CADTH

CADTH Reimbursement Review

CADTH Reimbursement Recommendation

(Draft)

Selpercatinib (Retevmo)

Indication: As monotherapy for the treatment of metastatic RET fusion-positive non-small cell lung cancer (NSCLC) in adult patients

Sponsor: Eli Lilly Canada Inc.

Recommendation: Reimburse with Conditions

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CADTH

Selpercatinib (Retevmo - Eli Lilly Canada Inc.)

Therapeutic Area: RET fusion-positive non-small cell lung cancer

Recommendation

The CADTH pCODR Expert Review Committee (pERC) recommends that selpercatinib be reimbursed for the treatment of metastatic RET fusion-positive non-small cell lung cancer (NSCLC) in adult patients only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One ongoing phase 1/2 multicenter, multi-cohort, open-label study (LIBRETTO-001) demonstrated a clinically meaningful benefit of selpercatinib based on high objective response rates and prolonged duration of responses in adult patients with metastatic RET fusion-positive NSCLC who have not received prior systemic therapy (previously untreated) and who have received prior systemic therapy (had one or more prior therapies). As well, evidence of penetration in the blood-brain barrier was demonstrated by the high CNS response rates in RET fusion-positive NSCLC patients who were previously untreated or who had one or more prior therapies. pERC noted that the majority of patients experienced either improvement in quality of life or their quality of life remained stable, however definitive conclusions on health-related quality of life (HRQoL) outcomes could not be drawn due to the exploratory nature and potential for bias in the open-label single-arm study. There is an unmet need for this patient population given their poor prognosis, high symptom burden and high risk of CNS metastases. Selpercatinib addresses an important therapeutic need, as there are currently no targeted therapies available for RET fusion-positive NSCLC patients. Selpercatinib was associated with a manageable toxicity profile.

Patients expressed a need for treatments that improve NSCLC symptoms, improve quality of life, have a manageable side effect profile, allow patients to live longer and maintain their independence, and delay disease progression and improve long-term remission. Given the totality of evidence, pERC concluded that selpercatinib met the needs identified by patients in terms of high responses with prolonged durability and manageable side effect profile.

Given the uncertain comparative clinical evidence for selpercatinib and the lack of transparency and flexibility with the submitted model, CADTH was unable to derive a reliable base case estimation of cost-effectiveness. An exploratory analysis was performed; however, this retained the sponsor base estimates of relative effect and assumed no vial sharing for all comparator therapies, therefore, the results of this analysis are likely biased in favour of selpercatinib. Using the sponsor-submitted price for selpercatinib and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for selpercatinib was between $418,720 per quality-adjusted life-year (QALY) and $529,397 per QALY. This range was dependent on whether selpercatinib was used in patients who were previously untreated or who had one or more prior therapies and alongside the proportion of testing costs incurred by the public payer. Selpercatinib is therefore not cost-effective at a $50,000 per QALY willingness-to-pay (WTP) threshold for the Health Canada approved indication. A reduction in price is required.

Table 1. Reimbursement Conditions and Reasons

Reimbursement Condition	Reason	Implementation Guidance
Initiation		
1. Treatment with selpercatinib should be reimbursed when initiated in adult (≥ 18 years) patients with metastatic RET fusion-positive NSCLC who meet one of the following criteria: 1.1. for first-line treatment 1.2. after prior systemic therapy	Evidence from the LIBRETTO-001 trial demonstrated that selpercatinib was associated with high responses with prolonged durability in adult patients with metastatic RET fusion-positive non-small cell lung cancer who were previously untreated or who had one or more prior therapies.	—
2. Patient must have: 2.1. good performance status 2.2. clinically stable CNS disease or no brain metastases	Patients enrolled in the LIBRETTO-001 study had an ECOG performance status of 0, 1 or 2. Patients with symptomatic CNS metastases were excluded from the LIBRETTO-001 study. However, patients with brain metastases were eligible to enroll in the LIBRETTO-001 study if neurological symptoms and CNS imaging were stable and the steroid dose was stable for 14 days prior to the first dose of selpercatinib and no surgery or radiation had been performed for 28 days, and 14 days if stereotactic radiosurgery.	pERC acknowledged that clinicians may consider using selpercatinib for patients with an ECOG performance status >2 at their discretion, regardless of patient's previous treatment status.
Renewal		
3. Assessment of renewal of selpercatinib should be based on assessment of: 3.1. Response using radiographic evaluation (CT or MRI scans) every 8 to 12 weeks or as per physician discretion to investigate new symptoms or concerns of progression 3.2. Tolerability every 3 to 4 weeks or as per physician discretion	Based on clinical expert opinion, response to treatment in practice is usually assessed using radiographic assessment (CT or MRI scans) which are the same methods implemented in the LIBRETTO-001 trial. The standard frequency of assessment in clinical practice is to perform radiographic assessments every 8 to 12 weeks or sooner if patient reports new symptoms or if their physical findings indicate disease progression. Symptom severity and adverse event occurrence are generally performed in practice every 3 to 4 weeks in patients receiving oral targeted therapies.	pERC acknowledged that it may be reasonable to continue treatment with selpercatinib in the following instances: oligoprogression amenable to a local intervention to achieve disease control (i.e., radiation or surgical) or progression in the CNS amenable to brain-targeted therapy such as radiation.
Prescribing		
4. Selpercatinib should be prescribed by clinicians with expertise in the management of NSCLC	To ensure that selpercatinib is prescribed only for appropriate patients and adverse effects are managed in an optimized and timely manner.	—
5. Selpercatinib should not be given or reimbursed in	Selpercatinib was administered as monotherapy in LIBRETTO-001 and has a	—

Reimbursement Condition	Reason	Implementation Guidance
combination with other systemic anti-cancer drugs.	Health Canada indication only as monotherapy.	
Pricing		
6. A reduction in price	The cost-effectiveness of selpercatinib is highly uncertain. CADTH undertook a price reduction analysis that applied a more appropriate extrapolation of treatment benefit, however, was unable to change assumptions regarding drug wastage and treatment efficacy that bias in favour of selpercatinib. Based on the CADTH exploratory analysis, a price reduction of 70 to 93% is required for selpercatinib to be considered cost-effective at a $50,000 per QALY threshold. The price reduction required is dependent on whether the drug is used in patients who are previously untreated or who had one or more prior therapies, as well as the degree of incremental testing costs incurred by the public payer.	—
Feasibility of Adoption		
7. The feasibility of adoption of selpercatinib must be addressed.	At the submitted price, the magnitude of uncertainty in the budget impact must be addressed to ensure the feasibility of adoption, given the difference between the sponsor's estimate and CADTH's estimates. This is due to the potential increase in first-line systemic therapy use which was not addressed by the sponsor.	—
8. Access to RET testing	RET testing is needed to identify patients who have RET fusion-positive tumours, however, may not be equally accessible across all jurisdictions.	pERC agreed it would be desirable for jurisdictions to have RET testing available across Canada in order to identify the eligible patient population.

