Canadian Journal of Health Technologies

CADTH

April 2022 Volume 2 Issue 4

CADTH Reimbursement Recommendation

Lorlatinib (Lorbrena)

Indication: As monotherapy for the first-line treatment of adult patients with anaplastic lymphoma kinase (*ALK*)-positive locally advanced (not amenable to curative therapy) or metastatic non–small cell lung cancer (NSCLC)

Sponsor: Pfizer Canada

Final recommendation: Reimburse with conditions

CADTH

ISSN: 2563-6596

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

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

Summary

CADTH

What Is the CADTH Reimbursement Recommendation for Lorbrena?

CADTH recommends that Lorbrena should be reimbursed by public drug plans for the treatment of adult patients with *ALK*-positive locally advanced or metastatic non–small cell lung cancer (NSCLC) if certain conditions are met.

Which Patients Are Eligible for Coverage?

Lorbrena should only be covered to treat adult patients with *ALK*-positive NSCLC who are diagnosed when their cancer has spread to lymph nodes (locally advanced disease) or other parts of the body (metastatic disease) and who have had no prior systemic treatment for advanced or metastatic NSCLC.

What Are the Conditions for Reimbursement?

Lorbrena should only be reimbursed by public drug plans when used as a single drug. It should be prescribed by an oncologist with experience in the treatment of *ALK*-positive NSCLC although thereafter it can be given in an outpatient clinic by the patient's health care team. The cost of Lorbrena should not be higher than the cost of treatment with alectinib or brigatinib for these patients.

Why Did CADTH Make This Recommendation?

- Evidence from a clinical trial demonstrated that Lorbrena delayed disease progression when compared with crizotinib in patients with metastatic *ALK*-positive NSCLC. Evidence suggested that Lorbrena was effective in treating and preventing brain metastases in patients with *ALK*-positive NSCLC.
- Lorbrena meets patient needs of improving disease control by delaying progression and having manageable side effects.
- Based on CADTH's assessment of the health economic evidence, Lorbrena does not represent good value to the health care system at the public list price. The committee determined that there is not enough evidence to justify a higher price for Lorbrena than alectinib and brigatinib.
- Based on public list prices, Lorbrena is estimated to cost the public drug plans approximately $8 million over the next 3 years; however, the actual budget impact is uncertain.

Additional Information

What Is Metastatic *ALK*-Positive NSCLC?

ALK-positive NSCLC is a subtype of lung cancer that is caused by a mutation in the *ALK* gene, which accounts for approximately 5% of NSCLC cases. Patients with an *ALK* gene mutation tend to have a poor life expectancy and a high chance of developing brain metastases.

Unmet Needs in Metastatic *ALK*-Positive NSCLC

Treatments that improve the survival of patients, are less toxic, and are better at treating brain metastases are needed.

How Much Does Lorbrena Cost?

The sponsor estimated that treatment with Lorbrena would cost approximately $8,982 per 28-day cycle.

Recommendation

The CADTH pCODR Expert Review Committee (pERC) recommends that lorlatinib be reimbursed as monotherapy for the first-line treatment of adult patients with *ALK*-positive locally advanced (not amenable to curative therapy) or metastatic NSCLC only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One open-label, phase III superiority trial (CROWN, N = 296) demonstrated that first-line treatment with lorlatinib resulted in a clinically meaningful improvement in progression-free survival (PFS) when compared with crizotinib in adult patients with locally advanced (not amenable to curative therapy) or metastatic *ALK*-positive NSCLC. At the interim analysis, median PFS was not reached in the lorlatinib group and was 9.3 months (95% confidence interval [CI], 7.6 to 11.1) in the crizotinib group (hazard ratio [HR] = 0.28, 95% CI, 0.19 to 0.41; P < 0.0001), a difference between groups that crossed the prespecified stopping boundary for statistical significance. The PFS benefit was consistent across all patient subgroups including patients with and without brain metastases at baseline. Overall survival (OS) results showed no difference between the treatment groups (HR = 0.72, 95% CI, 0.41 to 1.25), but these data were immature. Several intracranial (IC) efficacy outcomes were assessed (e.g., objective response rate [IC-ORR], duration of response [IC-DOR], time-to-progression [IC-TTP]), and results for these outcomes showed consistent treatment benefit in favour of lorlatinib, although their exploratory assessment limits the interpretation of these findings. The assessment of health-related quality of life (HRQoL) as a prespecified exploratory secondary end point suggested no difference between lorlatinib and crizotinib in multiple measures of HRQoL. Compared with crizotinib, the incidence of most categories of adverse events (AEs) was higher in patients treated with lorlatinib but this did not result in a higher rate of dose modification or interruption and treatment discontinuation, therefore pERC judged lorlatinib to have a manageable safety profile. The efficacy of lorlatinib compared with more relevant first-line treatments for this population in Canada (i.e., alectinib and brigatinib), which are known to have better penetration of the central nervous system (CNS), is uncertain given the lack of direct comparisons. Four indirect treatment comparisons (ITCs), including 1 submitted by the sponsor, compared lorlatinib with these agents, but there were limitations of the analyses that precluded definitive conclusions on comparative efficacy with respect to PFS, OS, and HRQoL.

