatic DTC (not amenable to surgery or radioactive iodine therapy) with the *RET* mutation and have had prior treatment with sorafenib and/or lenvatinib. Patients receiving Retevmo should be in relatively good health (i.e., have a good performance status, as determined by a specialist).

What Are the Conditions for Reimbursement?

Retevmo should only be reimbursed if it is prescribed by a specialist, the patients' cancer is *RET* positive, it is not given in combination with other anticancer drugs, and the price is reduced.

Why Did CADTH Make This Recommendation?

- Evidence from a clinical trial demonstrated tumour shrinkage in people with *RET* fusion-positive DTC treated with Retevmo.
- Retevmo may meet important patient-identified needs (i.e., another oral treatment option and potential to prolong survival).
- Retevmo is not considered cost-effective compared to best supportive care (BSC). Economic evidence suggests that a reduction in price of at least 89% would be needed for Retevmo to be considered cost-effective at a willingness-to-pay threshold of $50,000 per quality-adjusted life-year (QALY) in the indicated population.
- Based on public list prices, Retevmo will cost the public drug plans $4,845,673 over 3 years.
- The estimates of cost-effectiveness and price reduction are highly uncertain due to the quality of the evidence.

Additional Information

What is Differentiated Thyroid Cancer?

When cancer cells resemble healthy cells to some degree, it is called a “differentiated” cancer. Thyroid cancer is cancer that initiates in the thyroid gland. The most common types of thyroid cancer are papillary and follicular. People with thyroid cancer whose cancer cells have spread to other parts of the body, such as the lung or bones, likely have advanced or metastatic cancer.

Unmet Needs in Differentiated Thyroid Cancer

Patients with advanced or metastatic DTC have few treatment options available in Canada and not all respond to these treatments.

How Much Does Retevmo Cost?

Treatment with Retevmo is expected to cost between $11,172 and $14,896 per 28-day cycle, depending on patient weight.

Recommendation

The CADTH pan-Canadian Oncology Drug Expert Review Committee (pERC) recommends that selpercatinib be reimbursed for the treatment of adult patients with *RET* fusion-positive DTC with advanced or metastatic disease (not amenable to surgery or radioactive iodine therapy) following prior treatment with sorafenib and/or lenvatinib only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One ongoing, multicenter, open-label, phase I and II, single-arm, basket trial (LIBRETTO-001) demonstrated antitumour activity of selpercatinib among patients with *RET* fusion-positive DTC based on the response rates observed (e.g., objective response rate [ORR] = 78.9%; 95% confidence interval [CI], 54.4 to 93.9). Furthermore, although based on expert opinion, the results of the LIBRETTO -001 trial also suggest that treatment with selpercatinib may be associated with prolonged survival (overall survival [OS] = [redacted]; progression-free survival [PFS] = median of 20.1 months [range = 3.5 to 24.7+]). Selpercatinib treatment was associated with a manageable toxicity profile and clinical experts indicated that selpercatinib may offer an improved tolerability profile over current standard of care. Overall, pERC recognized that selpercatinib addresses a therapeutic need as there are currently no funded therapies available for patients with *RET* fusion-positive DTC who have progressed on lenvatinib.

Patients and clinicians expressed a need for effective treatments that improve survival and quality of life with fewer treatment-related harmful adverse effects. Given the totality of the evidence, pERC concluded that selpercatinib likely met some of the needs identified by patients and clinicians in terms of an additional oral treatment option, and potential improvement in survival with fewer treatment-related adverse effects.

The cost-effectiveness of selpercatinib relative to lenvatinib, sorafenib, or BSC is unknown due to the lack of comparative clinical effectiveness information, as well as limitations with the pharmacoeconomic model submitted by the sponsor. As such, a base-case cost-effectiveness estimate was unable to be determined in patients with *RET* fusion-positive DTC.

The committee considered exploratory analyses conducted by CADTH and determined that the incremental cost-effectiveness ratio compared to BSC was likely closer to $402,705 per QALY, and concluded that selpercatinib is not cost-effective at a $50,000 per QALY willingness-to-pay threshold. A price reduction of at least 89% would be required for selpercatinib to be considered cost-effective at this threshold. Due to the high degree of uncertainty around costs and comparative efficacy, additional price reduction may be warranted.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Treatment with selpercatinib	The LIBRETTO-001 trial demonstrated	Patients who are refractory to radioactive