CNS = central nervous system; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; NSCLC = non-small cell lung cancer; RET = rearranged during transfection

Discussion Points

- pERC acknowledged the efficacy results of LIBRETTO-001 were derived from analysis sets that were not pre-defined in the original statistical analysis plan. However, given that these analysis sets were finalized prior to unblinding, it was unlikely that bias was introduced. Ultimately, pERC considered the high responses with prolonged durability observed in LIBRETTO-001 to be clinically meaningfully.
- pERC discussed the natural history of patients NSCLC and acknowledged that patients habouring RET-fusion gene may have poorer prognosis compared to the RET negative NSCLC population. pERC discussed that while systemic treatments are available for patients who are RET fusion-positive, selpercatinib has the potential to fulfil a gap as there are currently no targeted therapies available for RET fusion-positive NSCLC patients
- pERC discussed the prevalence of RET fusion-positive NSCLC and deliberated on the rarity of disease, which is a subset of NSCLC.
- pERC acknowledged the uncertainty in the HRQoL, overall survival (OS) and progression-free survival (PFS) data. pERC noted one ongoing phase III trial randomized, multicenter, open-label study comparing selpercatinib to platinum-based (carboplatin or cisplatin) and pemetrexed therapy with or without pembrolizumab in previously untreated patients with locally advanced/metastatic RET fusion-positive NSCLC that may address this evidence gap. However, the study is expected to be completed in 2025 and does not include patients who had one or more prior therapies.
- pERC discussed the indirect treatment comparisons (ITCs) submitted by the sponsor. pERC noted that the results of the ITCs appeared to favour selpercatinib for OS, PFS and ORR when compared to monotherapy or platinum-based chemotherapy and immunotherapy in previously untreated patients, and when compared to monotherapy or a combination of chemotherapy agents and immunotherapy agents, such as docetaxel, cabozantinib, atezolizumab or nivolumab in the prior systemic therapy group. However, significant uncertainty in the ITCs exists due to limitations that impact the internal and external validity despite the various adjustments made by the sponsor.
- pERC acknowledged patients' concerns that coverage of cancer therapies that are administered orally differs across jurisdictions. Concerns were raised regarding the financial and administrative barriers in accessing oral cancer treatments in some Canadian jurisdictions (Ontario and the Atlantic provinces).

Background

Lung cancer is the most frequently diagnosed cancer in Canada and the leading cause of cancer-related deaths in males and females,[1] with over 29,600 new diagnoses or patients diagnosed (12.5% new cases in males and 13.3% new cases in females) and 21,000 disease-related deaths (24.2% in males and 25.8% in females) projected in 2021.[1] The adjusted five-year net survival estimate in Canada for all forms of lung cancers is 22%[1] and the anticipated 5-year survival for patients with NSCLC is approximately 25%, and 7% for patients with stage IV disease.[2] Smoking is an established risk factor for developing lung cancer, accounting for over 72% of newly diagnosed cases in Canada.[1,3]

Several treatments are available in practice for patients without prior testing for RET fusion. The drug plans and clinician input group highlighted the following treatment strategies: In previously untreated patients, first-line treatment combinations with platinum plus pemetrexed and pembrolizumab is a preferred option for patients with PD-L1 expression <50%, and possibly in those with PD-L1 expression > 50% who are non-smokers, female, have increased disease or symptom burdens. Pembrolizumab alone is preferred for those with PD-L1 expression > 50%. For patients who progressed on prior systemic therapy, treatment options with platinum plus pemetrexed are preferred for those who had received pembrolizumab as first-line therapy. Anti-PD-L1 therapy, including pembrolizumab, nivolumab and atezolizumab, are available for patients that had received platinum plus pemetrexed in the first-line setting, and docetaxel for those who have progressed on platinum plus pemetrexed and pembrolizumab. These treatments listed were consistent with those highlighted by the clinician experts consulted. The clinician experts consulted highlighted that the preferred therapy used in the first-line setting for patients with RET-fusion mutations across jurisdictions in Canada (except PEI were pembrolizumab is not funded) is the triple therapy combination of platinum-pemetrexed-pembrolizumab regardless of the PD-L1 TPS score because published literature highlighted limited activity for single-agent immunotherapy in the RET-fusion population.

Selpercatinib is a highly selective, adenosine triphosphate (ATP)-competitive small molecule inhibitor of the “rearranged during transfection” (RET) receptor tyrosine kinase (RTK), orally available in two formulations of 40 mg and 80 mg capsules. It received market authorization following the issuance of a notice of compliance with conditions (NOC/c) from Health Canada on June 16, 2021, for three indications: as a monotherapy in the treatment of metastatic RET fusion-positive NSCLC in adult patients, RET-mutant medullary thyroid cancer in adult and pediatric patients 12 years of age and older with unresectable advanced or metastatic disease, and RET fusion-positive differentiated thyroid carcinoma in adult patients with advanced or metastatic disease (not amenable to surgery or radioactive iodine therapy) following prior treatment with sorafenib and/or lenvatinib. Treatment initiation with selpercatinib is recommended only after an initial testing and confirmation of the RET gene mutation in patients. There are currently no past reviews submitted to CADTH for the RET fusion-positive NSCLC population.

The dosage recommended in the product monograph is 120 mg orally twice daily for patients who weigh less than 50 kg and 160 mg orally twice daily for patients who weigh 50 kg or greater.

Sources of Information Used by the Committee

To make their recommendation, the Committee considered the following information:

- A review of one single-arm clinical study in RET fusion-positive non-small cell lung cancer (NSCLC)
- Patient perspectives gathered by patient groups, Canadian Lung Cancer Advocacy Group Breathe Hope, CanCertainty, and Lung Cancer Canada.
- Input from public drug plans and cancer agencies that participate in the CADTH review process
- Two clinical specialists with expertise diagnosing and treating patients with metastatic RET fusion-positive NSCLC.
- Input from two clinician groups, including Lung Cancer Canada and Ontario Health (Cancer Care Ontario) Lung and Thoracic Cancers Drug Advisory Committee.
- A review of the pharmacoeconomic model and report, and ITCs submitted by the sponsor
- Other relevant evidence: SIREN study and LIBRETTO-431

Stakeholder Perspectives

Patient Input

This section was prepared by CADTH based on the input provided by patient groups.

Three patient groups submitted input for the review. The Canadian Lung Cancer Advocacy Group Breathe Hope, CanCertainty, and Lung Cancer Canada. A single respondent provided input from the Canadian Lung Cancer Advocacy Group Breathe Hope. The respondent highlighted symptom burden management owing to disease progression and treatment toxicity from chemotherapy as major drawbacks associated with disease and available treatment options. Access to selpercatinib was considered valuable to the patient as they were willing to accept side effects owing to treatment as a trade-off for a benefit in reducing tumour growth.

Input provided by the CanCertainty Coalition group highlighted potential limitations with access to treatments across jurisdictions in Canada citing Ontario and the Atlantic provinces as jurisdictions where variability exists in access to oral cancer medications. They recommend in their input that CADTH should examine equitable access to treatment across jurisdictions in Canada during the drug's review. They 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.

Lung Cancer Canada highlighted key concerns such as the lack of screening programs to detect disease in earlier stages. As well, Lung Cancer Canada highlighted the need for new treatments in the first- and second-line which improve patient reported outcomes, overcome resistance to treatment, decrease toxicity-related events, improve functionality, and increase independence of patients on caregivers.

Clinician input

Input from clinical experts consulted by CADTH.

Two clinical experts provided expertise knowledge regarding treatment strategies in Canada. The clinical experts cited that there is currently no available therapy for RET fusion-positive NSCLC patients. Treatment goals identified by experts were similar to those highlighted by the clinician group input. The clinical experts indicated that the most important goals are to achieve overall survival, reduce symptom burden, delay disease progression, prolong life with improved quality of life, decrease or eliminate hospital admissions and hospital stays, and all of these were considered valuable in this patient population.