Given the totality of the evidence, pERC concluded that lorlatinib meets some of the needs identified by patients, such as delaying disease progression, and may also be beneficial in terms of CNS efficacy outcomes. Further, there was no apparent detriment to quality of life, and side effects were manageable. In fulfilling these needs, and given that it is an oral medication, pERC considered that lorlatinib may reduce the burden placed on caregivers, which is also important to patients.

Using the sponsor-submitted price for lorlatinib and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for lorlatinib was $147,368 per quality-adjusted life-year (QALY) compared with brigatinib. At this ICER, lorlatinib is not cost-effective at a willingness-to-pay threshold of $50,000 per QALY gained for patients with *ALK*-positive locally advanced or metastatic NSCLC. A price reduction of 42% is required for lorlatinib to be considered cost-effective at this threshold. Several limitations could not be addressed due

to data limitations and constraints introduced by the submitted model structure, thus these results are associated with uncertainty.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason
Initiation	
1. Treatment with lorlatinib should only be initiated in adult patients (≥ 18 years) with NSCLC and confirmed *ALK*-positive status who meet the following criteria: 1.1. locally advanced (stage IIIB not amenable for multimodality treatment) or metastatic (stage IV) NSCLC (per AJCC 7th edition) 1.2. no prior systemic treatment for advanced or metastatic NSCLC.	Evidence from the CROWN trial demonstrated that first-line treatment with lorlatinib had superior treatment efficacy in terms of delaying disease progression compared with crizotinib in patients with locally advanced (not amenable to curative therapy) or metastatic *ALK*-positive NSCLC with or without asymptomatic brain metastases.
2. Patients must have good performance status.	The CROWN trial enrolled patients with an ECOG Performance Status of ≤ 2. It is recognized that performance status may be related to underlying disease or tumour symptoms; therefore, for some patients, an improvement in status is expected after initiation of treatment. As such, lorlatinib could be considered in patients with an ECOG Performance Status > 2, and this decision should be left to the judgment of the treating clinician.
3. Lorlatinib should not be used in patients with the following conditions or comorbidities: 3.1. severe acute or chronic medical or psychiatric conditions.	The CROWN trial excluded patients with acute or chronic medical or psychiatric conditions (including recent or active suicidal ideation or behaviour). The CADTH review CADTH review identified no evidence to demonstrate a treatment benefit of lorlatinib in these patients.
Renewal	
4. Renewal of lorlatinib should be based on radiographic assessment performed every 2 months to 6 months and clinical assessment performed every 2 months to 3 months.	In the CROWN trial, assessment of tumour response was performed every 8 (± 1) weeks and was based on imaging using RECIST (version 1.1) criteria and modified RECIST (version 1.1) criteria were used for determination of intracranial response. Clinical assessments were performed every treatment cycle (28 days). In clinical practice, imaging for tumour response and clinical assessments are performed less frequently when compared with the schedule used in the CROWN trial. Based on clinical expert input, imaging for tumour response should be performed every 2 months to 6 months, with more frequent imaging at the start of treatment, and clinical assessments should be performed every 2 months to 3 months.

Reimbursement condition	Reason
Discontinuation	
5. Treatment with lorlatinib should be discontinued upon occurrence of any of the following: 5.1. documented disease progression per RECIST (version 1.1) criteria or clinical progression 5.2. toxicity that cannot be managed by dose reduction.	In the CROWN trial, treatment with lorlatinib was discontinued upon confirmation of disease progression or unacceptable toxicity, whichever occurred first. However, a patient could receive treatment beyond disease progression if, in the opinion of the treating investigator, they were judged to be deriving clinical benefit from continued treatment based on overall benefit or risk assessment that took into consideration performance status, clinical symptoms, adverse events, and laboratory data. For patients who continued lorlatinib beyond disease progression, tumour assessments were performed every 8 (± 1) weeks.
Prescribing	
6. Lorlatinib should initially be prescribed by an oncologist with experience in the treatment of *ALK*-positive NSCLC but can be administered in the community setting thereafter by the patient's health care team.	To ensure that lorlatinib is prescribed only for appropriate patients and adverse effects are managed in an optimized and timely manner.
Pricing	
7. The cost of lorlatinib should be negotiated so that it does not exceed the drug program cost of treatment with alectinib or brigatinib for the treatment of *ALK*-positive locally advanced or metastatic NSCLC	There is insufficient clinical evidence to justify a cost premium for lorlatinib relative to alectinib and brigatinib.
Feasibility of adoption	
8. The feasibility of adoption of lorlatinib 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).