Reimbursement condition	Reason	Implementation guidance
should be reimbursed in adult patients with *RET* fusion-positive DTC with advanced or metastatic disease (not amenable to surgery or radioactive iodine therapy) following prior treatment with sorafenib and/or lenvatinib.	antitumour activity based on the response rates observed with selpercatinib in patients with *RET* fusion-positive differentiated thyroid carcinoma with advanced or metastatic disease.	iodine therapy and/or unable to undergo surgery, patients with a contraindication to radioactive iodine therapy, and patients who are intolerant to first-line treatment with lenvatinib should also be considered for selpercatinib treatment; these patients should be screened for somatic *RET* rearrangements.
2. Patients must have good performance status.	Patients enrolled in the LIBRETTO-001 study had an ECOG PS of 0, 1, or 2.	pERC acknowledged that clinicians may consider using selpercatinib for patients with an ECOG PS > 2 at their discretion.
Renewal		
3. Selpercatinib should be renewed for patients who exhibit a response to treatment, as per physician discretion, and for whom treatment is tolerable.	Based on clinical expert opinion, response would be measured by response rate, PFS, HRQoL, and toxicity. Different measures of response are evaluated based on clinical grounds and radiological examination, general symptoms, and HRQoL.	Patients with documented disease progression could continue selpercatinib if they were deriving clinical benefit.
4. Patients should be assessed for treatment response every 8 to 12 weeks for the first 6 months to 1 year, then every 12 to 16 weeks or as per physician discretion.	Based on clinical group input, response to treatment should be assessed every 8 to 12 weeks for the first 6 months to 1 year, then every 12 to 16 weeks; however, they noted that specific intervals should not be mandated.	—
Prescribing		
5. Selpercatinib should be prescribed by clinicians with expertise in the management of thyroid cancer.	To ensure that selpercatinib is prescribed only for appropriate patients and adverse effects are managed in an optimized and timely manner.	—
6. Selpercatinib should not be reimbursed if given in combination with other systemic anticancer drugs.	Selpercatinib was administered as monotherapy in LIBRETTO-001 and has a Health Canada indication only as monotherapy.	—
Pricing		
7. A reduction in price.	The cost-effectiveness of selpercatinib compared to BSC is unknown. Based on CADTH exploratory analyses, a price reduction of at least 89% would be required to achieve an ICER of $50,000 per QALY relative to BSC. Due to the high degree of uncertainty in the evidence, additional price reduction may be warranted.	—

Reimbursement condition	Reason	Implementation guidance
Feasibility of Adoption		
8. Access to *RET* testing.	*RET* testing is needed to identify patients with *RET* fusion-positive differentiated thyroid carcinoma; however, this may not be equally accessible across all jurisdictions.	pERC agreed it would be desirable for jurisdictions to have *RET* testing available across Canada to identify the eligible patient population before treatment with selpercatinib.

BSC = best supportive care; DTC = differentiated thyroid carcinoma; ECOG PS = Eastern Cooperative Oncology Group Performance Status; HRQoL = health-related quality of life; ICER = incremental cost-effectiveness ratio; pERC = pan-Canadian Oncology Drug Review Expert Review Committee; PFS = progression-free survival; QALY = quality-adjusted life-year; *RET* = rearranged during transfection.

Discussion Points

- pERC discussed the available data for relevant end points (ORR, PFS, OS, duration of response [DOR]) and while there is uncertainty due to the limitations associated with a small sample size; an open-label, single-arm study design; and lack of statistical testing, pERC noted that the LIBRETTO-001 trial is still ongoing and highlighted that longer follow-up data are still desired. Ultimately, pERC felt that selpercatinib produced antitumour activity based on the response rates observed in the LIBRETTO-001 trial and that *RET* fusion-positive DTC is a rare disease with poor prognosis and a high unmet need in the second-line setting, as there are no funded treatment options following treatment with lenvatinib. As a result, pERC recommended reimbursement of selpercatinib in this patient population.
- pERC acknowledged that the impact on health-related quality of life (HRQoL) to treatment with selpercatinib is unknown since HRQoL was not evaluated in the population of *RET* fusion-positive DTC patients in the LIBRETTO-001 trial. As a result, there is uncertainty related to improvement in HRQoL. While pERC acknowledged clinical experts would like to use selpercatinib in the first-line setting for treatment-naive patients with advanced or metastatic *RET* fusion-positive DTC, pERC discussed that reimbursement of selpercatinib in the first-line setting and in patients younger than 18 years is out of scope of the Health Canada indication.
- pERC discussed the indirect treatment comparisons (ITCs) submitted by the sponsor: a naive comparison to evaluate the relative clinical efficacy of selpercatinib to [redacted] and placebo for the treatment of advanced *RET* fusion-positive DTC. The results of the ITCs stem from highly uncertain evidence due to limitations that impact the internal and external validity.
- pERC noted that the estimated budget impact was highly sensitive to assumptions related to the number of eligible patients.
- Clinical experts indicated that no new notable harms were identified in the LIBRETTO-001 trial and that adverse effects are anticipated to be clinically manageable.

