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CADTH Reimbursement Recommendation

Pralsetinib (Gavreto)

Indication: For the treatment of adult patients with rearranged during transfection (*RET*) fusion–positive locally advanced unresectable or metastatic non–small cell lung cancer (NSCLC)

Sponsor: Hoffmann-La Roche Ltd.

Final recommendation: Reimburse with conditions

CADTH

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Summary

CADTH

What Is the CADTH Reimbursement Recommendation for Gavreto?

CADTH recommends that Gavreto be reimbursed by public drug plans for the treatment of adult patients with rearranged during transfection (*RET*) fusion–positive locally advanced unresectable or metastatic non–small cell lung cancer (NSCLC) if certain conditions are met.

Which Patients Are Eligible for Coverage?

Gavreto should only be covered to treat adult patients aged 18 years and older with locally advanced unresectable or metastatic *RET* fusion–positive NSCLC who have never received cancer treatment or who have received cancer treatment. Patients receiving Gavreto should be in relatively good health (i.e., have a good performance status as determined by a specialist) and not have cancer that has spread to the brain or if it has spread to the brain, is controlled.

What Are the Conditions for Reimbursement?

Gavreto should only be reimbursed if prescribed by a clinician with expertise in the management of NSCLC and if the cost of Gavreto is reduced. Gavreto should not be reimbursed in combination with other cancer treatment.

Why Did CADTH Make This Recommendation?

Evidence from a clinical trial demonstrated that people with locally advanced unresectable or metastatic *RET* fusion–positive NSCLC treated with Gavreto experienced tumour shrinkage or the tumour completely disappeared. As well, evidence from the clinical trial demonstrated brain tumour shrinkage in people whose cancer had spread to the brain.

Based on CADTH's assessment of the health economic evidence, Gavreto does not represent good value to the health care system at the public list price. Therefore, a reduction in price is required. Over 3 years, Gavreto is expected to increase drug costs to the public drug plans by approximately $22 million.

Additional Information

What Is *RET* Fusion–Positive Non–Small Cell Lung Cancer?

Non–small cell lung cancer is a type of lung cancer that originates from specific lung cell tissues and may include squamous, adenocarcinomas, or large cell–type carcinomas. People with lung cancer whose cancer cells have spread to other parts of the body, such as the bones, adrenal glands, brain, and liver, likely have metastatic cancer.

NSCLC can be driven by a gene in the body such as the *RET* gene. The *RET* gene is present naturally in the body, but some cancers form due to changes in the *RET* gene.

Unmet Needs in *RET* Fusion–Positive Non–Small Cell Lung Cancer

Patients with *RET* fusion–positive NSCLC are treated with chemotherapy and immunotherapy; however, not all patients respond to these available treatments.

How Much Does Gavreto Cost?

Treatment with Gavreto is estimated to cost approximately $12,426 per 30-day cycle.

Recommendation

The CADTH pCODR Expert Review Committee (pERC) recommends that pralsetinib be reimbursed for the treatment of adult patients with rearranged during transfection (*RET*) fusion–positive locally advanced unresectable or metastatic non–small cell lung cancer (NSCLC) only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One ongoing phase I and II, multi-centre, multinational, open-label, single-arm study (ARROW) demonstrated a clinically meaningful benefit of pralsetinib based on high overall response rate (ORR) (ORR = 64.4%; 95% confidence interval [CI], 57.9 to 70.5%) and prolonged duration of response (DOR) (median DOR = 22.3 months; 95% CI, 14.7 months to not reached) in adult patients with *RET* fusion–positive locally advanced unresectable or metastatic NSCLC. While pERC acknowledged the small number of patients evaluated for response of brain metastases (n = 10), evidence of penetration in the blood-brain barrier was demonstrated by the 70% (n = 7 of 10) central nervous system response rate in patients with *RET* fusion–positive NSCLC in this study. pERC noted that the change from baseline in health-related quality of life (HRQoL) scores was positive at all time points and consistent with a moderate clinical improvement. However, pERC acknowledged the potential for bias in the open-label, single-arm study, and the limitations due to protocol amendment to include HRQoL that resulted in low patient numbers and few patients with long-term data. There is a need for additional treatment options in this rare patient population given the poor prognosis, high symptom burden, and high risk of central nervous system metastases. pERC noted that pralsetinib addresses a therapeutic need because there are currently no targeted therapies funded for *RET* fusion–positive NSCLC patients. Pralsetinib was associated with a manageable toxicity profile.

Patients expressed a need for treatments that stop or delay the disease progression, improve survival, have manageable side effects, improve quality of life, and allow patients to maintain their independence and functionality. Considering all the evidence, pERC concluded that pralsetinib met the needs identified by patients in terms of stopping or delaying disease progression, having manageable side effects, improving quality of life, and allowing patients to maintain their independence and functionality.