The experts noted that if selpercatinib is approved for funding, it will likely be used as first-line therapy for patients with metastatic RET fusion-positive NSCLC. The experts highlighted that platinum plus pemetrexed and pembrolizumab (triplet therapy) was the preferred treatment option in the first-line across jurisdictions (except the province of PEI where pembrolizumab is not funded) regardless of a patient's PD-L1 TPS score. Beyond first-line, the experts noted that docetaxel is funded and can be administered depending on whether the patient received triplet therapy as first-line treatment. Patients may also receive single-agent immunotherapies (pembrolizumab, nivolumab or atezolizumab) in second-line if they had received platinum and pemetrexed in first-line, however, as highlighted in their input, patients with RET fusion are known to have shown low response rates to immunotherapy, therefore docetaxel may be administered in place of an immunotherapy in next-line settings. The clinical experts recommended that treatment be made available to all RET fusion-positive patients with advanced or metastatic NSCLC.

The clinician experts indicated that response to treatment in practice is usually assessed using the same methods implemented in the LIBRETTO-001 trial. However, the frequency of assessments differs from those of the trial setting. As described by the experts, the standard will be to perform radiographic assessments every 8 to 12 weeks or sooner if patient reports new symptoms or if their physical findings indicate disease progression. The experts also noted that symptom severity and adverse event occurrence are generally performed in practice every 3 to 4 weeks in patients receiving oral targeted therapies.

The experts highlight several molecular testing techniques are available to test RET fusion mutations across jurisdictions in Canada. The next-generation sequencing (NGS) technique was cited as the most commonly used technique while NGS with RNA sequence was considered the best test because of its sensitivity and specificity (e.g., 100% sensitivity and 99% specificity using the MSK IMPACT testing).

Clinician group input

This section was prepared by CADTH based on the input provided by clinician groups.

The clinician group input was submitted by two groups: The Lung Cancer Canada (LCC) and Ontario Health (Cancer Care Ontario) Lung and Thoracic Cancers Drug Advisory Committee (The OH-CCO). The OH-CCO's Drug Advisory Committees provide timely evidence-based clinical and health system guidance on drug-related issues in support of CCO's mandate, including the Provincial Drug Reimbursement Programs (PDRP) and the Systemic Treatment Program. Twelve clinicians from Lung Cancer Canada and 2 clinicians from Ontario Health (Cancer Care Ontario) Lung and Thoracic Cancers Drug Advisory Committee provided input for this review. Both groups highlighted similar treatment goals for patients with advanced or metastatic NSCLC disease. Key goals noted by both clinician group inputs included: improvement in median overall survival in patients, achieving quick and prolonged improvement in symptoms, achieving a median progression- free survival (mPFS), and reducing toxicity-related adverse events. Experts from LCC also added that treatment goals include: the prevention or treatment of brain metastases, the reduction of resource utilization, and the evaluation of the impact of COVID on the safety of systemic therapy. Input from LCC highlighted that current treatments for RET fusion-positive NSCLC patients have not improved overall survival in patients and are lacking in rapid and prolonged improvement in lung cancer symptoms measured by median time-to-response, ORR, or progressive disease rate and median PFS.

Both groups mention that adding selpercatinib to the Canadian treatment paradigm will allow the drug to be administered as first-line therapy in newly diagnosed patients with RET fusion-positive metastatic NSCLC. Clinicians in the LCC group mention that newly diagnosed patients with ECOG performance status of 0 to 3 could benefit from selpercatinib if approved for funding, although they expressed uncertainty related to the best therapy for second-line and suggested that subsequent therapy could include docetaxel and anti-PD-L1 therapy for those who have not received such agents in prior lines of therapy.

Drug program input

The drug programs provide input on each drug being reviewed through CADTH's reimbursement review processes by identifying issues that may impact their ability to implement a recommendation. For the CADTH review of selpercatinib, the drug plans highlighted different treatment strategies in place for patients with NSCLC, provided questions pertaining to the initiation of therapy, the prescribing of therapy, generalizability, funding algorithms, care provision issues, and system and economic issues. These questions were addressed by the clinician experts consulted for the CADTH review and their responses were based on the evidence presented by the sponsor in the LIBRETTO-001 trial.

Table 2. Responses to Questions from the Drug Programs

Implementation Issues	Response
Relevant Comparators	
The trial did not have a comparator. If patients are not tested for RET-fusion status, the funded treatments for treatment-naïve patients would be pembrolizumab single agent if PD-L1 >=50%; or pembrolizumab + pemetrexed + platinum; or platinum-based chemotherapy based upon histology. For previously treated patients, the funded treatment options would be an immune checkpoint inhibitor if no prior PD-L1 inhibitor (either pembrolizumab, nivolumab, atezolizumab depending on the PD-L1 status), or chemotherapy if prior PD-L1 inhibitor (docetaxel or pemetrexed).	pERC noted that the trial did not have a comparator and discussed current available treatment options for patients with RET fusion-positive NSCLC. While treatment options are available for these patients, there are currently no targeted therapies available for RET fusion-positive NSCLC patients. Selpercatinib is a RET-targeted therapy. pERC discussed that existing treatment options appear to have worse outcomes in the RET fusion-positive NSCLC population as compared to the RET fusion-negative NSCLC population.
Considerations for Initiation of Therapy	

Implementation Issues	Response
Relevant Comparators	
Should patients who are currently receiving systemic therapy and have not experienced disease progression be eligible to switch to selpercatinib on a time-limited basis?	pERC agreed with the clinical experts; patients should not switch to selpercatinib if they are not progressing on current therapy. Patients can stop treatment if they have disease progression, intolerable adverse effects, or want to stop for another reason (e.g., unable/unwilling to continue IV therapy).
The trial included several analysis sets, including patients who received one or more lines of prior platinum-based chemotherapy and patients who received prior systemic therapy other than platinum-based chemotherapy. Should eligible patients be required to receive a certain class of systemic therapy prior to selpercatinib? Should there be a limit on the number of lines of therapy a patient can receive prior to selpercatinib?	pERC agreed with the clinical experts that patients should not be required to receive a certain class of systemic therapy prior to selpercatinib in order to be eligible for selpercatinib. pERC also agreed with the clinical experts that there should be no limit on the number of lines of therapy prior to selpercatinib.
Considerations for continuation or renewal of therapy	
In the trial, patients with documented disease progression could continue to receive selpercatinib if the patient was thought to still benefit from treatment. Can pERC clarify the discontinuation criteria for selpercatinib?	pERC agreed with the clinical experts regarding the following discontinuation criteria for selpercatinib: • Presence of unacceptable/unsafe adverse effects that cannot be managed using appropriate dose reductions and/or supportive care medications • Patient preference • Symptomatic disease progression, with the exception of oligoprogression amenable to a local intervention to achieve disease control (i.e., radiation or surgical) or progression in the CNS amenable to brain-targeted therapy such as radiation.
Considerations for prescribing of therapy	
The recommended dose is approximately every 12 hours and is based on body weight: Less than 50kg = 120mg orally twice daily 50kg or greater = 160mg orally twice daily Patients with severe hepatic impairment (Child-Pugh C) should receive a reduced dose of 80mg orally twice daily	pERC acknowledged the recommended dosage as per the Health Canada product monograph and agreed with proceeding with the recommended dosage.
Generalizability	
In the study, all patients in the treatment-naïve population had an ECOG 0 to 1. Only 2% of patients in the previously treated population had an ECOG of 2. Can all patients with an ECOG 0 to 2 be considered eligible, whether treatment-naïve or not? Can patients with an ECOG >2 be considered eligible?	Patients enrolled in the LIBRETTO-001 study had an ECOG performance status of 0, 1 or 2. pERC acknowledged that clinicians may consider using selpercatinib for patients with a higher ECOG performance status at their discretion, regardless of patient's previous treatment status.
Funding algorithm (oncology only)	
This drug may change the place in therapy of drugs reimbursed in subsequent lines.	pERC acknowledged the drug plan statement. pERC noted that there are currently no targeted therapies available for RET fusion-positive NSCLC patients and that selpercatinib is a RET-targeted therapy.
Care provision issues	
RET testing needs to be in place to identify eligible patients.	pERC discussed access to RET testing across Canada and agreed with the drug plan statement.