AJCC = American Joint Committee on Cancer; ECOG = Eastern Cooperative Oncology Group; GI = gastrointestinal; NSCLC = non–small cell lung cancer; RECIST = Response Evaluation Criteria in Solid Tumors.

Implementation Guidance

Issues that may impact the drug plan's ability to implement a recommendation as identified by pERC and the drug plans are summarized in Table 2.

Table 2: Implementation Guidance From pERC

Condition # from Table 1	Implementation considerations and guidance
1.2	Patients with prior systemic treatment for advanced or metastatic *ALK*-positive NSCLC, including other TKIs and chemotherapy, were excluded from the CROWN trial. pERC agreed that intolerance to any TKI in the first-line setting (alectinib or brigatinib) would be reasonable grounds for consideration of a switch in treatment to lorlatinib in patients who do not have evidence of disease progression. It is recognized that TKIs have differences in their toxicity profiles and patients may have better side effect profiles with an alternate agent.

Condition # from Table 1	Implementation considerations and guidance
	pERC agreed that if first-line treatment with chemotherapy has been initiated in a patient before confirmation of *ALK* status, then a switch in treatment to lorlatinib would be reasonable once *ALK*-positivity is known.
5.1	In clinical practice, some patients who have oligometastatic progression may continue their first-line TKI therapy after completion of treatment for the localized progression. pERC agreed this treatment approach would also be reasonable for patients treated with lorlatinib.

NSCLC = non–small cell lung cancer; pERC = pCODR Expert Review Committee; TKI = tyrosine kinase inhibitor.

Discussion Points

- Current standards of care for the first-line treatment of advanced or metastatic *ALK*-positive NSCLC include second- generation tyrosine kinase inhibitors (TKIs) alectinib and brigatinib. pERC agreed that although there is not an unmet need for treatments in the first-line setting, lorlatinib would provide more treatment choice for patients who experience intolerance or toxicity, recognizing that individual TKIs have distinct side effect profiles. Further, given the high susceptibility of developing brain metastases among patients with *ALK*-positive NSCLC, as a third-generation TKI designed to have better penetration of the blood-brain barrier, lorlatinib may offer improved disease control in the CNS and reduce the need for radiation therapy to the brain. pERC acknowledged the value of more effective treatments in patients with brain metastases, which are associated with significant morbidity and a greater risk of mortality in this type of lung cancer that typically affects younger adults.
- The CROWN trial demonstrated that lorlatinib had a superior and clinically meaningful treatment benefit compared with crizotinib in terms of PFS. pERC agreed with the clinical experts consulted by CADTH that the prespecified exploratory secondary end point assessment of IC outcomes indicated that the magnitude and consistency of the results for all IC end points assessed in the trial were clinically meaningful. The OS data from the trial were immature but pERC noted that longer-term survival data will be confounded and difficult to interpret given the use of various subsequent therapies in the treatment groups.
- A limitation of the evidence is that there is no direct comparison of lorlatinib to more relevant treatment comparators (alectinib and brigatinib) that are standard of care in Canada. The indirect evidence from 4 ITCs (1 submitted by the sponsor and 3 from the literature) suggests potentially better PFS and IC efficacy with lorlatinib when compared with brigatinib and no differences in toxicity as well as potentially no difference in PFS and IC efficacy between lorlatinib and alectinib but more toxicity with lorlatinib. However, pERC discussed that definitive conclusions could not be drawn from these results due to limitations of the analyses arising from methodological (e.g., trial designs, different doses of alectinib) and clinical (e.g., prior therapies, proportion of patients with brain metastases) heterogeneity of the included trials. None of the ITCs assessed HRQoL outcomes.
- HRQoL data suggested no difference between the lorlatinib and crizotinib treatment groups; however, these findings were based on the pre-specified exploratory secondary end point analyses, and the instruments available at the time of trial may not have fully captured the impact of *ALK*-positive disease and treatment on patient cognition. However, given the consistency of the results across HRQoL instruments and scales, pERC was satisfied that lorlatinib did not negatively impact patients' quality of life. Further, patient

group input supported this conclusion based on patients' experience with lorlatinib who indicated that being on the drug improved their quality of life and permitted them to live functional and active lives with greater independence.