Given the uncertain comparative clinical evidence for pralsetinib, CADTH was unable to derive a reliable base-case estimation of cost-effectiveness so exploratory analyses were performed. Using the sponsor-submitted price for pralsetinib and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio for pralsetinib was between $282,322 per quality-adjusted life-year (QALY) and $4,108,183 per QALY gained. This range was dependent on whether pralsetinib was used in patients who were previously untreated or who had 1 or more prior therapies, the possible overall survival benefit with pralsetinib, and the testing costs to identify patients with NSCLC with *RET* fusion abnormalities incurred by the public payer. Therefore, pralsetinib is not cost-effective at a $50,000 per QALY willingness-to-pay threshold. A reduction in price is required.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Treatment with pralsetinib should be reimbursed when initiated in adult patients with *RET* fusion–positive locally advanced unresectable or metastatic NSCLC who meet 1 of the following criteria: 1.1. for first-line treatment 1.2. after prior systemic therapy.	Evidence from the ARROW trial demonstrated that pralsetinib was associated with high response rates and prolonged durability in adults with *RET* fusion–positive locally advanced unresectable or metastatic NSCLC.	—
2. Patient must have: 2.1. good performance status 2.2. clinically stable CNS disease or no brain metastasis.	The initial eligibility criteria of the ARROW trial included patients with an ECOG PS of 0 to 2. Following a protocol amendment, eligibility was limited to patients with ECOG PS of 0 to 1. Hence, there were few patients enrolled with ECOG PS of 2. Patients were excluded from the ARROW trial if they had active CNS metastases.	pERC acknowledged that clinicians may consider using pralsetinib for patients with an ECOG PS greater than 1 at their discretion.
Renewal		
3. Assessment of renewal of pralsetinib 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's discretion to investigate new symptoms or concerns of progression 3.2. tolerability every 3 to 4 weeks or as per physician's discretion.	Based on clinical expert opinion, radiographic assessments of patients receiving pralsetinib would generally be conducted every 8 to 12 weeks, and sooner if new symptoms or physical findings suggest disease progression. Clinical assessments for the presence and severity of symptoms and adverse events would be conducted every 3 to 4 weeks initially, and then at longer intervals depending on the patient's tolerance of the drug.	—
Prescribing		
4. Pralsetinib should be prescribed by clinicians with expertise in the management of NSCLC.	To ensure that pralsetinib is prescribed only for appropriate patients and adverse effects are managed in an optimized and timely manner.	—
5. Pralsetinib should not be given or reimbursed in combination with other systemic anticancer drugs.	Pralsetinib was administered as monotherapy, not in combination with other systemic anticancer drugs in the ARROW trial.	—

Reimbursement condition	Reason	Implementation guidance
6. Pralsetinib should not be given to or reimbursed for patients who have previously progressed on selpercatinib.	Based on clinical expert opinion, pralsetinib should not be prescribed if the patient has previously progressed on selpercatinib.	Patients with intolerance to selpercatinib could be considered for treatment with pralsetinib.
Pricing		
7. A reduction in price	The cost-effectiveness of pralsetinib is highly uncertain. CADTH undertook a price reduction analysis. Based on the CADTH exploratory analysis, a price reduction of 70% to 99% is required for pralsetinib to be considered cost-effective at a $50,000 per QALY threshold. The price reduction is dependent on whether the drug is used in patients who are previously untreated or who had 1 or more prior therapies, the possible overall survival benefit with pralsetinib, as well as the degree of incremental testing costs incurred by the public payer.	—
Feasibility of adoption		
8. The feasibility of adoption of pralsetinib 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 estimate(s).	—
9. Organizational feasibility must be addressed so that jurisdictions have the infrastructure in place to implement treatment with pralsetinib.	Access to *RET* testing is needed to identify patients who have *RET* fusion–positive tumours; however, this may not be equally accessible across all jurisdictions.	It would be desirable for jurisdictions to have *RET* testing available across Canada to identify the eligible patient population.

CNS = central nervous system; ECOG PS = European Cooperative Oncology Group Performance Status; NSCLC = non–small cell lung cancer; pERC = CADTH pCODR Expert Review Committee; RET = rearranged during transfection; QALY = quality-adjusted life-year.

Discussion Points

- Because there was uncertainty with the clinical evidence given the single-arm study design, pERC deliberated on pralsetinib considering the criteria for significant unmet need described in section 9.3.1 of the Procedures for CADTH Reimbursement Reviews. Considering the rarity and severity of the condition, and the absence of clinically effective alternatives, the committee concluded that the available evidence suggests that pralsetinib has the potential to reduce morbidity and mortality associated with the disease.
- pERC acknowledged the uncertainty in the overall survival (OS) given that the median OS was not reached in the ARROW study and there was a lack of direct comparative effectiveness data related to important outcomes such as OS, progression-free survival (PFS), and HRQoL given the single-arm study design of the ARROW trial.

- pERC discussed the indirect treatment comparisons (ITCs) submitted by the sponsor which compared pralsetinib to pembrolizumab monotherapy, pembrolizumab plus platinum-based chemotherapy in combination with pemetrexed, and platinum-based chemotherapy in combination with pemetrexed in treatment-naive patients, as well as pralsetinib against docetaxel, nivolumab, and pemetrexed plus carboplatin in previously treated patients. The ITCs suggest favourable results in terms of OS and PFS (e.g., compared with pembrolizumab monotherapy or pembrolizumab plus platinum-based chemotherapy in combination with pemetrexed in treatment-naive patients and compared with docetaxel in previously treated patients). pERC noted certain limitations in the ITCs, including differences between groups in smoking history, age, and the presence of the *RET* mutation in the comparison arm; large reduction in effective sample sizes after adjustment; and naive comparisons. Ultimately, pERC acknowledged that conclusions cannot be drawn based upon the naive comparisons and conclusions drawn from the propensity score weighted analysis were limited.

Background

Lung cancer is the most frequently diagnosed cancer in Canada and the leading cause of cancer-related deaths; more than 29,600 new diagnoses and 21,000 disease-related deaths were projected for 2021. Lung cancers are classified into 2 types based on histology: small cell lung cancer and non–small cell lung cancer (NSCLC). NCLCs are the most common histology. Patients may experience worsening cough, chest pain, hemoptysis, malaise, weight loss, dyspnea, and hoarseness at clinical presentation or upon chest imaging. The adjusted 5-year net survival estimate in Canada for all forms of lung cancers is 22%, and the anticipated 5-year survival for patients with NSCLC is approximately 25% — 7% for patients with stage IV disease. Unfortunately, almost 50% of NSCLC cases in Canada are diagnosed at stage IV, with only about 23.1% of cases diagnosed at early stage I. Abnormal *RET* receptor activation by rearrangement or mutation was recognized as an oncogenic driver for many cancers, including NSCLC. These alterations were commonly associated with patients with adenocarcinoma histology, younger patients (usually ≤ 60 years), and in patients with non-smoking or light smoking status.