BID = Twice a day; CNS = central nervous system; ECOG = Eastern Cooperative Oncology Group; NSCLC = non-small cell lung cancer; PD-1 = Programmed cell death protein 1; PD-L1 = Programmed cell death ligand 1; RET = rearranged during transfection

Clinical Evidence

Pivotal Studies and Protocol Selected Studies

Description of studies

A single ongoing phase 1/ 2 multicenter, multi-cohort, open-label study met the criteria for the CADTH systematic review. The LIBRETTO-001 trial evaluated the safety and efficacy of selpercatinib in patients with advanced solid tumors, including RET fusion-positive solid tumors (e.g., NSCLC, thyroid, pancreas, colorectal), RET-mutant MTC, and other tumors with RET activation (e.g., mutations in other tumor types or other evidence of RET activation). Patients recruited were 12 years or older (depending on the site and country).

The study was initiated in May of 2017 and has over 84 participating centers, including in Canada. There were 3 interim analyses planned to support regulatory submissions in different jurisdictions. This review presents data obtained at the second (December 16, 2019) and third (March 30, 2020) interim data cut-offs. Data obtained at interim 1 were updated at interim 2 and formed the basis of the Health Canada submission.

The study consisted of a dose escalation (phase 1) and a dose expansion (phase 2) phase. The phase 1 portion was conducted initially as a 3+3 design (cohorts of three patients assigned to increasing dose levels until one or more dose-limiting toxicities is observed) but was later updated to a Fibonacci dose escalation design after the third escalation was implemented in patients in increments of ~67%, ~50%, and ~33%. The primary objective at phase 1 was to assess the maximum tolerable dose (MTD)/ recommended dose at phase 2 (RP2D) and dose-limiting toxicities (DLT). The secondary objective at phase 1 is to evaluate the safety and tolerability of selpercatinib, to characterize the pharmacokinetic (PK) properties, and to assess the anti-tumor activity of selpercatinib.

The phase 2 portion which is ongoing, has five cohorts which included patients with a confirmed RET gene alteration in their tumour. Cohort 1 included RET fusion-positive solid tumor patients who progressed on or were intolerant to 1 or more prior standard first-line therapy. Cohort 2 was composed of patients with RET fusion-positive solid tumor without prior standard first-line therapy. The primary objective at phase 2 was to evaluate the anti-tumour activity of selpercatinib in patients recruited into the 5 cohorts. This was achieved by measuring the objective response rate (ORR) using the Response Evaluation in Solid Tumors version 1.1 (RECIST 1.1) guidelines or Response Assessment in Neuro-Oncology (RANO), as per tumor type, performed by an independent radiographic committee (IRC) and the study investigator. Other outcomes were assessed as secondary objectives in phase 2, which included best change in tumor size from baseline, duration of response (DOR), central nervous system (CNS) ORR, CNS DOR, time to any and best response, clinical benefit rate (CBR), progression-free survival (PFS), overall survival (OS), safety and tolerability of selpercatinib, and the characterization of the pharmacokinetic properties. Health-related quality of life (HRQoL) was assessed as an exploratory outcome.

This CADTH review focuses on outcomes observed in NSCLC patients with a confirmed RET fusion gene mutation enrolled into cohort 1 and 2 at phase 2 of the LIBRETTO-001 trial. These patients were further subgrouped into three datasets based on clinically meaningful distinctions observed during the trial. These subgroups include: the Primary Analysis Set ((PAS): consisting of the first consecutively enrolled patients previously treated with platinum-based chemotherapy), the Integrated Analysis Set ((IAS): consisting of patients treated with platinum-based chemotherapy), and the supplementary analysis sets ((SAS): SAS1: consisting of previously untreated patients; SAS 2: consisting of patients treated with other systemic therapies that are not platinum-based; SAS3: consisting of patients without measurable disease according to RECIST v1.1. These data sets supported the regulatory submission for marketing approval at Health Canada, the FDA, and the EMA.

Efficacy Results

The key efficacy outcomes investigated in the LIBRETTO-001 trial consist of findings obtained at interim analysis 2 (December 16, 2019) and interim analysis 3 (the March 30, 2020).

Overall survival

PAS and IAS sets (RET fusion-positive NSCLC with prior platinum chemotherapy): At the December 16, 2019 data cut-off, the median OS in the PAS was not estimable and the median follow-up was 16.72 months. In the IAS population, the median OS was not estimable, and the median follow-up was 12.62 months.

At the March 30, 2020 data cut-off, the median OS in the PAS was not estimable and the median follow-up was 19.94 months. In the IAS population, the median OS was not estimable, and the median follow-up was 14.26 months.

The sponsor conducted a follow-up analysis in the IAS population at a new cut-off date of June 15, 2021. The median OS was not estimable at this data cut-off. The median follow-up of survival was 26.4 months.

Previously untreated RET fusion-positive NSCLC (SAS1): At the December 16, 2019 data cut-off, the median OS was not estimable and the median follow-up was 9.86 months.

At the March 30, 2020 data cut-off, the median OS was not estimable and the median follow-up was 12.58 months.

The sponsor conducted a follow-up analysis in the previously untreated population at a new cut-off date of June 15, 2021. The median OS was not estimable at this data cut-off. The median follow-up of OS was 25.2 months.

Prior other systemic therapy RET fusion-positive NSCLC (Supplemental Analysis Set 2) and non-measurable disease RET fusion-positive NSCLC (Supplemental Analysis Set 3): At the December 16, 2019 data cut-off, the median OS and the median follow-up were not reported in both groups.

At the March 30, 2020 data cut-off, the median OS was 28.88 months (95% CI: 11.0-NE) and the median follow-up was 17.05 months for prior other systemic therapy RET fusion-positive NSCLC (Supplemental Analysis Set 2); the median OS was not estimable and the median follow-up was 10.48 months for non-measurable disease RET fusion-positive NSCLC.

Health related quality of life

Health related quality of life was assessed as an exploratory outcome in the entire NSCLC population (n=253) using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) disease-specific instrument. Scores were collected at baseline (cycle 1, day 1), every 8 weeks (until cycle 13), and every 12 weeks after cycle 13 (until end of treatment). A change of ≥10 points from baseline scores in the different domains was considered clinically meaningful.

There were no EORTC QLQ-C30 data available at the March 30, 2020 data cut-off.

At the December 16, 2019 data cut-off, three subgroups were created which included the previously untreated (n=39) group, the 1 prior line of therapy (n=64) group and a group with ≥2 prior lines of therapy (n=136). Lower scores obtained in functional subscales were compared to the following defined thresholds: 83 (physical function), 71 (emotional function), 58 (role function, social function), or 75 (cognitive function)) and were considered a clinically meaningful problem for patients. Higher scores obtained in symptom subscales were compared to the following thresholds: (8 (nausea/vomiting), 39 (fatigue), 25 (pain), 17 (diarrhea, dyspnea, financial difficulties), or higher than 50 (appetite loss, insomnia, constipation) and were considered clinically meaningful problems.

The mean score for global health status (GHS)/ QoL at baseline in the overall population (all NSCLC patients, n=253) was 61.5. In the previously untreated group, 1 line of prior therapy, and ≥2 prior lines of therapy group, the GHS/QoL obtained was 60.2, 65.2, and 60.4 respectively.