- Compared with crizotinib, most categories of AEs were higher in patients treated with lorlatinib; however, pERC noted that the greater toxicity did not result in more dose modification and/or interruption or treatment discontinuation. Patient and clinician input to CADTH support the conclusion that the side effects of lorlatinib are manageable.
- pERC also discussed the results from the CROWN trial related to cognitive and mood effects, which are unique to lorlatinib. The clinical experts consulted by CADTH indicated that these can be effectively managed in clinical practice through patient and family education and dose reduction but acknowledged that older patients with existing cognitive impairment may not be suitable candidates for lorlatinib.
- Patients and clinicians expressed a strong desire to have access to lorlatinib in subsequent lines of therapy for advanced or metastatic *ALK*-positive NSCLC. Currently, there are no TKIs publicly reimbursed for use beyond the first-line treatment setting. In 2019, pERC reviewed evidence for lorlatinib in patients who have progressed on crizotinib and at least 1 other anaplastic lymphoma kinase (ALK) inhibitor or patients who have progressed on ceritinib or alectinib, but pERC did not recommend reimbursement based on the low quality of the submitted evidence (i.e., non-randomized trial with no hypothesis testing). pERC acknowledged that despite demonstrated efficacy of platinum and pemetrexed chemotherapy in *ALK*-positive NSCLC after treatment with a TKI, there is a high unmet need for targeted therapy downstream. However, because there was no evidence included in the current submission to inform on the optimal sequencing of TKIs in subsequent treatment lines, pERC agreed that no recommendation could be made on their use after first-line treatment with lorlatinib.

Background

Lorlatinib is approved by Health Canada and indicated for use as monotherapy for the first-line treatment of adult patients with *ALK*-positive locally advanced (not amendable to curative therapy) or metastatic NSCLC. Lorlatinib is a selective, adenosine triphosphate (ATP)–competitive small molecule that can penetrate the blood-brain barrier and inhibit ALK and ROS1 tyrosine kinases. The Health Canada–recommended dose of lorlatinib is 100 mg taken orally once daily. The sponsor has requested the reimbursement of lorlatinib as per the Health Canada indication.

Sources of Information Used by the Committee

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

- a review of 1 phase III, open-label, randomized controlled trial in patients with locally advanced or metastatic *ALK*-positive NSCLC
- patient perspectives gathered by 2 patient groups: Lung Cancer Canada (LCC) and CanCertainty

- input from public drug plans and cancer agencies that participate in the CADTH review process
- 2 clinical specialists with expertise diagnosing and treating patients with *ALK*-positive NSCLC
- input from 2 clinician groups, including the Ontario Health (Cancer Care Ontario [CCO]) Lung and Thoracic Cancer Drug Advisory Committee (Lung DAC) and LCC
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

The information in this section is a summary of input provided by the patient and clinician groups who responded to CADTH's call for input and from clinical experts consulted by CADTH for the purpose of this review.

Patient Input

Input was received from 2 patient groups: LCC and the CanCertainty Coalition. Patients did not contribute to the submission from CanCertainty. The input received highlighted the financial burdens associated with oral lung cancer treatments, which are not funded in the same manner as IV therapies and coverage varies by province. In Ontario and the Atlantic provinces, only individuals older than age 65 years are automatically covered for oral oncology medications. According to CanCertainty, for patients without private insurance, access to medication requires navigating a complicated process of funding applications that are associated with approval delays, which most often result in patients incurring out-of-pocket costs. CanCertainty also indicated that the high cost of oral therapies may result in medication nonadherence, especially among younger and lower-income patients.

The submission from LCC was based on data retrieved through interviews, questionnaires, and environmental scanning of patients and caregivers of patients with *ALK*-positive NSCLC. In total, data were received from 17 patients, including 9 females and 8 males, most of whom were 35 years of age or older. Twelve of the respondents were patients and 5 were caregivers. The majority of LCC respondents were from Spain, the US, Canada, the UK, Switzerland, Philippines.

Respondents to LCC highlighted the unmet need for treatments that provide a cure for their lung cancer. Currently, all treatment options are considered palliative. Unmet need was also highlighted for patients with brain metastases because there are limited effective treatment options to treat brain involvement. Respondents described their experiences receiving crizotinib, ceritinib, alectinib, and chemotherapy. Crizotinib, although an effective treatment option, was stated not to be as effective against brain metastases, which results in the need for radiation therapy. Patients also reported difficult side effects with crizotinib and ceritinib. Alectinib was described by LCC as the current standard of care for patients with *ALK*-positive NSCLC due to its efficacy and reduced toxicity compared with crizotinib, and that it can be an effective treatment for patients with brain metastases. Chemotherapy was described to be associated with toxic side effects and limited benefit. LCC also described the burden of disease on caregivers who are frequently at the centre of their loved one's care, and who often require time off work, resulting in further financial burden.