Pralsetinib is an orally available, highly selective inhibitor of the *RET* receptor tyrosine kinase. It is available in 100 mg capsules. Pralsetinib received a Notice of Compliance with conditions from Health Canada on June 30, 2021, indicated for the treatment of adult patients with RET fusion–positive locally advanced unresectable or metastatic NSCLC. The recommended dose is 400 mg, taken as four 100 mg capsules, once daily.

Sources of Information Used by the Committee

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

- 1 phase I and II clinical study in patients with thyroid cancer, NSCLC, and other solid tumours

- 1 phase III randomized controlled trial in patients with *RET* fusion–positive metastatic NSCLC who have not previously received systemic anticancer therapy for metastatic disease is currently ongoing, although no results are currently available for this study
- patients' perspectives gathered by 1 patient group: Lung Cancer Canada (LCC)
- input from public drug plans and cancer agencies that participate in the CADTH review process
- a clinical specialist with expertise diagnosing and treating patients with *RET* fusion–positive locally advanced unresectable or metastatic NSCLC
- input from 2 clinician groups, including LCC and Ontario Health (OH)–Cancer Care Ontario (CCO) Lung Cancer Drug Advisory Committee
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

Patient Input

One patient advocacy group, LCC, provided input regarding patients' experiences, values, and preferences related to *RET* fusion–positive NSCLC and its treatment. LCC was able to gather information from the following respondents: 4 patients with *RET* fusion–positive NSCLC who had received pralsetinib treatment and 1 caregiver from 4 countries (Canada, US, Ireland, and Norway). Input was gathered in March 2022.

Patients and caregiver respondents highlighted the delayed diagnosis due to mild and unspecific symptoms such as lower back pain, weight loss, cough, and shortness of breath. As a result, patients are often diagnosed at an advanced or metastatic stage in which the prognosis is relatively poor. Patients reported that chemotherapy has limited long-term effectiveness due to toxicity. Patients experienced harsh side effects such as fatigue, hair loss, and blood clots, which had a negative impact on patients' functionality and quality of life and created additional burdens on patients.

Patients who had experience with pralsetinib indicated that the drug had showed effectiveness in terms of shrinking the tumour size, having less severe side effects compared with other treatment options (chemotherapy, immunotherapy, and radiation), and improving functionality. For all 5 patients, the benefit of pralsetinib treatment allowed them to continue working or doing household chores and continue their daily lives with autonomy and dignity. The most frequently reported side effect was fatigue, which happened during onboarding and the first initial weeks of treatment. Patients also reported other general side effects such as dry mouth, anemia, constipation, loss of appetite, and itchiness or dry skin. One patient was re-hospitalized due to liver function conditions and had a severe headache. Patients reported the side effects alleviated once their dosages were reduced.

Outcomes important to patients are treatment effectiveness in managing symptoms, stopping or delaying the disease progression, settling patients into long-term remission for improved survivorship, having manageable side effects, maintaining patients' independence and functionality which would minimize the burden on their caregivers and family members, and improving quality of life.

Clinician Input

Input From the Clinical Expert Consulted by CADTH

One clinical expert with experience in the diagnosis and management of NSCLC highlighted the differences in patients with *RET* fusion–positive NSCLC and the broader NSCLC population, with some key differences being that patients with *RET* fusion–positive NSCLC are younger, less likely to have a history of tobacco use, and more likely to develop brain metastases. The expert noted that single-agent immunotherapy has limited activity in this population and chemotherapy, although effective for patients with *RET* fusion as the broader NSCLC population, does not have activity in the brain. Pralsetinib, a targeted oral therapy, represents an option with good response rates and activity in the brain. The expert also noted the potential to reduce hospital burden through its oral administration. This is in contrast to the IV administration of immunotherapy and chemotherapy, which is more likely to require in-person or hospital care for adverse events (AEs). The clinical expert noted that radiographic assessments would generally be conducted every 8 to 12 weeks, clinical assessments every 3 to 4 weeks, and patients would be discontinued from treatment in the presence of unacceptable adverse effects, patient preference, and symptomatic disease progression, with the exception of oligoprogression amenable to local intervention.

Clinician Group Input

Clinician group input on the review of pralsetinib for the treatment of *RET* fusion–positive locally advanced unresectable or metastatic NSCLC was received from 2 groups: LCC and OH-CCO Lung Cancer Drug Advisory Committee. The input was generally consistent with that received by the clinical expert. The submission from OH-CCO suggested that patients with European Cooperative Oncology Group (ECOG) Performance Status (PS) of 3 or greater would be least suitable for treatment with pralsetinib, whereas the clinical expert felt that access to pralsetinib should be extended to patients with an ECOG PS of 2 to 3. The submission from LCC highlighted pandemic considerations and the potential for reduced patient footprint in cancer centres when using an oral therapy such as pralsetinib.

Drug Program Input

Table 2: Summary of Drug Plan Input and Clinical Expert Response

Drug program implementation questions	Response
Relevant comparators	
The ARROW trial is a phase I and II study and does not include a comparator. At present, there are no publicly funded treatments in Canada for advanced NSCLC that specifically target *RET* fusion. Publicly funded options for patients with advanced unresectable or metastatic NSCLC who are treatment-naive include either pembrolizumab as a single agent if PD-L1 is greater than or equal to 50% or pembrolizumab + pemetrexed + platinum or platinum-based chemotherapy based upon histology. Nivolumab in combination with ipilimumab + platinum-doublet chemotherapy is under consideration for listing in provinces. For previously treated patients, the funded treatment options would be an immune checkpoint inhibitor if no prior treatment	pERC noted the drug plan input reflects clinical expert opinion.