The baseline scores for physical function in the overall population (all NSCLC patients, n=253) was 75.9. In the individual groups, the baseline scores for physical function were 72.6 in the previously untreated group, 79.8 in the 1 prior line of therapy, and 76.1 in the ≥2 prior lines of therapy). These were lower than the threshold score of 83 and so were considered clinically important impairments at baseline. Improvements (≥10-point increase) in physical function were reported at cycle 3 in all three groups (previously untreated = 43.5%; 1 prior line of therapy= 28.1%; and ≥2 prior lines of therapy=29.8%).

Baseline scores for dyspnea exceeded the clinically meaningful threshold of 17 points in the overall population (all NSCLC patients, n=253) and in each subgroup (overall=31.3; previously untreated =28.4; 1 prior line of therapy=23.1; ≥2 prior lines=37.7, SD=28.3) thus, were considered clinically meaningful impairments. The proportion of patients that experienced a change in dyspnea from baseline by cycle of study treatment was higher in patients that reported improved symptoms compared to patients that reported worsened symptoms across cycles 3 to 13.

Baseline scores for fatigue and insomnia did not meet a clinically meaningful threshold in the overall population (all NSCLC patients, n=253) and so were not considered clinically meaningful impairments). The threshold was exceeded in the previously untreated group (baseline mean 41.6) and the group with 2 or more prior lines of therapy (baseline mean fatigue = 41.8) and so were considered clinically meaningful impairments. Threshold was not met in the one prior line of therapy group so was not considered a clinically meaningful impairment. More patients experienced improved outcomes in the change in baseline by cycle in insomnia scores compared to those who reported worsened outcomes across cycles 3 to 13. However, owing to the decrease in the number of patients completing the questionnaires from baseline to cycle 13, these findings are uncertain. Data for the change from baseline by cycle in fatigue scores was not available.

Baseline scores for pain met a clinically meaningful threshold of 25 points in the overall population (mean 29.4) and in all subgroups, thus it was considered a clinically meaningful impairment. All lines of therapy subgroups exceeded the clinically meaningful threshold of 8 points for nausea and vomiting. Data for the change from baseline by cycle in pain scores was not available.

Progression Free Survival

PAS and IAS sets (RET fusion-positive NSCLC with prior platinum chemotherapy): At the December 16, 2019 data cut-off, the median PFS in the PAS by the IRC was 16.53 months (95% CI:13.7 to NE). In the IAS population, the median PFS was 19.32 months (95%CI: 13.9 to NE).

At the March 30, 2020 data cut-off, the median PFS in the PAS by the IRC was 19.3 months (95% CI:13.9 to NE). In the IAS population, the median PFS was 19.3 months (95%CI: 16.5 to NE).

The sponsor conducted a follow-up analysis at a new data cut-off of June 15, 2021. The median PFS estimated in the IAS population was 24.94 months (95% CI: 19.3 to NE).

Previously untreated RET fusion-positive: At the December 16, 2019 data cut-off, the median PFS by IRC assessment was not estimable and the median follow-up estimated was 9.17 months.

At the March 30, 2020 data cut-off, the median PFS by IRC assessment was not estimable and the median follow-up estimated was 10.84 months.

The sponsor conducted a follow-up analysis at a new data cut-off of June 15, 2021. The median PFS estimated in the previously untreated population was 21.95 months (95% CI: (13.8 to NE).

Prior other systemic therapy RET fusion-positive NSCLC (Supplemental Analysis Set 2) and non-measurable Disease RET fusion-positive NSCLC (Supplemental Analysis Set 3): At the December 16, 2019 data cut-off, the median PFS by IRC assessment was not reported for both groups.

At the March 30, 2020 data cut-off, the median PFS by IRC assessment was not estimable in both groups.

Objective Response Rate

PAS and IAS sets (RET fusion-positive NSCLC with prior platinum chemotherapy): At the December 16, 2019 data cut-off, the ORR estimated by IRC was 64% (95% CI: 53.9 to 73.0) in the PAS population, and in the IAS population, the ORR was 57% (104 of 184; 95% CI: 49.0 to 63.8).

At the March 30, 2020, data cut-off, the ORR by IRC was 63.8% (53.9 to 73.0) and 56.9% (CI: 50.0 to 63.6) in the PAS and IAS, respectively.

The sponsor conducted a follow-up analysis at a new data cut-off of June 15, 2021. The ORR estimated in the IAS population was 61.1% (95% CI: (54.7 to 67.2) which was consistent with previous analysis.

Previously untreated RET fusion-positive NSCLC (SAS1): At the December 16, 2019 data cut-off, the ORR estimated by the IRC for the previously untreated RET fusion-positive NSCLC population was 84.6% (95% CI: 69.5 to 94.1).

At the March 30, 2020 data cut-off, the ORR by IRC assessment was 85.4% (95% CI: 72.2 to 93.9).

The sponsor conducted a follow-up analysis at a new data cut-off of June 15, 2021. The ORR estimated in the previously untreated population was 84.1% (95% CI: (73.3 to 91.8) which was consistent with previous analysis.

Prior other systemic therapy RET fusion-positive NSCLC (Supplemental Analysis Set 2) and non-measurable Disease RET fusion-positive NSCLC (Supplemental Analysis Set 3): The ORR obtained by the IRC assessment in the Prior Other Systemic Therapy RET fusion-positive NSCLC (Supplemental Analysis Set 2) was 43.8% (7 of 16; 95% CI: 19.8 to 70.1) at the December 16, 2019 analysis date and 44.4% (8 of 18; 95% CI: 21.5 to 69.2) at the March 30, 2020 data cut-off.

The ORR obtained by the IRC assessment in the non-measurable disease RET Fusion-positive NSCLC (Supplemental Analysis Set 3) was 28.6% (95%CI: 8.4 to 58.1) at the December 16, 2019 data cut-off and 33.3% (95% CI: 13.3 to 59.0) at the March 30, 2020 data cut-off.

Subgroup Analysis

CNS metastasis at baseline

At the December 16, 2019 data cut-off, the IRC identified 22 patients with measurable CNS disease out of the 80 patients with CNS metastasis at baseline. The CNS ORR in the 22 patients was 82% (18 of 22; 95% CI: 59.7 to 94.8). The CNS ORR in the 80 patients (with measurable and non-measurable disease) was 48% (38 of 80; 95% CI: 36.2 to 59.0).

At the March 30, 2020 data cut-off, 23 patients of 96 were assessed with measurable disease at baseline and the CNS ORR obtained was 87% (95% CI: 66.5 to 97.2). In the 96 patients with CNS disease at baseline (measurable and non-measurable disease), the CNS ORR was 46.9% (95% CI: 36.6 to 57.3).

Performance status, number of prior therapies, prior Anti-PD-1/PD-L1 therapy, and prior multi-kinase inhibitor therapy

At the December 16, 2019 data cut-off, the ORR in the following subgroups were as follows:

- ECOG PS: ECOG 0: ORR 74.2% (95% CI:55.4 to 88.1); ECOG 1-2: ORR 59.5% (95% CI: 7.4 to 70.7)
- Number of prior therapies: 1 to 2: ORR 58.7% (95% CI: 43.2 to 73.0); 3 or more: ORR 67.8% (95% CI: 54.4 to 79.4)
- Prior anti-PD-1/PD-L1 therapy: Yes: ORR 65.5% (95% CI: 51.9 to 77.5); No: ORR 61.7% (95% CI: 46.4 to 75.5)
- Prior multi-kinase inhibitor: Yes: ORR 64.0% (95% CI: 49.2 to 77.1); No: ORR 63.6% (95% CI: 49.6 to 76.2)
- There were no ORR subgroup data available at the March 30, 2020 data cut-off.