Background

Thyroid cancer is 1 of the most commonly diagnosed cancers in Canada. Approximately 8,200 new cases of thyroid cancer will be diagnosed in Canadians in 2019 and about 230 people will die from it. For 2020, the incidence of thyroid cancer in Canada is estimated to be 23 per 100,000 patients, or about 8,600 new cases. Thyroid cancers arising from follicular cells include DTC (which includes papillary thyroid cancer [PTC], follicular thyroid cancer, and Hurthle cell cancer), poorly differentiated thyroid cancer, and anaplastic thyroid cancer. Among all types of thyroid cancer, DTC is the most common, accounting for more than 95% of cases. Tumours that are localized and well-differentiated are usually curable with total thyroidectomy or lobectomy, followed by postoperative treatment with radioactive iodine therapy for patients at high risk of persistent disease or disease recurrence after total thyroidectomy. Up to 30% of patients with DTC may have recurrence of disease and 60% of these recurrences occur within the first decade after initial therapy. In patients with primary or secondary radioiodine-refractory thyroid carcinoma, the prognosis becomes significantly worse (estimated median survival time of 2.5 to 3.5 years). The overall mortality rates 5 and 10 years after diagnosis of distant metastases are 65% and 75%, respectively. Early diagnosis and early appropriate surgical treatment are considered to positively affect the prognosis of these patients.

The treatment goals are aimed at curing the disease, improving survival, delaying disease progression, and improving HRQoL. In Canada, the only approved drug for progressive metastatic radioiodine-resistant thyroid cancer is lenvatinib; however, it is associated with frequent adverse effects that often result in dose reductions and sometimes drug discontinuation. Once patients progress on currently available therapies, or if lenvatinib has to be discontinued due to side effects, there are no further best options. Clinical experts consulted by CADTH consider that an ideal treatment for patients with DTC should reduce treatment-related toxicities while increasing survival and improving HRQoL.

Selpercatinib (Retevmo or LOXO-292), as 40 mg and 80 mg oral capsules, is a selective, competitive small molecule inhibitor of the *RET* receptor. Selpercatinib is indicated as monotherapy for the treatment of *RET* fusion-positive DTC in adult patients with advanced or metastatic disease (not amenable to surgery or radioactive iodine therapy) following prior treatment with sorafenib and/or lenvatinib. The sponsor's reimbursement request for this submission is the same as the indication.

Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- a review of 1 single-arm, open-label clinical study in patients with *RET* fusion-positive DTC
- patients' perspectives gathered by 2 patient groups, the CanCertainty Coalition, and a joint submission by the Canadian Cancer Society (CCS) with Thyroid Cancer Canada
- input from public drug plans and cancer agencies that participate in the CADTH review process
- 2 clinical specialists with expertise diagnosing and treating patients with thyroid cancer

- input relevant to the indication under review from clinician group: Ontario Health (Cancer Care Ontario) Head and Neck and Thyroid Cancer Drug Advisory Committee
- ongoing trials
- a review of the pharmacoeconomic model and report and ITCs submitted by the sponsor.

Stakeholder Perspectives

Patient Input

Input was obtained from 2 patient groups: CanCertainty Coalition and CCS with Thyroid Cancer Canada. At the time of the call for patient input, input from both medullary thyroid cancer (MTC) and DTC indications was collected. Therefore, input may include overall information for both MTC and DTC.

The CanCertainty Coalition is composed of more than 30 Canadian patient groups, caregiver organizations, and charities, as well as oncologists and cancer care professionals, and strives to improve the accessibility of cancer treatment. The group estimates that about 495 people in Canada are diagnosed with *RET* fusion-positive thyroid cancer each year (100 with *RET*-mutant MTC and 395 with *RET* fusion-positive PTC). The group states that a cancer diagnosis could lead to financial hardships, especially when patients do not have private health insurance. Even though multiple programs support individuals with high drug costs, there are administrative barriers in many provinces and territories. As a result, patients often face weeks of delay in starting cancer treatments. The CanCertainty Coalition group also cited potential issues associated with safety and the dispensing of take-home oral cancer treatments and recommended that these issues be considered during the review if the drug were to receive public funding.

CCS provides research, advocacy, and support to patients living with cancer. CCS's patient panels and networks provided survey results from patients with thyroid cancer. In addition, the Thyroid Cancer Canada patient network submitted survey results and 2 testimonials from its staff and board members who have had thyroid cancer. A total of 17 survey responses were collected across Canada between October 22, 2021, and November 10, 2021. None of the respondents had direct or indirect experiences with selpercatinib. Patients living with thyroid cancer referred to issues with daily work and life, such as fatigue, brain fog, mental health, body image, cognitive ability, concerns about cancer returning, and regulation of thyroid medications. Overall, 71% reported a financial barrier related to treatments, especially blood tests and drug costs. Patients responded that they would like to see improvements in new treatments regarding cost, access, and support to improve their quality of life.

Clinician Input

Input From Clinical Experts Consulted by CADTH

The clinical experts consulted by CADTH agreed that there is an unmet need for drugs that are better tolerated and with better safety profiles that can be used in patients with *RET* fusion-positive thyroid cancer, who, after surgery and radioiodine therapy, have very few options. Treatment goals are improving OS, PFS, and HRQoL by controlling symptoms such as diarrhea and flushing; minimizing adverse effects of treatments; and increasing work and life productivity. The experts considered that selpercatinib would be an appropriate therapy for

RET-driven thyroid malignancies, including using it as first-line therapy. There is currently only 1 approved and funded therapy (lenvatinib) in Canada, and the experts expect selpercatinib to cause a shift in the current treatment paradigm.