Drug program implementation questions	Response
with a PD-1 inhibitor (either pembrolizumab, nivolumab, atezolizumab depending on the PD-L1 status) or chemotherapy if prior treatment with a PD-1 inhibitor (docetaxel or pemetrexed).	
pERC recently reviewed and issued a draft recommendation for selpercatinib for the treatment of metastatic *RET* fusion–positive NSCLC. What is the comparative efficacy of pralsetinib vs. selpercatinib?	pERC agreed with the clinical expert that there is no evidence to suggest that 1 drug is more efficacious than the other. According to the clinical expert, in practice, the adverse effect profile of either drug would be considered in relation to the medical history of the patient to determine the most suitable option. The clinical expert noted that beyond adverse effect considerations, the 2 drugs are considered equivalent.
Considerations for initiation of therapy	
Initial eligibility criteria of the ARROW trial included patients with an ECOG PS of 0 to 2. Following a protocol amendment, eligibility was limited to patients with an ECOG PS of 0 to 1. Should patients with an ECOG PS of 2 or greater be eligible for pralsetinib?	pERC acknowledged that clinicians may consider using pralsetinib in patients with an ECOG PS > 1 at their discretion. According to the clinical expert, access to pralsetinib should be extended to patients with an ECOG PS of 2 to 3 because pralsetinib is well tolerated with a significant likelihood of improving symptom burden, hence improving the ECOG functional status.
Initial eligibility criteria of the ARROW trial limited enrolment to patients who were previously treated with standard of care or who were treatment-naive and not candidates for available standard therapies. After the enrolment cut-off for efficacy analysis, a protocol amendment expanded eligibility to include treatment-naive patients regardless of whether they were candidates for standard therapies. Should pralsetinib be used in patients who are treatment-naive as well as those who have been previously treated?	pERC agreed with the clinical expert that all patients with *RET* fusion–positive NSCLC should be treated with pralsetinib, regardless of whether they have been pre-treated or not. pERC also agreed with the clinical expert that the 1 exception would be in a patient who had previous treatment with selpercatinib and progressed on selpercatinib, in which case it would not be appropriate to treat them with pralsetinib. According to the clinical expert, pralsetinib is more effective and less toxic than chemotherapy and immunotherapy checkpoint inhibitors. Based on those same principles, it is most appropriate to use pralsetinib in first-line or in the next line of therapy after progression on a current line of therapy.
In the ARROW trial, patients with untreated CNS metastases were permitted if they were not associated with progressive neurological symptoms. Patients requiring corticosteroids for management of CNS disease must have been on a stable dose for 2 weeks or more before initiating pralsetinib. Should patients with stable CNS metastases be eligible for pralsetinib?	pERC agreed that patients with stable CNS metastases should be eligible for pralsetinib and recognized that there are limited data to support this from the ARROW trial. The clinical expert highlighted that pralsetinib is a drug with CNS activity. In the updated results from the ARROW trial, there were 10 patients with brain metastases. Seven of the 10 patients had responses in the brain (70%), 3 of which were complete responses. Thus, the clinical expert stated that pralsetinib is an ideal drug for any patient with brain metastasis.
Should the funding criteria for pralsetinib be aligned to that of selpercatinib?	pERC acknowledged that although selpercatinib received a reimburse with conditions recommendation, it is currently not publicly funded. However, should selpercatinib become a funded treatment option, pERC agreed with the clinical expert that the funding criteria of pralsetinib should be aligned to that of selpercatinib. According to the clinical expert, selpercatinib and pralsetinib are highly comparable in terms of both efficacy and incidence of significant toxicity. Both should not be used in a single patient (unless a patient is switched from 1 to another due to toxicity with no progression of disease), but the option should be made to have equal access to both to facilitate choice for patients and oncologists which will enhance the

Drug program implementation questions	Response
	ability to provide best care. pERC also noted the instances in which 1 treatment may be favoured over the other as highlighted by the clinical expert. For instance, there are some differences in adverse effect profiles in which having the option to use either drug would be important; for example, selpercatinib is associated with a risk to develop a prolonged QT interval, whereas pralsetinib had no clinically relevant or significant effect on QT interval prolongation. Therefore, pralsetinib would be a more appropriate choice in a patient with *RET* fusion–positive NSCLC with a pre-existent prolonged QT interval or who requires the use of concomitant medications that can prolong the QT interval. For a second example, pralsetinib can cause pneumonitis. Thus, selpercatinib would be a more appropriate choice in a patient with pre-existing limited pulmonary reserves or who already has pneumonitis from a different cause such as palliative chest radiation.
Considerations for discontinuation of therapy	
In the trial, treatment after disease progression was allowed if this was the best medical interest of the patient as determined by the treating physician. What should the discontinuation criteria be for pralsetinib?	pERC agreed with the clinical expert that treatment should be discontinued based on unacceptable toxicity; 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; and patient choice.
Considerations for prescribing of therapy	
The recommended dose of pralsetinib is 400 mg (4 × 100 mg) once daily on an empty stomach. Bottles contain 60, 90, or 120 capsules. Dosage adjustment is required for patients receiving pralsetinib concurrently with known combined P-glycoprotein and CYP3A inhibitors and strong CYP3A inducers or inhibitors.	pERC acknowledged the recommended dose and dosage adjustment required for patients receiving pralsetinib concurrently with known combined P-glycoprotein and CYP3A inhibitors and strong CYP3A inducers or inhibitors as per Health Canada product monograph.
Should prescribing criteria for pralsetinib align with selpercatinib?	pERC agreed with the clinical expert that the prescribing criteria should align with selpercatinib, with the addition that pralsetinib should not be prescribed if the patient has previously progressed on selpercatinib. pERC also agreed with the clinical expert that intolerance to selpercatinib, in the absence of disease progression, would not preclude the use of pralsetinib.
Generalizability	
Should patients currently receiving systemic therapy but whose disease has not yet progressed switch over to pralsetinib?	Based on clinical expert response, patients should not switch over to pralsetinib unless there is an unacceptable toxicity or the patient decides they no longer want to receive treatment with a current line of therapy on which there has not been progression; that line of therapy should continue until progression after which it would be appropriate to switch to pralsetinib.