LCC highlighted the following goals for treatments: improving disease symptoms, preserving patients' quality of life, manageable toxicity profiles for treatments, delayed progression, and maintenance of patients' functionality and independence. LCC gathered the experiences of 17 patients who had experience with lorlatinib; however, only 1 of these patients (from Spain) had received lorlatinib as first-line treatment. The respondents reported positively about treatment with lorlatinib, citing that it showed efficacy against their disease, including metastases, which provided them with a sense of hope. Patients also commented that lorlatinib had a tolerable toxicity profile, improved disease symptoms, and preserved independence and quality of life, as patients described being able to return to work, engage in social activities, and have more energy.

Clinician Input

Input From Clinical Experts Consulted by CADTH

The 2 clinical experts consulted by CADTH stated that, in Canada, alectinib is the first-line treatment used for most patients with *ALK*-positive NSCLC, although brigatinib is also an option. Lorlatinib would serve as another first-line option for patients; however, the clinicians highlighted that the use of lorlatinib would also be beneficial in later lines of therapy. According to the clinical experts, the goals of therapy are to prolong life, improve disease symptoms, maintain quality of life, delay disease progression, reduce severity and frequency of symptoms, and reduce loss of cognition. Both clinical experts highlighted the need for curative therapies that are better tolerated and preserve patients' quality of life. Further, they noted that improved biomarker-targeted therapies are needed to allow for multiple lines of therapy that provide patients with additional treatment options upon disease progression. Patients with brain metastases were highlighted as a group of patients with unmet need because currently there are a limited number of therapies that also have efficacy in the brain. The identification of patients eligible for treatment is done through imaging and *ALK* gene testing. Assessment of patients varies by line of therapy, but typically patients are assessed every 3 months, with brain imagining occurring every 6 months. The clinical experts indicated that lorlatinib could be administered in an inpatient and outpatient setting, and discontinuation of the drug would occur once patients experience clinical deterioration and cognitive dysfunction that affects their quality of life.

Clinician Group Input

Two clinician group inputs were received from the Ontario Health (CCO) Lung DAC and LCC. In total, input was received from 26 clinicians. Identification of the patients who would be eligible for treatment was stated to occur upfront, as ALK testing occurs at initial diagnosis. Both inputs identified alectinib and brigatinib, which are currently accessed though Special Access Programs, as the available first-line treatments for patients with *ALK*-positive NSCLC. Both inputs cited that treatment goals include prolonging life; delaying disease progression and CNS progression; maintaining or improving quality of life; reducing severity of symptoms; minimizing AEs; reducing the loss of cognition, memory, and other sequalae of CNS metastases and its local treatments; and maintaining patients' independence. The input from Ontario Health (CCO) Lung DAC stated that many of these needs are addressed through alectinib; however, new treatments are desired that provide longer control of symptomatic disease and improved PFS and OS. Input from LCC indicated an unmet need for more effective therapies in the first-line setting, the need for alternative therapies to allow for individualization of therapy, convenient dosing of treatments, and more effective therapies that treat brain metastases. Both clinician groups highlighted the need for more effective treatments in later lines of therapy because patients will eventually become refractory to

currently available treatment options. Although both groups acknowledged that lorlatinib would be an option for patients in the first-line setting, they indicated that lorlatinib could address treatment gaps in later lines of therapy. After patients progress on lorlatinib in the first line, TKIs are not typically available to patients in later lines of therapies; both clinician groups stated that use of ALK TKIs after first-line therapy would be preferential.

According to the clinician groups, assessment of a patient's response to treatment is based on improvement of symptoms, assessment of radiographic response, and through PFS, OS, and intra- and extracranial PFS. The clinician groups agreed that testing for response should occur every 2 months to 3 months with imaging being conducted every 2 months to 6 months, or as needed. Patients would be discontinued from treatment due to disease progression or unmanageable toxicities. Lorlatinib would be administered in an outpatient setting, although community or inpatient settings were stated to be acceptable at times under the supervision of the prescribing oncologist.

Drug Program Input

The drug programs provide input on each drug being reviewed through CADTH's reimbursement review process by identifying issues that may impact their ability to implement a recommendation. For the review of lorlatinib, the drug programs provided input and/or had questions pertaining to the initiation of therapy, the prescribing of therapy, generalizability, funding algorithms, care provision issues, and system and economic issues. pERC weighed evidence from the CROWN trial and other clinical considerations to provide responses to questions, which can be found in Table 3.