The clinical experts consider that patients with *RET* fusion-positive thyroid cancer that cannot be managed or cured by locoregional interventions (surgical interventions) and radioiodine therapy, and who are experiencing symptomatic disease progression or expected to experience symptomatic disease progression within the near future are the most likely to benefit from the use of selpercatinib. The experts did not identify specific baseline characteristics or variables of prognostic value and consider that is unlikely that patients' response will differ based on any disease characteristics (e.g., presence or absence of certain symptoms, stage of disease).

Clinical experts suggested that patients need to be screened for *RET* mutations and rearrangements with locally available comprehensive molecular tests should be available in institutions treating patients with thyroid cancer.

Patients should be assessed to measure evidence of response or stabilization of the disease, based on clinical grounds and radiological examination such as the Response Evaluation Criteria in Solid Tumours (RECIST) criteria, number and severity of symptoms, and PFS. All of these measurements are mostly aligned with clinical trial end points. Improvement in OS and PFS, and reduction in frequency and severity of symptoms (e.g., diarrhea) will be used to measure an adequate response approximately every 3 to 6 months. Deterioration of symptoms, functional status, radiological evidence of disease progression (together with other clinical criteria), and unacceptable toxicity from treatment are among the issues that could be used to decide to discontinue treatment on a case-by-case basis.

The experts stated that patients should only receive selpercatinib from clinicians with experience in the treatment of thyroid cancer in a specialty outpatient clinic setting. Targeted therapies can have significant toxicity and related harms.

Clinician Group Input

One clinician group input relevant to the indication under review was received: Ontario Health – Cancer Care Ontario Head and Neck and Thyroid Cancer Drug Advisory Committee gathered input from a total of 4 clinicians. Overall, the clinician group agreed with the input provided by the clinical experts consulted by CADTH.

The clinical group stated that PFS was the most important treatment goal. For radioactive iodine refractory DTC, lenvatinib is the only option currently funded and approved. Once patients have progressed on currently available therapies, there is no other option. Cancer Care Ontario explained that in patients with previously treatment experience, selpercatinib will fill a gap as an additional line of treatment. This opinion differed slightly from the clinical experts consulted by CADTH, in that they considered selpercatinib can be "line agnostic," and that the desirable effects of selpercatinib as first-line therapy can outweigh the limitations of the evidence. Selpercatinib as first-line therapy is not covered in the current Health Canada indication and is considered out of scope for this review.

The groups state that to identify eligible patients, *RET* testing is available in Ontario as part of reflex testing on radioactive iodine refractory DTC. Response to selpercatinib would be primarily measured by response rates while addressing other key outcomes such as PFS and toxicity. Clinically meaningful response to treatment can be determined by a reduction

in tumour burden (based on clinical assessment and/or imaging), cancer-related symptoms, and tumour marker levels. Treatment with selpercatinib should be reassessed every 8 to 12 weeks for the first 6 months to 1 year, then every 12 to 16 weeks thereafter, especially in patients who had initial responses, feel well, and have reduced carcinoembryonic antigen and/or calcitonin levels. However, specific intervals should not be mandated. In case of a lack of response and/or emergence of treatment-related toxicities, selpercatinib should be discontinued. As an oral, take-home cancer drug, selpercatinib is suitable for the community setting.

Drug Program Input

Input was obtained from the drug programs that participate in the CADTH reimbursement review process. The clinical experts consulted by CADTH provided advice on the potential implementation issues raised by the drug programs.

Table 2: Responses to Questions From the Drug Programs

Drug program implementation questions	Response
Relevant comparators	
The LIBRETTO-001 trial was an open-label, non-randomized, non-comparative phase I and II trial evaluating selpercatinib in patients with advanced solid tumours, including *RET* fusion-positive solid tumours, *RET*-mutant MTC, and other tumours with *RET* activation. There are currently no funded treatment options for patients with *RET* fusion-positive thyroid cancer. Only lenvatinib is currently funded for the treatment of advanced or metastatic RAI-refractory DTC. Patients are eligible to receive lenvatinib whether they have received prior therapy with a TKI or not. As there are no funded treatment options following treatment with lenvatinib, BSC is an appropriate comparator. There may be a small number of patients who receive sorafenib or another TKI in the first line and then go on to receive lenvatinib in the second line or vice versa. In these cases, lenvatinib or sorafenib could be a second-line comparator.	pERC acknowledged the input from the drug plans.
Considerations for initiation of therapy	
The requested reimbursement is for patients who have disease that is "not amenable to radio-active iodine therapy (RAI)." Does this equate to RAI-refractory disease? Does this include patients who are unable to receive RAI therapy due to a contraindication?	The clinical experts considered that for the denomination "not amenable to surgery or radio-active iodine," it is sensible to include patients who are refractory to RAI and/or unable to undergo surgery. pERC agreed that reimbursement of selpercatinib should include patients who are unable to receive RAI therapy due to a contraindication.
Should patients who are intolerant to first-line therapy with sorafenib or lenvatinib be eligible for treatment with selpercatinib?	Yes, patients in this category should be able to receive selpercatinib. Experts emphasized that sorafenib is not funded in Canada. pERC agreed that reimbursement of selpercatinib should include patients who are intolerant to first-line therapy with sorafenib or lenvatinib.