Drug program implementation questions	Response
Funding algorithm	
Pralsetinib may change the place in therapy of comparator drugs and drugs reimbursed in subsequent lines.	pERC acknowledged that pralsetinib may change the place in therapy of comparator drugs and drugs reimbursed in subsequent lines. pERC agreed with the clinical expert that it is most appropriate to use pralsetinib in the first line or the next line of therapy after progression on a current line of therapy.
Selpercatinib recently received a positive recommendation. How would pralsetinib be sequenced relative to selpercatinib? In what clinical circumstances would pralsetinib use be preferred over selpercatinib and vice versa? Can pralsetinib be used in later lines of therapy (e.g., third line or later)? Should patients who are unable to tolerate selpercatinib and who have not progressed on therapy be eligible to switch to pralsetinib and vice versa?	pERC agreed with the clinical expert that there should be no sequencing of pralsetinib and selpercatinib. Pralsetinib, if funded, would be an alternative to selpercatinib if selpercatinib is also funded. According to clinical expert opinion, there are no significant differences in efficacy between selpercatinib and pralsetinib to suggest a clear superior option between the 2 on the basis of expected outcomes. pERC also noted the instances in which 1 treatment may be favoured over the other as highlighted by the clinical expert. The clinical expert stated that, in clinical circumstances, the differential adverse effect profiles in the context of each patient may be critical in the choice between pralsetinib and selpercatinib. The clinical expert explained that if patients have already received or are currently receiving treatment other than a *RET*-specific TKI due to lack of availability of pralsetinib and selpercatinib at the time of initiation of first-line therapy, pralsetinib or selpercatinib should be used in the next line of therapy upon progression. pERC noted that the trial allowed patients with up to 3 prior lines of therapy and felt that treatment beyond this could be given on a case-by-case and time-limited basis, while acknowledging efficacy in this setting is unknown. pERC also agreed with the clinical expert that intolerance to selpercatinib would not preclude the use of pralsetinib; these patients could be considered for treatment with pralsetinib if there is no progression of disease.
Care provision issues	
RET testing is required to identify eligible patients. Pralsetinib has the potential for drug-drug and drug-food interactions requiring assessment and potential intervention or monitoring. Therefore, additional pharmacy resources would be used to assess potential interactions.	pERC acknowledged and agreed with the care provision highlighted by the drug plans.
System and economic issues	
Confidential pricing agreements are in place for comparator therapies.	pERC noted the input from the drug plans.

Drug program implementation questions	Response
The public drug programs have concerns regarding recommendations that are issued with preliminary phase I and II clinical trial data when phase III confirmatory trials are currently being conducted with planned results in the next several years. The concerns include the following: • The preliminary estimates of effect from phase II trials may not be an accurate assessment of the clinical efficacy for the drug under review. • The pharmacoeconomic evaluation incorporates data that include extrapolations (e.g., overall survival, quality of life) which contribute to considerable uncertainty in the results of the analyses. Thus, the evaluation may overestimate the value for money of the drug under review. This would also benefit from re-evaluation should the phase III data demonstrate different results than what was reported in the phase I and II data. • The public drug programs have limited ability to compel the sponsor to file the pending phase III data for review by CADTH to validate the assumptions that have been used in the economic model. These issues could result in the public drug programs providing reimbursement for pralsetinib at a price which is not cost-effective. This creates concerns regarding the ability to reimburse drugs, such as pralsetinib, while ensuring that the oncology drug formularies are managed in a sustainable manner.	pERC acknowledged the concerns from the public drug programs regarding the phase I and II data for pralsetinib and would welcome the opportunity to review the phase III data through a formal reassessment once the clinical trial results become available.

CNS = central nervous system; ECOG PS = European Cooperative Oncology Group performance status; NSCLC = non–small cell lung cancer; PD-1 = programmed cell death protein 1; PD-L1 = programmed death-ligand 1; pERC = CADTH pCODR Expert Review Committee; *RET* = rearranged during transfection; TKI = tyrosine kinase inhibitors.

Clinical Evidence

Description of Studies

ARROW (N = 281 safety population at the November 6, 2020, data cut-off) is an ongoing phase I and II, open-label, single-arm study of pralsetinib in patients with *RET* fusion–positive locally advanced or metastatic NSCLC. The primary objective of the phase II portion of the study was to determine the efficacy (measured by ORR and safety of pralsetinib 400 mg once daily. The phase II portion of the study and the 400 mg once daily dose are the focus of this report because this represents the Health Canada–approved indication. Intracranial ORR, DOR, PFS, OS, and HRQoL were secondary end points in the trial. There was no predefined duration of treatment, and patients with progressive disease could remain on treatment if the investigator determined that it was in the best interest of the patient to do so. There were 2 unplanned interim clinical data cut-offs presented in this report, the first was a November 18, 2019, data cut-off presented in a provided clinical study report and a November 6, 2020, data cut-off that was summarized in an European Medicines Agency report. The efficacy

population in both analyses were a subset of patients that had been enrolled at the time of data cut-off to allow for an appropriate amount of time for patients to achieve an ORR, which was July 11, 2019, and May 22, 2020, respectively. Safety analysis was provided for all patients who had been enrolled up to each data cut-off date. At the November 6, 2020, data cut-off, the median age of patients was 60 years, there was a similar proportion of women (52.4%) and men (47.6% male), and 51.9% of patients were White and 39.5% of patients were Asian.