Table 3: Responses to Questions From the Drug Programs

Implementation issues	Response
Relevant comparators	
Comparators are crizotinib (first-generation ALK TKI) and alectinib or brigatinib (second-generation ALK TKIs). Alectinib and brigatinib have demonstrated superiority over crizotinib. Alectinib and crizotinib are funded by most jurisdictions. Brigatinib has a conditional positive recommendation from CADTH pCODR and is at pCPA for negotiation. Lorlatinib is a third-generation ALK TKI designed to have efficacy in patients with CNS metastases and ALK-resistance mutations. The CROWN trial compared lorlatinib against crizotinib, which is no longer the standard first-line ALK inhibitor. The sponsor submitted a network meta-analysis, as well as the NCCN 2021 guidelines to support lorlatinib as the preferred first-line treatment option.	pERC acknowledged the lack of direct head-to-head comparisons of relevant first-line treatments including lorlatinib, alectinib, and brigatinib. CADTH's appraisal of 4 ITCs for this submission (1 submitted by the sponsor and 3 from the literature) indicated no definitive conclusions could be drawn on comparative efficacy and safety given limitations of this evidence. Therefore, which ALK TKI has superior treatment efficacy and safety in the first-line setting is uncertain.
Considerations for initiation of therapy	
The sponsor noted improved CNS response rates from lorlatinib compared to other ALK inhibitors. What is the preferred ALK inhibitor for patients with *ALK*-positive NSCLC with active CNS disease?	pERC agreed that the optimal ALK inhibitor for use in patients with active CNS disease is uncertain in the absence of direct evidence comparing lorlatinib, alectinib, and brigatinib.

Implementation issues	Response
For consistency with initiation criteria associated with other drugs reviewed by CADTH for this indication, consider alignment with the initiation criteria for alectinib and brigatinib.	pERC agreed that the initiation criteria for lorlatinib should align with the initiation criteria for alectinib and brigatinib.
Considerations for prescribing of therapy	
Dosing, schedule or frequency, and dose intensity: • 100 mg taken orally once daily continuously • Continue until disease progression or unacceptable toxicity • May be taken with or without food; swallow whole; do not chew, crush, or split the tablets. • Dose modifications for hypercholesterolemia or hypertriglyceridemia, CNS effects (seizures, psychotic effects, changes in cognitive function, mood, speech, mental status, sleep), interstitial lung disease or pneumonitis, hypertension, hyperglycemia, or AV block • First dose reduction: 75 mg taken orally once daily • Second dose reduction: 50 mg taken orally once daily • Discontinue if patient is not able to tolerate 50 mg orally once daily • Available in 25 mg and 100 mg tablets; in bottles of 30, 60, or 100 tablets, or aluminum foil blisters with 120 tablets (25 mg; 12 cards of 10 tablets) or 30 tablets (100 mg – 3 cards of 10 tablets)	pERC agreed with the recommendations for administration and dose reduction of lorlatinib based on the CROWN trial and Health Canada product monograph.
Generalizability	
The CROWN clinical trial included patients with an ECOG PS of 0 to 2. Should patients with ECOG PS > 2 be eligible?	pERC agreed with the clinical experts that it would be reasonable to offer lorlatinib to patients who have an ECOG PS > 2. It is recognized that performance status may be related to underlying disease or tumour symptoms and therefore, for some patients, an improvement in status is expected after initiation of treatment. As such, lorlatinib could be considered in patients with an ECOG PS > 2, and this decision should be left to the judgment of the treating clinician.
Could patients being treated with crizotinib, alectinib, or brigatinib be switched to lorlatinib?	pERC agreed with the clinical experts that if a patient is responding to a treatment they are currently receiving (i.e., crizotinib, alectinib, or brigatinib), then they should remain on that treatment while they are responding and tolerating that therapy. Patients receiving other treatments (i.e., crizotinib, alectinib, or brigatinib) who experience toxicities typically will undergo dose reduction, dose interruption, or receive supportive medications. In patients whose toxicities cannot be managed in these ways, pERC agreed that switching to another TKI would be reasonable in patients with intolerance in the absence of disease progression.

Implementation issues	Response
Funding algorithm	
Lorlatinib may change the place in therapy of drugs reimbursed in subsequent lines and may be used preferentially over alectinib or brigatinib. Is there any information on sequential use of TKIs after treatment with lorlatinib?	Although in the CROWN trial patients received alternative therapy following progression on lorlatinib or crizotinib, there was no evidence included in the submission to inform the optimal sequencing of TKIs in subsequent treatment lines. Therefore, pERC agreed no recommendation could be made on their use after first-line treatment with lorlatinib.
Care provision issues	
Management of adverse effects:[a] • ECG monitoring is required before starting treatment and monthly thereafter.	pERC acknowledged that patients treated with lorlatinib will require monitoring to adequately manage adverse effects.
Companion diagnostics: • *ALK* mutation status is incorporated into standard diagnostic work-up in jurisdictions.	pERC acknowledged that testing for *ALK* mutation status is already incorporated as part of standard diagnostic work-up in all jurisdictions.
System and economic issues	
Concerns regarding the anticipated budget impact and sustainability: • The cost of lorlatinib should not be more than alectinib or brigatinib.	pERC acknowledged the drug plan input.
Additional costs to be considered (other than related to care provision as detailed above): • ECG monitoring is required before starting treatment and monthly thereafter.	pERC acknowledged the drug plan input.
Involvement of additional payers: • Oral medications are funded differently between jurisdictions.	pERC acknowledged the drug plan input.
Presence of confidential negotiated prices for comparators: • There are pCPA-negotiated prices for crizotinib and alectinib.	pERC acknowledged the drug plan input.