Drug program implementation questions	Response
Is the efficacy of selpercatinib expected to be similar across the subtypes of DTC?	The experts mentioned that efficacy should be similar across subtypes of DTC if they are selected according to the mutation status (i.e., according to the driver mutation). pERC agreed with the clinical experts.
Considerations for continuation, renewal, and/or discontinuation of therapy	
The LIBRETTO-001 trial evaluated patients via radiologic assessments every 8 weeks for 1 year and then every 12 weeks thereafter. In clinical practice, how will treatment response to selpercatinib be assessed?	pERC noted the clinical experts stated that patients should be assessed approximately every 3 to 6 months during follow-up visits, and clinicians will evaluate different measures of response (besides OS and PFS), based on clinical grounds and radiologic examinations. pERC also noted that the clinician group input indicated that response to selpercatinib would be primarily measured by response rates while addressing other key outcomes such as PFS and toxicity. According to the clinician group, clinically meaningful response to treatment can be determined by a reduction in tumour burden (based on clinical assessment and/or imaging), cancer-related symptoms, and tumour marker levels. Treatment with selpercatinib should be reassessed every 8 to 12 weeks for the first 6 months to a year, then every 12 to 16 weeks thereafter, especially in patients who had an initial response, feel well, and have reduced CEA and/or calcitonin levels. However, specific intervals should not be mandated. Ultimately, pERC felt patients should be assessed for treatment response every 8 to 12 weeks for the first 6 months to 1 year, then every 12 to 16 weeks or as per physician discretion.
In the LIBRETTO-001 clinical trial, patients with documented disease progression could continue on selpercatinib if they were deriving clinical benefit. What are the discontinuation criteria for selpercatinib?	Both clinical experts agreed that deterioration of symptoms, functional status, radiological evidence of disease progression (together with other clinical criteria), and unacceptable toxicity from treatment are among the issues commonly used in clinical practice to decide to discontinue treatment on a case-by-case basis. pERC felt that patients with documented disease progression could continue selpercatinib if they were deriving clinical benefit.
Considerations for prescribing of therapy	
Selpercatinib dose is based on weight. Under 50 kg: 120 mg orally twice daily 50 kg or greater: 160 mg orally twice daily	pERC acknowledged the recommended dosage as per the Health Canada product monograph and agreed with proceeding with the recommended dosage.
Generalizability	
Patients with an ECOG PS greater than 2 were excluded from the trial. Can patients with an ECOG PS > 2 be considered eligible for treatment?	pERC noted that the clinical experts stated that yes, patients should be eligible if they have an ECOG PS of 3 and above. pERC acknowledged that an ECOG PS of 3 could be a clinical condition resulting from underlying comorbidities. pERC highlighted that clinicians may consider using selpercatinib for patients with an ECOG PS > 2 at their discretion.

Drug program implementation questions	Response
Should patients currently being treated with lenvatinib or sorafenib in the second line who have not progressed, but are known or found to have a *RET* fusion, be eligible to switch to selpercatinib (assuming all other criteria are met)?	pERC noted that the clinical expert stated "yes, it would be reasonable to proceed, according to the clinical experts." While pERC agreed with the clinical experts, pERC expressed that patients can also remain on lenvatinib or sorafenib and switch to selpercatinib once they have progressed.
Care provision issues	
Selpercatinib is supplied as 40 mg capsules (60 capsules per bottle) and 80 mg capsules (60 or 120 capsules per bottle). There are multiple dosing schedules and potential for dose adjustments with selpercatinib. Current manufacturer packaging and storage requirements allow for flexible dispensing options (e.g., blister packaging of doses, using capsules from 1 bottle for multiple prescriptions, if necessary).	pERC acknowledged the recommended dosage per the Health Canada product monograph and noted the care provisions highlighted by the drug plans. pERC noted that patient education and counselling will be necessary to avoid over- or underdosing with selpercatinib.
Should all patients with DTC be tested for *RET* fusions? Can other driver mutations (e.g., TRK, BRAF, PI3K) coexist with *RET* fusion in DTC, or are they mutually exclusive?	pERC noted the clinical experts' response that all patients with metastatic RAI-resistant thyroid cancers and all patients with high risk of recurrence should be screened for somatic *RET* rearrangements and that driver mutations are usually mutually exclusive. pERC felt that all patients with metastatic RAI-resistant thyroid cancers, all patients with high risk of recurrence, as well as patients who are intolerant to first-line therapy should be screened for somatic *RET* rearrangements.
Selpercatinib has multiple significant drug-drug, drug-food, and drug-herb interactions requiring assessment and potential intervention or monitoring.	pERC discussed access to *RET* testing across Canada and agreed with the drug plan statement.
System and economic issues	
There is confidential pricing for lenvatinib.	pERC acknowledged that lenvatinib is a funded treatment option for adult patients.