Efficacy Results

Overall Survival and Progression-Free Survival

At the November 18, 2019, data cut-off, the median (95% confidence interval [CI]) OS follow-up time was [redacted] and the median OS [redacted]. At the data cut-off, [redacted] of patients had died and [redacted] were censored. Median (95% CI) PFS was [redacted] with [redacted] of patients censored at data cut-off.

At the November 6, 2020, data cut-off, the median OS follow-up time was 17.1 months (95% CI, 13.7 to 19.6) and the median OS had not been reached. At the data cut-off, 24.5% of patients had died and 75.5% were censored. Median PFS was 16.4 months (95% CI, 11.0 to 24.1) with 56.2% of patients censored at data cut-off.

Health-Related Quality of Life

Baseline mean (standard deviation [SD]) EORTC QLQ-C30 global health status score was [redacted] recorded from a total of [redacted] patients. At the 24-week time point, the mean (SD) global health status score, recorded from [redacted] patients was [redacted] which corresponded to a mean (SD) change from baseline of [redacted] meeting the published minimally important difference (MID) for a moderate improvement. HRQoL was only available at the November 18, 2019, data cut-off.

ORR, Intracranial ORR, and DOR

At the November 18, 2019, data cut-off, ORR was 56.8% (95% CI, 47.9% to 65.4%). Among patients who achieved a response (75 of 132), the median DOR had not been reached (median = not estimable [NE]; 95% CI, 11.3% to NE). In the 9 patients with measurable intracranial lesions, the ORR was 55.6% (95% CI, 21.2% to 86.3%). At the November 6, 2020, data cut-off, the ORR was 64.4% (95% CI, 57.9% to 70.5%). Among patients that achieved a response (150 of 233), the median DOR was 22.3 months (14.7% to not reached). In the 10 patients with measurable intracranial lesions, the ORR was 70.0% (95% CI, 34.8% to 93.3%). Additional subgroups reported for patients that received prior systemic therapy, prior platinum therapy, prior non-platinum therapy, and no prior systemic therapy, along with analysis of the measurable disease population, showed results similar to that of the primary analysis.

Harms Results

At the November 18, 2019, data cut-off, [redacted] of a total of 179 patients in the safety analysis set experienced at least 1 AE. The most common AEs were increased aspartate aminotransferase (AST) [redacted], constipation [redacted], anemia [redacted], and increased alanine aminotransferase (ALT) [redacted]. At the November 6, 2020, data cut-off, 99.3% of the total 281 patients in the safety analysis set experienced at least 1 AE. The most common AEs were anemia (45.9%), increased AST (44.8%), constipation (42.0%), hypertension (34.2%), and increased ALT (32.7%).

At the November 18, 2019, data cut-off, pneumonitis was reported as a grade 3 to grade 5 AE by [redacted] of patients, serious adverse event (SAE) by [redacted] of patients, and resulted in a dose reduction in [redacted] of patients, dose interruption in [redacted] of patients, and treatment discontinuation in [redacted] of patients. There were no deaths attributed to pneumonitis at the November 18, 2019, data cut-off. At the November 6, 2020, data cut-off, pneumonitis was reported as a grade 3 to grade 5 AE by 2.1% of patients, SAE by 4.6% of patients, and resulted in a dose reduction in 6.4% of patients, dose interruption in 9.6% of patients, and treatment discontinuation in 2.5% of patients. There were no deaths attributed to pneumonitis at the November 6, 2020, data cut-off.

Critical Appraisal

The most important limitation with the ARROW trial stems from the single-arm design. This design increases the risk of bias in estimating treatment effects due to the potential for confounding related to unidentified prognostic factors and treatment effect modifiers that could impact the activity of the study drug. Although *RET* fusion in patients is considered rare, accounting for 1% to 2% of all NSCLC patients, there is a phase III randomized trial currently being conducted for pralsetinib in this patient population.

The results for the primary end point of ORR did reject the null hypothesis for response and the clinical expert consulted did note that the response rates and duration of responses were impressive. There were no pre-specified interim analyses planned in the statistical analysis plan for ARROW, increasing the potential for bias and type I error with successive ad hoc data cut analyses.

Patients recruited to the treatment-naive group were initially required to be deemed unsuitable for standard-of-care chemotherapy, which was later amended to allow all treatment-naive patients. It is noted that this amendment may have biased the results against pralsetinib if the patients recruited before this amendment had a worse prognosis compared with the average first-line patient. Important protocol deviations further increased uncertainty given that 16 patients at the November 6, 2020, data cut-off did not have measurable disease at baseline and 1 patient had inconclusive evidence of a *RET* fusion. Patients that did not have measurable disease would be unlikely to record a response, biasing the results against pralsetinib for ORR; however, OS and PFS would be unaffected. Subgroup analyses of the post-eligibility revision group as well as the measurable disease only group were provided, and the results were similar to that of the primary analysis.

There remains uncertainty regarding long-term effects of pralsetinib on secondary outcomes such as PFS, OS, and HRQoL given the lack of comparator and immaturity of the survival data because the median OS was not reached. The HRQoL results, which are important to patients, appear to be positive, reaching the MID for a moderate improvement. However, the number of patients in the analysis is low due to this measure being added to the protocol through an amendment after initiation of the study, and patient numbers were further reduced as the time points progressed. There is potential for selection bias over time given that long-term survivors in the trials tend to be healthier patients. In the absence of a comparator arm and the open-label design which introduces reporting bias, the impact of pralsetinib on patient-reported outcomes in relation to other therapies is unknown.

According to the clinical expert consulted by CADTH, the demographic and disease characteristics of the patient population in the ARROW trial were reflective of the population of patients with *RET* fusion–positive NSCLC living in Canada.