ALK = anaplastic lymphoma kinase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CNS = central nervous system; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; NCCN = National Comprehensive Cancer Network; NSCLC = non–small cell lung cancer; pCPA = pan-Canadian Pharmaceutical Alliance; pERC = pCODR Expert Review Committee; TKI = tyrosine kinase inhibitor.

[a]The drug plan included the following statement about the management of adverse effects in their input that was provided before the product monograph change (effective November 24, 2021): "Drug-drug interaction with CYP3A inducers – discontinue use. If concomitant use of moderate CYP3A inducers is required, monitor AST, ALT, and bilirubin 48 hours after initiation and at least 3 times during the first week." Since the wording for the concomitant use of moderate CYP3A inducers and lorlatinib has changed and the required monitoring for AST, ALT, and bilirubin 48 hours after lorlatinib initiation was removed from the updated product monograph, consideration of this item is no longer required.

Clinical Evidence

Pivotal Studies and Protocol-Selected Studies

Description of Studies

One multinational, multi-centre, randomized, active-controlled, open-label superiority trial met the criteria for the CADTH systematic review. The CROWN trial evaluated the efficacy and safety of lorlatinib compared with crizotinib as first-line treatment in adult patients with locally advanced or metastatic *ALK*-positive NSCLC who had not received previous systemic treatment for metastatic disease. Patients who were diagnosed and treated for an earlier stage of disease were eligible for enrolment if their treatment was completed more than 12 months before randomization. Eligible patients were required to have their *ALK* status confirmed through an approved immunohistochemistry test and have good performance status defined as an ECOG Performance Status of 0 to 2. Patients with brain metastases were eligible for enrolment.

The trial recruited patients from 104 sites in 23 countries (Asia, the European Union, and North America) including Canada. A total of 296 patients were randomized in a 1:1 ratio using an interactive web-based response technology system; 149 patients were randomized to the lorlatinib group and 147 patients were randomized to the crizotinib group. Randomization was stratified according to presence of brain metastases (yes versus no) and ethnic origin (Asian versus non-Asian). Patients randomized to the lorlatinib group received treatment at 100 mg once daily, and patients randomized to the crizotinib group received treatment at 250 mg twice daily. Both lorlatinib and crizotinib were administered orally.

The primary objective of the study was to determine whether lorlatinib was superior to crizotinib in prolonging PFS based on Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 per blinded independent central review (BICR) assessment. The trial was designed as a group-sequential trial using a Lan-DeMets (O'Brien-Fleming) alpha spending function to determine efficacy boundaries. The overall significance level was preserved at 0.025 with a 1-sided stratified log-rank test. The trial results were based on the interim analysis (data cut-off date was March 20, 2020), after approximately 133 PFS events (75%) had occurred per BICR assessment. A final analysis of PFS was specified only if the boundary for efficacy was not crossed at the interim analysis.

OS was planned as a secondary end point hierarchically tested upon statistical significance being obtained for PFS. Other prespecified exploratory secondary end points of the trial included PFS per investigator assessment, objective response rate (ORR), duration of response (DOR), time to response (TTR), and IC efficacy end points (IC-ORR, IC-TTP, IC-DOR, IC-TTR); these end points were not part of the statistical testing hierarchy. HRQoL was measured using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30), its corresponding survey for lung cancer (QLQ-LC13), and the EQ-5D-5L.

Patient characteristics at baseline were mostly balanced between the treatment groups. Mean age was 59 years (standard deviation [SD] = 13) in the lorlatinib group and 56 years (SD = 14) in the crizotinib group. A higher proportion of patients in the lorlatinib group were aged 65 years or older compared with patients in the crizotinib group (39.6% versus 29.9%, respectively). There were more females in both the lorlatinib (56.4%) and crizotinib (61.9%) groups. Most patients were White (48.2% versus 49.0%) or Asian (43.6% versus

44.2%). Almost all patients had measurable disease at baseline (96.6% versus 97.3%), with approximately one-quarter of patients presenting with brain metastasis (25.5% versus 27.2%). Most patients had an ECOG Performance Status of 0 (45.0% versus 38.8%) or 1 (53.0% versus 55.1%), with adenocarcinoma type of NSCLC (94.0% versus 95.2%) and stage IV metastatic disease (90.6% versus 94.6%). Most patients were classified as either never smokers (54.4% versus 63.9%) or former smokers (36.9% versus 29.3%).