BSC = best supportive care; CEA = carcinoembryonic antigen; DTC = differentiated thyroid carcinoma; ECOG PS = Eastern Cooperative Oncology Group Performance Status; MTC = medullary thyroid cancer; OS = overall survival; pERC = pan-Canadian Oncology Drug Review Expert Review Committee; PFS = progression-free survival; PI3K = phosphoinositide 3-kinases; RAI = radioactive iodine; *RET* = rearranged during transfixion; TKI = tyrosine kinase inhibitor; TRK = tropomyosin receptor kinase.

Clinical Evidence

Description of Studies

One clinical study, LIBRETTO-001, is included in this report. This is an ongoing, multicenter, open-label, phase I and II, single-arm study of oral selpercatinib (LOXO-292) in patients with advanced solid tumours, including *RET* fusion-positive solid tumours, MTC, and other tumours with *RET* activation. The focus of this CADTH report is on the *RET* fusion-positive DTC in adult patients with advanced or metastatic disease (not amenable to surgery or radioactive iodine therapy) following prior treatment with sorafenib and/or lenvatinib. The sponsor has used different cut-off dates, on June 17, 2019, for FDA and European Medicines Agency submissions, and December 16, 2019, to support the FDA submission with additional data; furthermore, data for a cut-off of March 30, 2020, is described. The main analyses of

efficacy are presented in this report with a data cut-off date of December 16, 2019, where the preplanned primary analysis set is described. An additional cut-off date of March 30, 2020, was provided by the sponsor and is also described in this report.

There were 2 main phases in the LIBRETTO-001 study. Phase I or dose escalation phase, and phase II or dose expansion phase. In both phases, patients were planned to be enrolled to 1 of 5 phase II cohorts to characterize the safety and efficacy of selpercatinib in specific *RET* abnormalities. This CADTH review focuses on the thyroid cancer population obtained from cohort 1.

For phase I, the primary objective of the study was to determine the maximum tolerated dose or recommended phase II dose of selpercatinib. For phase II, the primary objective was to assess, for each expansion cohort, the antitumour activity of selpercatinib by determining ORR. Of note, the LIBRETTO-001 trial was not specifically powered for this group of previously treated patients with *RET* fusion-positive thyroid cancer. Secondary objectives for phase II included best change in tumour size from baseline, DOR, central nervous system ORR, central nervous system DOR, time to any and best response, clinical benefit rate, PFS, OS, determination of the safety and tolerability of selpercatinib, and characterization of the pharmacokinetic properties. Exploratory objectives were pharmacokinetic and collection of patient-reported outcomes data to explore disease-related symptoms and HRQoL.

Patients in the previously treated *RET* fusion-positive thyroid cancer population with a cut-off date of December 16, 2020 (n = 19), had a mean age of 55.9 years, all patients were older than 18 years and nearly half of them (n = 10) were between 45 and 75 years. Most patients had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) status of 0 or 1, with only 2 (10.5%) presenting an ECOG PS of 2, with an average of 134 months since diagnosis. All patients had a history of metastatic disease. All 19 patients had received prior therapy; 8 patients had received lenvatinib, and 7 patients had received sorafenib.

Efficacy Results

The population of previously treated patients with *RET* fusion-positive thyroid cancer from LIBRETTO-001 (cut-off date of December 16, 2019), had a median duration of follow-up of [redacted] with a range that went from [redacted] Among the 19 patients, the rate of survival at 12 months or more was [redacted] of the population [redacted] At the March 30, 2020, data cut-off, [redacted] The OS at 1 year was [redacted] and remained consistent since the previous data cut-off.

For PFS (cut-off date of December 16, 2019), the median duration of follow-up was 13.7 months [redacted] and the median for PFS was 20.1 months [redacted] The duration of PFS of 12 months or more was [redacted] of the previously treated population. For the cut-off date of March 30, 2020, the duration of PFS was 20.07 months (range = 3.5 to 30.2+) among the 22 patients previously treated, with a median duration of follow-up of 16.49 months (interquartile range = 10.9 to 27.2 months). The rate of PFS of 12 months or more was seen in 15 patients (68.6%).

The percentage of patients reaching an ORR for the previously treated *RET* fusion-positive thyroid cancer population at the cut-off date of December 16, 2019, was 78.9% (95% CI, 54.4 to 93.9) or 15 of the 19 patients included. For the cut-off of March 30,2020, results for ORR were 77.3% (95% CI, 54.6 to 92.2).