Indirect Comparisons

Description of Studies

In the absence of direct comparative evidence from trials, the aim of each analysis was to compare the efficacy (OS and PFS) of pralsetinib in patients with *RET* fusion–positive locally advanced or metastatic NSCLC versus patients with wild-type NSCLC receiving comparators of interest. The studies identified for comparators of interest were KEYNOTE042 (pembrolizumab monotherapy), KEYNOTE189 (pembrolizumab plus platinum-based chemotherapy plus pemetrexed), IMpower132 (platinum-based chemotherapy plus pemetrexed), OAK (second-line docetaxel), CheckMate057 (second-line nivolumab), and GOIRC 02-2006 pooled with NVALT7 (carboplatin plus pemetrexed). IMpower132 and OAK were chosen due to the availability of individual patient data, allowing a propensity score weighting method to be applied to adjust for differences in study populations for the first-line platinum-based chemotherapy plus pemetrexed and second-line docetaxel comparisons. All other comparisons were naive unadjusted analyses that did not account for differences in population characteristics.

Efficacy Results

Propensity Score Weighted Analysis

The adjusted OS hazard ratio (HR) (95% CI) for the pralsetinib versus platinum-based chemotherapy plus pemetrexed comparison was [redacted] The adjusted OS HR (95% CI) for the pralsetinib versus docetaxel comparison was [redacted] The adjusted PFS HR (95% CI) for the pralsetinib versus platinum-based chemotherapy plus pemetrexed comparison was [redacted] The adjusted PFS HR (95% CI) for the pralsetinib versus docetaxel comparison was [redacted].

Naive Comparisons

The HRs for OS and PFS for the naive comparisons of pralsetinib versus first-line pembrolizumab monotherapy, first-line pembrolizumab plus pemetrexed-platinum, second-line nivolumab and second-line pemetrexed plus carboplatin all favoured pralsetinib.

Critical Appraisal

A key limitation of the ITC submitted by the sponsor comes from the single-arm design of the ARROW trial, precluding any connected network of trials resulting in a reliance on unanchored comparisons. For 2 comparisons, first-line platinum-based chemotherapy plus pemetrexed and second-line docetaxel, the sponsor had access to individual patient data and was able to conduct a propensity score weighting method to attempt to adjust for between-trial differences in population characteristics. The methodology for choosing the prognostic factors to adjust for relied on data availability in place of a rigorous literature search. The analysis assumed the presence of *RET* fusion was not a predictive factor and not included in the model. Although a lack of evidence available in patients with *RET* fusion–positive NSCLC required this assumption, patients who are *RET* fusion–positive tend to be younger, less likely to smoke, and have mostly non-squamous histology. Patients who are *RET* fusion–positive are more likely to respond to targeted *RET* therapy and less likely to respond to immunotherapy. The sponsor provided evidence from Hess et al. (2021) suggesting that before the introduction of *RET* inhibitors, there was no relationship between *RET* status and outcomes in an adjusted model. However, the consulted clinical expert suggested that the presence of *RET* fusion is a positive predictor for the efficacy of *RET*-targeted therapy and a negative predictor for the effect of immunotherapy. Methodology to adjust for prognostic

factors other than *RET* status was used; however, all differences in patient characteristics could not be accounted for. With regards to the naive comparisons specifically, no adjustments were made. Therefore, patients with positive or negative *RET* fusion status are expected to respond differently to pralsetinib, and it is unclear how similar the patient populations in the comparator studies are to those enrolled in the ARROW trial despite the adjustments in propensity score weighted analysis. Once adjusted, the trial populations were vastly reduced in size (in the case of the OAK trial), likely as a result of the imbalance in baseline covariates.

Because individual patient data were available for only 2 comparisons in the sponsor-submitted ITC, the remaining comparisons were unadjusted naive comparisons (i.e., no adjustments for between-trial differences in population characteristics were made). This introduces major uncertainty in the results given that the important prognostic factors, identified by the sponsor as being impactful to treatment effects, remained heterogenous for the naive comparisons. Given these limitations, conclusions cannot be drawn based upon the naive comparisons, and conclusions drawn from the propensity score weighted analysis are uncertain.

With these limitations in mind, it should also be noted that all results were directionally consistent and in line with the clinical expert's expectations that pralsetinib is likely a better option for patients than the comparators included in the ITC analysis.

An additional ITC was identified from the literature. A published ITC from Popat et al. (2022) was identified that compared first-line patients receiving pralsetinib in the ARROW trial to synthetic control arms sourced from 3 real-world data populations. The first real-world data population was patients with *RET* fusion–positive NSCLC who received best alternative therapy (most commonly pembrolizumab plus chemotherapy). The remaining 2 real-world data populations were patients with wild-type NSCLC who received pembrolizumab monotherapy and pembrolizumab plus chemotherapy, respectively. The analysis used inverse probability weighting methodology if possible to adjust for differences in prognostic factors. The results found patients receiving pralsetinib showed a statistically significant benefit in OS and PFS compared with the comparators chosen, which is consistent with the expectations of the clinical expert consulted; however, the same limitations are present as in the sponsor-submitted ITC. The analysis is an unanchored ITC relying on a limited number of prognostic factors and small effective sample size compared to the original sample sizes of the populations.

Other Relevant Evidence

Description of Studies

AcceleRET-Lung*:* The CADTH review team identified an ongoing, phase III, randomized, open-label study (AcceleRET-Lung) comparing pralsetinib to physician's choice of platinum chemotherapy–based regimen based on standard-of-care treatments for the first-line treatment of patients with *RET* fusion–positive metastatic NSCLC who have not previously received systemic anticancer therapy for metastatic disease. No results are currently available because 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 or treatment to collect final data for the primary outcome measures, secondary outcome measures, and AEs) are September 30, 2023, and December 31, 2024, respectively.