Duration of response

PAS and IAS sets (RET fusion-positive NSCLC with prior platinum chemotherapy): At the December 16, 2019 data cut-off, a median DOR by IRC of 17.5 months (95% CI: 12.0 to NE) was reported, with a median DOR follow-up of 12.1 months in the PAS population. In the IAS, a median DOR of 17.5 months (95% CI: 12.1 to NE) by IRC assessment, with an estimated median DOR follow-up of 9.2 months was reported.

At the March 30, 2020 data cut-off, the median DOR by IRC was 17.51 months (95% CI: 12.1 to NE) in the PAS and a median DOR by IRC of 17.51 months (95% CI: 12.1 to NE) in the IAS population.

The sponsor conducted a follow-up analysis at a new data cut-off of June 15, 2021. The median DOR obtained in the IAS population was 28.6 months (95% CI: 20.4 to NE).

Previously Untreated RET Fusion-positive NSCLC: At the December 16, 2019 data cut-off, the DOR by IRC was assessed in 33 patients in the previously untreated cohort. The median DOR was not estimable.

At the March 30, 2020 data cut-off, 65% of the responses were ongoing at 12 months, by IRC assessment.

The sponsor conducted a follow-up analysis at a new data cut-off of June 15, 2021. The median DOR estimated in the previously untreated population was 20.2 months (95% CI:13.0 to NE).

Prior other systemic therapy RET fusion-positive NSCLC (Supplemental Analysis Set 2) and non-measurable disease RET fusion-positive NSCLC (Supplemental Analysis Set 3): At the December 16, 2019 data cut-off, the median DOR was 12.02 months (95% CI: NE to NE) for prior other systemic therapy RET fusion-positive NSCLC (Supplemental Analysis Set 2) and not estimable for non-measurable disease RET fusion-positive NSCLC (Supplemental Analysis Set 3).

At the March 30, 2020 data cut-off, DOR was not estimable in both groups.

Harms Results

At the December 16, 2019 data cut-off, the most common adverse events reported in the NSCLC patient population in LIBRETTO-001 trial were dry mouth, diarrhea, hypertension, aspartate aminotransferase (AST) increase, alanine aminotransferase (ALT) increase, fatigue, constipation, peripheral edema, headache and nausea. Serious events in the NSCLC population were commonly associated with pneumonia, ALT increase, AST increase, abdominal pain, pleural effusion, drug hypersensitivity, diarrhea and acute kidney injury.

At the December 16, 2019 data cut-off, AEs leading to dose withdrawal, interruption, and dose reductions in the RET fusion-positive NSCLC population were consistent with those in the overall population. Adverse events commonly associated with treatment discontinuations in the NSCLC population were ALT increase, sepsis, AST increase, drug hypersensitivity, fatigue and thrombocytopenia. Alanine aminotransaminase (ALT) increase and AST increase were commonly associated with dose reductions and dose interruptions.

At the December 16, 2019 data cut-off, treatment was discontinued owing to death in 6 patients and 38 patients discontinued the study due to death. At the March 30, 2020 data cut-off, in the NSCLC population, treatment was discontinued owing to death in 6 (1.7%) patients and 55 (15.9%) patients discontinued the study due to death. In total, 36 (10.4%) patient deaths were attributed to disease progression, 13 (3.9%) deaths occurred due to adverse events, and 6 (1.7%) deaths were attributed to other reasons. One (0.3%) report of death was identified in the NSCLC population which had occurred more than 28 days after the last selpercatinib dose. In the overall safety analysis set (OSAS) population, treatment was discontinued owing to death in 11 (1.5%) patients and 103 (13.8%) patients discontinued the study due to death.

Notable harms reported in the NSCLC set were consistent with the OSAS at the March 30, 2020, and December 16, 2019 data cut-offs. The most common adverse events were ALT increase (32.8%), AST increase (31%), hypertension (31.9%), drug hypersensitivity (2.4%) and electrocardiogram QT prolongation (16.7%). All notable harms identified in the LIBRETTO-001 trial have been properly labelled under the warnings and precaution section of the Canadian product monograph. These notable harms were considered manageable by the clinical experts.

Critical Appraisal

The open-label, non-comparative design of the LIBRETTO-001 trial, with no statistical testing, is the key limitation. The sponsor did not state in the statistical analysis plan, hypothesis statements for statistical significance for the primary outcome including secondary and subgroup analyses conducted. The design increases the risk of bias in estimating treatment effects because the potential for confounding related to variation in health status, and other unidentified prognostic factors that could affect subjectively-assessed outcomes (i.e., response, HRQoL, AEs). The potential for bias was reduced by using IRC assessment for key study outcomes such as ORR and DOR.

Nonetheless, the lack of direct comparative data means there is uncertainty regarding the magnitude of effects obtained for the efficacy outcomes. Although the clinician experts consulted highlighted that the safety profile of selpercatinib was favourable compared to the other therapies available as standard of care in Canada, CADTH notes that in the absence of a comparative arm, the findings obtained from the safety analysis are uncertain as the single-arm design does not allow for the differentiation of the symptoms of underlying NSCLC disease from treatment-related adverse events. The sponsor agreed to provide results from the [redacted] to confirm the clinical benefit of selpercatinib in patients with previously treated RET fusion-positive NSCLC according to the NOC/c issued by Health Canada. The sponsor had noted in their response that [redacted] The sponsor submitted additional data with a new cut-off date of June 15, 2021 during the completion of this CADTH review (refer to appendix for new data). Despite the results obtained from the updated analyses performed on June 15, 2021, there remains uncertainty on whether the endpoints investigated are durable for long-term in this patient population.

The primary objective investigated at the phase 2 portion of the LIBRETTO-001 study was the ORR measured by the RECIST v1.1 criteria. The FDA considers ORR alone as a surrogate measurement when assessing treatment response in advanced or metastatic NSCLC patients that may not correlate well with survival, unless the effect size of the ORR is large and the responses are durable. The sponsor hypothesized a true ORR of ≥ 50% in the primary analysis of effectiveness, ruling out a lower limit of 30% for the ORR which was considered clinically meaningful and consistent with the estimated response rates seen with approved targeted therapies in molecularly-defined patient populations who have failed prior therapies (e.g., osimertinib, crizotinib, alectinib, and others). The ORR obtained by IRC in the PAS, IAS, and SAS1 sets were above the lower limit of 30% that the sponsor assumed in the sample size calculation for RET fusion-positive NSCLC patients who progressed on or after receipt of platinum-based chemotherapy. Although the FDA review team noted that the magnitude of the ORR and DOR obtained in RET fusion-positive NSCLC patients of the LIBRETTO-001 trial was large, and considered it sufficient to establish clinical benefit, the Health Canada reviewer's input underlined [redacted] Further, the Health Canada reviewers report highlighted that [redacted] The sponsor agreed to provide results from the [redacted] to confirm the clinical benefit of selpercatinib in patients with previously treated RET fusion-positive NSCLC according to the NOC/ c issued by Health Canada. The sponsor also noted that [redacted] In the LIBRETTO-001 trial radiographic scans were performed by an accredited laboratory and assessed by an independent radiology committee therefore, reducing bias. Results obtained from both IRC and investigator assessments did not differ greatly which increases the validity of the ORR-related outcomes.