At the cut-off of December 16, 2019, in the previously treated *RET* fusion-positive thyroid cancer population, the DOR had a median follow-up of 17.5 months [redacted] and the median DOR was 18.4 months [redacted] For the cut-off date of March 30, 2020, among the 22 patients included, the DOR had a median follow-up of 20.27 months (interquartile range = 12.6 to 25.4), and a median DOR of 18.43 months (range = 1.9 to 26.7 months). A total of [redacted] at the December 16, 2019, cut-off date reached a DOR for more than 12 months, while this occurred in 10 patients (58.8%) at the March 30, 2020, cut-off date.

Overall, ORR, PFS, and OS effect estimates were consistent between the December 16, 2019, and March 30, 2020, data cut-offs.

Harms Results

A total of [redacted] patients within the *RET* fusion-positive thyroid cancer population were included in the safety analysis for the cut-off date of December 16, 2019 (all patients so far included and who received at least 1 dose of selpercatinib). The most commonly reported adverse events (AEs) (> 20% of patients with at least 1 of these) included dry mouth, hypertension, diarrhea, constipation, fatigue, headache, peripheral edema, nausea, aspartate aminotransferase (AST) or alanine aminotransferase (ALT) elevations, and abdominal pain. At a later cut-off date of March 30, 2020, 42 patients were included in the safety analysis set. All 42 patients had at least 1 AE. Harm events were similar in distribution to the ones presented at the cut-off date of December 16, 2019. A total of [redacted] presented with 1 serious AE, and [redacted] a serious AE related to selpercatinib. Of the [redacted] No patient had fatal AEs that were considered related to the study drug.

Harms of special interest stated in the protocol for this review included diarrhea, bleeding, hepatotoxicity (AST or ALT increase), corrected QT prolongation, hypertension, and photosensitivity. Liver enzymes elevations occurred in [redacted], for AST and ALT respectively, as of the December 16, 2019, cut-off date. Hypertension was reported in [redacted] patients. Diarrhea was present in [redacted] patients at any point, and electrocardiogram QT prolongation occurred in | patients. For the cut-off date of March 30, 2020, additional safety data demonstrated similar results for hypertension (18 patients [42.9%]), diarrhea (16 [38.1%]), ALT increases (10 [23.8%]), AST increases (9 [21.4%]), electrocardiogram QT prolongation (4 [9.5%]), and [redacted]

Critical Appraisal

The main limitation from the LIBRETTO-001 study is its single-arm, open-label design. As such, the study is descriptive in nature and did not evaluate the primary or secondary end points (e.g., ORR, DOR, OS, PFS) formally with adjustments for multiple comparisons. These limitations stem from the single-arm design and lack of comparator groups and limit the ability to estimate with certainty the relative effects of treatment with selpercatinib. While acknowledging that the primary analysis was based on blinded, central Independent Review Committee, the open-label study design introduces bias due to measurements of subjective outcomes. The clinical experts and CADTH acknowledged that the uncertainty in this body of evidence in the context of scarcity of comparative (randomized) evidence reflects the challenges for conducting phase III studies in rare and indolent conditions such as *RET* fusion-positive thyroid cancer.

The small sample size for the previously treated *RET* fusion-positive thyroid cancer population (n = 19 and n = 22 in the December 2019 and March 2020 data cut-offs, respectively)

create uncertainty due to imprecision of the data. The small sample size also precludes the exploration or potential subgroup effects for the DTC populations. Overall, only descriptive analyses can be used at this time due to the lack of formal hypothesis testing in the previously treated *RET* fusion-positive thyroid cancer population. Furthermore, similarly due to the challenges commonly faced in rare and indolent conditions, no HRQoL outcomes were reported in this population. While the majority of the thyroid cancer population consists of DTC (PTC), few patients with anaplastic histologies were included, further contributing to the small size for the DTC population and uncertainty in the results in the DTC population.

The baseline characteristics of the population included in the LIBRETTO-001 study were overall representative of the population of patients with *RET* fusion-positive thyroid cancer seen in Canadian clinical practice. Age, ECOG PS status, initial disease stage, cancer history, *RET* mutation types, and prior therapies were similar to those expected in clinical practice. The clinical experts did not consider any of these variables to be a concern for applicability. Most patients had good baseline performance status with a small number of patients with an ECOG PS of 2 or higher, suggesting that the included population might be healthier than those in Canadian clinical practice; however, clinical experts did not consider it highly different from what is expected. All outcomes measured in the LIBRETTO-001 study and reported in this review (OS, ORR, PFS) are of clinical relevance and, according to the clinical experts, important for patients and well known and used by clinicians in Canada. The only concern was the limitation of the short follow-up for assessing longer periods of observations in those patients continuing the study and for assessing OS.