Economic Evidence

Table 3: Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Partitioned survival model
Target populations	Adult patients with metastatic *RET* fusion–positive NSCLC who were not previously treated with a *RET* inhibitor, assessed in the following subgroups: • treatment-naive • treatment-experienced.
Treatment	Pralsetinib
Submitted price	Pralsetinib, 100 mg: $102.06 per capsule
Treatment cost	$12,426 per 30-day cycle
Comparators	Treatment-naive: pembrolizumab + pemetrexed + carboplatin or cisplatin (triple therapy), pembrolizumab alone, PBC (carboplatin or cisplatin) + pemetrexed Treatment-experienced: docetaxel, nivolumab, PBC + pemetrexed (cisplatin)
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	20 years
Key data source	• Single-arm non-randomized phase I and II ARROW trial for *RET* fusion–positive NSCLC patients not previously treated with a RET inhibitor • Systematic literature review of clinical trials for comparator therapies, not restricted to *RET* fusion–positive NSCLC patients (i.e., wild-type NSCLC patients), used to inform indirect treatment comparison to derive relative treatment effects
Key limitations	• The relative treatment effect of pralsetinib on OS, PFS, and time to treatment discontinuation in comparison with relevant comparators was primarily based on an unanchored and, in some cases naive, indirect treatment comparison, adjusting for few, if any, prognostic factors. Data for comparators were not specific to *RET* fusion–positive NSCLC. The relative effect of pralsetinib on outcomes of interest is highly uncertain. • The sponsor's model is based on the assumption that long-term survival is independent of progression status and that pralsetinib would continue to be associated with a relative reduction in mortality long after treatment has been discontinued, despite a lack of evidence to support a post-progression survival benefit. Furthermore, the OS data for pralsetinib was immature. This, along with a lack of comparative evidence, makes it highly uncertain whether pralsetinib is associated with any overall survival benefit. • The sponsor's choice of parametric survival functions to extrapolate PFS for pralsetinib were implausible, overestimating the time to progression. • Dosing and stopping rules for several comparator drugs did not align with clinical practice, leading to the overestimation of comparator drug costs.

Component	Description
	• The sponsor's implementation of subsequent therapy use lacked face validity (including duration of subsequent therapy, available treatment options, and treatment distributions) in both the treatment-naive and treatment-experienced setting.
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 could not fully address the limitations with the sponsor's estimate of comparative clinical effectiveness, and therefore may bias results in favour of pralsetinib. • To inform the exploratory reanalysis, CADTH revised the sponsor's model to assume equal overall survival for each comparator within each subgroup, select alternative PFS extrapolation distributions, revise comparator drug costs to reflect dosing and stopping rules in alignment with product monographs and clinical practice, and revise subsequent therapy use to reflect clinical practice. • Treatment-naive: ICER for pralsetinib: ◦ $3,063,599 per QALY ($4,108,183 per QALY including testing) vs. triple therapy ◦ $1,626,594 per QALY ($1,842,863 per QALY including testing) vs. PBC + pemetrexed ◦ $1,481,688 per QALY ($1,709,056 including testing) vs. pembrolizumab ◦ an 81% (92% with inclusion of full testing costs) price reduction is needed to be considered cost-effective in treatment-naive patients at a $50,000 per QALY threshold. • Treatment-experienced: ICER for pralsetinib: ◦ $1,567,170 per QALY ($1,726,230 including testing) vs. docetaxel ◦ $1,487,336 per QALY ($1,679,844 including testing) vs. nivolumab ◦ $1,413,900 per QALY ($1,571,655 including testing) vs. PBC + pemetrexed ◦ a price reduction of at least 96% is required (at least 99% with inclusion of full testing costs) for pralsetinib to be considered cost-effective in treatment-experienced patients at a $50,000 per QALY threshold. • Scenario analyses considering the sponsor's optimistic OS benefits with pralsetinib suggested price reductions in excess of 60% and 75% in the treatment-naive and exposed settings respectively, were necessary for pralsetinib to be considered cost-effective at a $50,000 per QALY threshold when excluding testing costs.

ICER = incremental cost-effectiveness ratio; LY = life-year; NSCLC = non–small cell lung cancer; OS = overall survival; PBC = platinum-based chemotherapy; PFS = progression-free survival; PSM = partitioned survival model; QALY = quality-adjusted life-year; *RET* = rearranged during transfection; TTD = time to discontinuation.

Budget Impact

CADTH identified several key limitations with the sponsor's analysis. The sponsor underestimated the anticipated market uptake for pralsetinib and the proportion of patients assumed to be eligible for second-line treatment, the assumption that clinical trials possess a market share is inappropriate, the sponsor did not specifically select for the *RET* fusion–positive patient population in the derivation of their target population in the reference scenario, and duration of treatment used to inform drug acquisition costs was associated with uncertainty. The sponsor also assumed that the majority of jurisdictions would include *RET* fusion testing as part of existing screening and that no costs related to screening would be incurred, which is uncertain. In the CADTH base case, the budget impact of the reimbursement of pralsetinib for the treatment of metastatic *RET* fusion–positive NSCLC is expected to be $8,114,211 in year 1, $7,589,974 in year 2, and $6,515,821 in year 3, for a 3-year total of $22,220,006. In the first-line setting, the 3-year total budget impact was $12,108,611; in the second-line setting, the 3-year total budget impact was $10,039,395. This estimate is substantially different from the sponsor's estimate. CADTH found the

budget impact to be sensitive to the duration of treatment and the inclusion of testing costs. Uncertainty surrounding duration of treatment could not be addressed in reanalysis.

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: August 10, 2022

Regrets: 2 expert committee members did not attend

Conflicts of interest: None