The time-to-events analyses, particularly the OS and PFS results, were considered exploratory by [redacted] the FDA.25, 30, and CADTH due to lack of control arm. Health Canada highlighted in their report that, [redacted] Owing to immature data in the PAS, IAS, and SAS1 populations at the March 31, 2020 and December 16, 2019 cut-offs, the results were considered exploratory by CADTH. The sponsor submitted additional data to CADTH for a new cut-off date of June 15, 2021 later during the completion of the review. Although they report a median PFS of 24.94 months (95% CI: (19.3 to NE) in the IAS and a median PFS of 21.95 months (95% CI: (13.8 to NE) in the SAS1 population, the information was considered insufficient to form concrete conclusions on the PFS in this population because of the single-arm design of the LIBRETTO-001 trial and immature data. The median OS was non-estimable in the IAS and SAS1 data sets at the June 15, 2021 cut-off. Thus, there is uncertainty on whether the observed magnitude of benefit related to tumour response with selpercatinib would be translated as overall survival in patients in the 2 groups.

The analysis sets – PAS, IAS, and 3 SAS sets - were not pre-defined in the original statistical analysis plan. They were developed following consultation with the FDA and EMA. A key concern therefore is that these were post hoc analyses and may have been susceptible to bias. [redacted] CADTH reviewers agree with [redacted] these were unlikely to introduce bias because the investigators remained blinded to results until after the revisions were made.

The 3 planned interim analyses were prespecified. However, the analyses were performed on observed data only with no formal hypothesis testing and only descriptive statistics were provided, further complicating assessing the magnitude of effect observed in the different groups investigated.

HRQoL was evaluated as an exploratory outcome. There is uncertainty regarding these findings because the number of patients that completed questionnaires decreased from baseline through to cycles 13, thereby resulting in considerable missing data at later time points. In the absence of a comparator arm and open label design which introduces reporting bias, the impact of selpercatinib on patient reported outcomes in relation to other therapies is unknown. Although CADTH recognizes that the rarity of RET fusion-positive mutations in NSCLC may have contributed to the small sample size in the datasets at baseline, and may have influenced the number of patients available to complete the questionnaires at later stages of the trial, no strong definitive conclusions can be made from the findings obtained for HRQoL attained in the different population sets of NSCLC patients.

The clinical experts consulted during this CADTH review thought that findings obtained for outcomes (ORR, DOR, CNS ORR, and HRQoL) investigated in the LIBRETTO-001 study are clinically meaningful for patients in practice. The LIBRETTO-001 trial recruited patients with ECOG PS of 0, 1 and 2. The clinician experts consulted considered these findings generalizable to patients with ECOG PS of 0 to 3 (except for patients with ECOG PS 4). The experts also considered the baseline findings obtained in the trial similar to those observed practice, thus the findings are generalizable to patients in Canada. The RET fusion mutation in patients was identified in the LIBRETTO-001 trial using PCR and NGS. The clinician experts highlighted that NGS is available across several jurisdictions in Canada for testing oncogenic driver mutations at initial diagnosis.

Indirect Comparisons

Description of studies

Two sponsor-submitted indirect treatment comparisons (ITCs) were summarized and critically appraised. The sponsor-submitted ITCs aimed to evaluate the relative clinical efficacy of selpercatinib to other active treatments for RET fusion-positive NSCLC, in patients with or without prior systemic therapies. All included studies enrolled patients with unknown RET fusion status with the exception of LIBRETTO-001. Three outcomes that were analyzed were OS, PFS and ORR.

Efficacy Results

The sponsor-submitted ITCs conducted a systematic review to identify relevant individual studies and used Bayesian network meta-analysis to evaluate the relative clinical efficacy of selpercatinib to other treatments for NSCLC. In both ITCs, a pseudo-control arm was needed due to the lack of comparison arm in the study of selpercatinib. Adjustments on a number of prognostic factors for NSCLC, such as [redacted] were performed to match the comparator arm with selpercatinib arm.

In the ITC of patients who were previously untreated, results demonstrated that selpercatinib was favored compared to other treatments for OS [redacted] PFS [redacted] and ORR [redacted] Selpercatinib was compared to monotherapy or combination of platinum-based chemotherapy and immunotherapy agents.

In the ITC of patients who had one or more prior therapies, results suggested that selpercatinib was favored compared to other treatments for OS [redacted], PFS [redacted] and ORR [redacted]. Selpercatinib was compared to monotherapy or combination of chemotherapy agents and immunotherapy agents, such as docetaxel, cabozantinib, atezolizumab or nivolumab.

Harms Results

Harms were not assessed in the sponsor-submitted ITCs.

Critical Appraisal

These ITCs have a number of limitations that impact their internal and external validity, such as not being able to comprehensively assess the clinical heterogeneities across the included individual studies and their influence on the study results due to the lack of

reporting certain patient characteristics, uncertainty still exists on the treatment effect of selpercatinib despite of various adjustments, and generalizability of the study findings to patients with RET fusion-positive could be limited. In addition, other important outcomes such as DOR, HRQoL and safety, were not assessed.

Other Relevant Evidence

Description of studies

LIBRETTO-431: The CADTH Review team identified an ongoing phase 3, randomized, open label study (LIBRETTO-431) comparing selpercatinib to platinum-based (carboplatin or cisplatin) and pemetrexed therapy with or without pembrolizumab in previously untreated patients with locally advanced/metastatic RET fusion-positive nonsquamous non-small-cell lung cancer (NSCLC). No results are currently available, as this trial is actively recruiting patients. The estimated primary completion date (the date on which the last participant in a clinical study was examined or received an intervention to collect final data for the primary outcome measure) and study completion date (the date on which the last participant in a clinical study was examined or received an intervention/treatment to collect final data for the primary outcome measures, secondary outcome measures, and adverse events) are January 15, 2023 and August 18, 2025, respectively.

SIREN study: The CADTH Review team identified another study analyzing the safety and efficacy of selpercatinib in a real-world setting (SIREN study), where the data was retrospectively collected and analyzed from RET fusion-positive NSCLC patients participating in a selpercatinib access program.

The ORR (defined as complete or partial response) was 68% (95% CI, 53–81), and the median PFS was 15.6 months (95% CI, 8.8–22.4) after a median follow-up of 9.4 months among all patients. In patients with untreated or previously progressed and measurable brain metastases (n=8), the intracranial ORR reached 100%. In terms of adverse events, 43 (88%) of 50 patients experienced TRAEs of any grade, a large majority of them indicating grade 1 or 2. The most frequent TRAEs reported were fatigue/asthenia (40%), increased liver enzyme levels (34%), hypertension (26%), dry mouth (26%), and peripheral edema (20%). TRAEs of grade ≥3 were reported in 12 (24%) patients, with the most common TRAEs being increased liver enzyme levels (10%), abdominal pain (4%), prolonged QTc time (4%), hypertension (4%), and fatigue/asthenia (4%).

The following limitations were identified: The retrospective study design is prone to bias (e.g., reporting bias and non-differential biases), the patient population recruited may not be similar to the LIBRETTO-001 trial owing to differences in the eligibility and exclusion criteria applied in the study (potential selection bias). The ORR, although measured using the RECIST v1.1 criteria, was assessed by an unblinded review of practicing physicians. There is also a potential measurement bias owing to differences in the frequency and conduct of disease assessments in clinical practice versus the trial setting, the follow-up time frame in the study which differs from that of the trial and the therapies administered beyond disease progression. The small sample size of the study also limits the generalizability of the findings. Although the SIREN study provides additional data on the effectiveness and safety of selpercatinib in the real-world setting, the limitations identified introduces uncertainty.