Indirect Comparisons

Description of Studies

The sponsor-submitted ITC conducted a systematic review and used a naive ITC to evaluate the relative clinical efficacy of selpercatinib to [redacted] and placebo for the treatment of advanced *RET* mutation positive thyroid cancer (DTC). Three outcomes were analyzed, including OS, PFS, and ORR.

Critical Appraisal

The sponsor-submitted ITC had several limitations, including not using an adjusted ITC due to patient incomparability between the selected trials, and the lack of data on several outcomes of interest, including OS, PFS and ORR, for some of the selected trials. Given these limitations and the available evidence, it is not possible to make any conclusions about the efficacy of selpercatinib versus [redacted] or placebo in *RET* fusion-positive DTC.

Other Relevant Evidence

CADTH identified 2 ongoing studies relevant to this submission; the LIBRETTO-321 (phase II trial conducted in China), and LIBRETTO-121 (phase I and II trial in pediatric population), none of which have available data at this time but are expected to be completed by 2025 and 2024, respectively.

Economic Evidence

Table 3: Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis PSM
Target population	Adults who had prior treatment with lenvatinib and/or sorafenib requiring second- or subsequent-line systemic treatment for advanced or metastatic *RET* fusion-positive DTC
Treatment	Selpercatinib
Submitted price	40 mg: $66.50 per oral capsule ($3,990 per 60 capsule bottle) 80 mg: $133.00 per oral capsule ($7,980 per 60 capsule bottle)
Treatment cost	$11,172 to $14,896 per 28 days
Comparator	BSC (consisting of monitoring and palliative care)
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	10 years
Key data source	Selpercatinib: Single-arm non-randomized LIBRETTO trial; naive comparison to BSC (informed by the SELECT trial)
Key limitations	• The comparative efficacy of selpercatinib on PFS and OS is unknown due to the lack of head-to-head or comparative evidence for selpercatinib to BSC. The sponsor's use of naive comparisons to inform the pharmacoeconomic model introduces unresolvable uncertainty into the economic evaluation. • The choice of a PSM to evaluate the cost-effectiveness of selpercatinib is inappropriate given the high level of uncertainty associated with the immature PFS and OS data from the LIBRETTO trial. The sponsor's model assumes that patients are at risk of death only after disease progression, which is not supported by data from LIBRETTO. • Adjustment of drug acquisition costs by dose intensity observed in the LIBRETTO trial biased the ICER in favour of selpercatinib. • The model lacks transparency and is inefficiently programmed. Numerous errors were identified in the analysis, and CADTH could not ensure that the model results were accurately calculated.
CADTH reanalysis results	• Due to the identified limitations regarding the lack of comparative clinical effectiveness, as well as issues with the submitted model (including poor modelling practices and structural limitations), the comparative clinical effectiveness, and, as a result, the cost-effectiveness, of selpercatinib relative to BSC is unknown. • CADTH conducted an exploratory analysis, which included adjusting for preprogression mortality and adopting appropriate estimates of drug acquisition costs. • In CADTH exploratory reanalyses, the ICER for selpercatinib is $402,705 per QALY ($405,245 per QALY, when including *RET* mutation testing) compared to BSC. Price reductions of at least 89% would be required for selpercatinib to be considered cost-effective at a willingness-to-pay threshold of $50,000 per QALY. The results of these reanalyses should be viewed only as exploratory given the previously mentioned limitations, and, given the extensive uncertainty associated with the comparative clinical effectiveness, a higher price reduction may be warranted.

BSC = best supportive care; DTC = differentiated thyroid carcinoma; ICER = incremental cost-effectiveness ratio; LY = life-years OS = overall survival; PFS = progression-free survival; PSM = partitioned survival model; QALY = quality-adjusted life-year; *RET* = rearranged during transfection.

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis: the number of patients eligible for selpercatinib is uncertain; the drug cost of selpercatinib was underestimated; and the sponsor's base case included a drug cost for BSC that conflicts with BSC costing in the cost-utility analysis.

CADTH reanalysis included assuming a dose intensity of 100% for selpercatinib. In the CADTH base case, the budget impact of reimbursing selpercatinib is expected to be $953,691 in year 1; $1,688,774 in year 2; and $2,203,208 in year 3; with a 3-year total of $4,845,673.

The estimated budget impact is highly sensitive to the proportion of patients with radioactive iodine refractory disease and the proportion of patients who receive first-line treatment.

pERC Information

Members of the Committee

Dr. Maureen Trudeau (Chair), Mr. Daryl Bell, Dr. Jennifer Bell, Dr. Matthew Cheung; Dr. Winson Cheung, Dr. Michael Crump, Dr. Leela John, Dr. Christian Kollmannsberger, Mr. Cameron Lane, Dr. Christopher Longo, Dr. Catherine Moltzan, Ms. Amy Peasgood, Dr. Anca Prica, Dr. Adam Raymakers, Dr. Patricia Tang, Dr. Marianne Taylor, and Dr. W. Dominika Wranik.

Meeting date: May 11, 2022

Regrets: None

Conflicts of interest: None