Conclusions

The evidence supporting the funding request of selpercatinib was derived from an ongoing phase 1/ 2, open-label, non-randomized, multi-cohort, single arm study (LIBRETTO-001). The ORR observed in the LIBRETTO-001 trial suggested favourable tumour response in both groups (i.e., patients who were previously untreated and patients who had one or more prior therapies) and was consistent with further follow-up analyses. The ORR and DOR, including the CNS ORR, obtained in both patient populations were considered clinically meaningful by the clinician experts consulted during the review. Time-to-event endpoints like OS were not estimable at the March 30, 2020 and December 16, 2019, data cut-offs in the PAS, IAS, and SAS1 population owing to data immaturity. The median PFS was non-estimable in the treatment-naïve patient population at the March 30, 2020 and December 16, 2019, data cut-offs. Combined with the single arm trial design, the evidence was considered insufficient to interpret OS and PFS findings. The sponsor provided additional data to CADTH for a new data cut-off of June 15, 2021. Although estimates obtained at the June 15, 2021 data cut-off suggested an improvement in median PFS in the IAS and SAS1 population, the median OS was not estimable. CADTH considered these findings insufficient to provide concrete conclusions on the comparative treatment effect (PFS and OS) owing to the single-arm trial design and immature data. Thus, there is uncertainty on whether the observed magnitude of benefit related to tumour response with selpercatinib would be translated to overall survival in patients in who were previously

untreated and who had one or more prior therapies. As well, the limitations related to the single-arm, non-randomized design of LIBRETTO-001 precluded drawing strong definitive conclusions on the effects of selpercatinib on HRQoL, though HRQoL findings were noted by clinician experts consulted by CADTH as clinically meaningful. Safety information was reported for all patients that received a single dose of selpercatinib in the LIBRETTO-001 trial at both data cut-offs. Selpercatinib was associated with QTc prolongation, AST and ALT increases, hypertension, and drug hypersensitivity. These events have been labelled under the warnings and precaution section of the Canadian approved product monograph for selpercatinib. Nonetheless, these notable harms were considered by the clinical experts as manageable and favourable compared to current SOC treatment options. Although the SIREN study provided additional data on both effectiveness and safety of selpercatinib in the RET fusion NSCLC population, several limitations were identified with the study, thus, concrete conclusions could not be drawn to support the primary data obtained from the LIBRETTO-001 trial. The ITCs submitted to inform the comparative effects of selpercatinib were associated with limitations that prevented drawing conclusions on the results. Thus, there remains uncertainty in the comparative effectiveness and safety of selpercatinib.

Economic Evidence

Cost and Cost-Effectiveness

Table 2: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost utility analysis Partitioned survival model
Target populations	As monotherapy for the first-line treatment of adult patients with metastatic RET fusion-positive non-small cell lung cancer (NSCLC). As monotherapy for the treatment of adult patients with metastatic RET fusion-positive non-small cell lung cancer (NSCLC) and who have received prior systemic therapy.
Treatment	Selpercatinib
Submitted price	Selpercatinib, 80mg $133 per oral capsule ($7,980 per 60 capsule bottle) Selpercatinib, 40mg $66.50 per oral capsule ($3,990 per 60 capsule bottle)
Treatment cost	$11,172 to $14,896 per 28 days given 120mg to 160mg orally twice daily depending on whether the patient weight exceeds 50kg.
Comparators	Previously untreated patients: Pembrolizumab + pemetrexed + carboplatin/cisplatin (triple therapy), Pemetrexed + carboplatin/cisplatin (dual therapy) Patients who had one or more prior therapies: Docetaxel, Atezolizumab, Nivolumab
Perspective	Canadian publicly funded health care payer
Outcome	QALYs, LYs
Time horizon	Ten years
Key data sources	• Single-arm nonrandomized “basket trial" (LIBRETTO) – analysis of data limited to RET fusion-positive NSCLC patients – previously untreated patients (n=39), patients who had one or more prior therapies (n=184) • Network meta-analysis of clinical trials for comparator therapies not restricted to RET fusion-positive NSCLC patients • Interpolation of RET fusion-positive NSCLC patient data from the LIBRETTO study to general NSCLC data based on US administrative data (RET fusion-positive patients: previously untreated patients [redacted], patients who had one or more prior therapies [redacted]
Submitted results	Previously untreated patients: sequential ICER for selpercatinib = $190,169 per QALY versus triple therapy Patients who had one or more prior therapies: sequential ICER for selpercatinib = $211,869 per QALY versus atezolizumab
Key limitations	• Non-randomized data to inform relative effects of selpercatinib versus currently reimbursed therapies was not related to RET fusion-positive NSCLC, therefore potential prognostic factors associated with the RET fusion mutation were not accounted for. The analysis was also based on methodology associated with the optimistic estimate of relative treatment effects with no flexibility to adopt alternative methods despite request. • 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. • Sponsor assumed disease progression was the only reason for death in the model, despite evidence showing numerous deaths occurring pre-progression in the LIBERTTO trial. • Sponsor’s model framework assumes long-term survival is independent of progression status and that selpercatinib would continue to be associated with a relative reduction in mortality long after treatment has been discontinued, despite the lack of evidence to support this. • Assumptions relating to treatment wastage and dose intensity were biased in favor of selpercatinib. • The sponsor’s estimate of subsequent therapy costs lacked face validity in the setting with patients who had one or more prior therapies.

Component	Description
CADTH reanalysis results	• Given the absence of comparative data and inappropriate modelling approach, CADTH results are presented as an exploratory analysis with or without the inclusion of testing costs. The reanalysis did not address the sponsor's estimate of treatment effectiveness and the assumption of drug wastage with comparators and therefore, likely favor selpercatinib. • To inform the exploratory reanalysis, CADTH revised the sponsor's model to more accurately reflect how patients transition between the progression-free, post-progression and dead states. CADTH also adopted appropriate estimates of treatment costs and subsequent therapy costs for those who progress on second line therapy. • Previously untreated patients: ICER for selpercatinib: $418,720 per QALY ($495,313 including testing) versus triple therapy; $408,722 per QALY ($445,455 including testing) versus dual therapy. A 70% (77% with inclusion of full testing costs) price reduction is needed to be considered cost- effective in previously untreated patients at a $50,000 per QALY threshold. • Patients who had one or more prior therapies: ICER for selpercatinib: $422,880 ($453,673 including testing) versus Nivolumab; $500,589 ($529,397 including testing) versus Docetaxel, $440,326 ($471,292 including testing) versus Atezolizumab. An 87% (93% with inclusion of full testing costs) price reduction is needed to be considered cost-effective in patients who had one or more prior therapies at a $50,000 per QALY threshold.

ICER = incremental cost-effectiveness ratio; LY = life-year; NSCLC = non-small cell lung cancer; PSM = partitioned survival model; QALY= quality-adjusted life-year; RET = rearranged during transfusion

Budget Impact

In the CADTH reanalysis, the budget impact of selpercatinib is expected to be $792,667 in year 1, $2,921,482 in year 2, and $7,031,748 in year 3, with a three-year total of $10,745,897. Among previously untreated patients only, the three-year budget impact was $536,959. Among patients who had one or more prior therapies, the three-year budget impact was $10,208,939. CADTH found the budget impact to be sensitive to assumptions about the proportion of lung adenocarcinoma patients, the proportion of patients receiving first-line therapy, and the inclusion of testing costs. If the availability of a targeted therapy increases the proportion of patients who end up receiving systemic therapy, then the budget impact is substantially increased especially in the previously untreated population where a scenario analysis showed the three-year budget impact goes from $536,959 to $40,950,860.

pCODR Expert Review Committee (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: March 9, 2022

Regrets

None

Conflicts of Interest

None