Efficacy Results

Two analyses for PFS were planned, including an interim and final analysis. At the time of the data cut-off date (March 20, 2020), results for PFS crossed the prespecified stopping boundary for statistical significance, which favoured the lorlatinib group (stratified HR = 0.28; 95% CI, 0.19 to 0.41; stratified log-rank 1-sided P < 0.0001). The results for PFS at the interim analysis were considered final. At the time of the data cut-off date, OS was also tested in accordance with the statistical testing hierarchy and the results showed that the majority of patients remained alive; there were 23 deaths (15.4%) in the lorlatinib group and 28 deaths (19.0%) in the crizotinib group although the between-group difference was not statistically significant (HR = 0.72; 95% CI, 0.41 to 1.25). The results for IC efficacy outcomes (IC-ORR, IC-DOR, IC-TTP, IC-TTR) demonstrated a consistent improved response among patients with brain metastases treated with lorlatinib compared with crizotinib. However, the CROWN trial was not powered to assess these end points; therefore, the analyses of IC efficacy end points are considered exploratory.

HRQoL was assessed as a prespecified exploratory secondary end point in the CROWN trial. No clinically meaningful differences between treatment groups, based on a difference of 10 points or more, were observed in any of the EORTC QLQ-C30 functioning domains. In general, the mean change in scores from baseline to the end of the study period were similar for the EORTC QLQ-C30 and QLQ-LC13 in both treatment groups in the global health scale and subscales. Also, the mean scores in the EQ-5D-5L and EQ-VAS scores and index values were similar in both treatment groups. The time to deterioration analysis conducted for lung cancer symptom scales in the EORTC QLQ-C30 also showed no differences between the lorlatinib and crizotinib groups.

Harms Results

In general, AEs were more commonly reported in patients treated in the lorlatinib group than in the crizotinib group. The most common AEs in the lorlatinib group were hypercholesterolemia (70.5% versus 3.5%), hypertriglyceridemia (63.8% versus 5.6%), edema (55.0% versus 39.4%), weight increase (38.3% versus 12.7%), peripheral neuropathy (33.6% versus 14.8%), cognitive effects (21.5% versus 5.6%), diarrhea (21.5% versus 52.1%), and dyspnea (20.1% versus 16.2%). There were more AEs related to CNS effects reported in the lorlatinib group than in the crizotinib group (cognitive effects: 21.5% versus 5.6%, respectively; mood effects: 16.1% versus 4.9%; speech effects: 4.7% versus 0; psychotic effects: 3.4% versus 0). Serious AEs (SAEs) of any-grade (34.2% versus 27.5%) and grade 3 or grade 4 AEs (72.5% versus 55.6%) were higher in the lorlatinib group than in the crizotinib group, respectively.

AEs that resulted in dose reductions were generally infrequent, occurring in 31 patients (20.8%) in the lorlatinib group and 22 patients (15.5%) in the crizotinib group. Grade 3 AEs resulting in dose reductions occurred in 9 patients (6.0%) in the lorlatinib group and 7 patients (4.9%) in the crizotinib group; no grade 4 AEs resulted in dose reductions in either treatment group. AEs resulting in dose interruptions occurred in similar proportions of patients in the

lorlatinib (49.0%) and crizotinib (44.4%) treatment groups, of which 32.9% and 36.6% of interruptions, respectively, were due to grade 3 or grade 4 AEs.

Deaths occurred in 23 patients (15.4%) in the lorlatinib group and 28 patients (19.7%) in the crizotinib group, with most deaths considered to be due to disease progression (11.4% versus 16.2%, respectively).

Notable harms identified by the sponsor included hypercholesterolemia, hypertriglyceridemia, edema, peripheral neuropathy, CNS effects, vision disorder, pneumonitis, weight gain, liver function test increase, QT prolongation, AV block, and pancreatitis. The incidence of these AEs was higher in the lorlatinib group, except for vision disorder and liver function test increases, which were more common in the crizotinib group than in the lorlatinib group (39.4% versus 18.1% and 37.3% versus 20.8%, respectively). The most common notable AEs were hypercholesterolemia (70.5% in the lorlatinib group versus 3.5% in the crizotinib group), hypertriglyceridemia (63.8% versus 5.6%, respectively), edema (55.0% versus 39.4%), weight gain (38.3% versus 12.7%), peripheral neuropathy (33.6% versus 14.8%), cognitive effects (21.5% versus 5.6%), liver function test increases (20.8% versus 37.3%), and mood effects 16.1% versus 4.9%).

Critical Appraisal

The CROWN trial was a multinational, multi-centre, open-label, phase III trial that employed a group-sequential design. BICR was implemented for the assessment of end points that involved judgment of patient's clinical progression (i.e., PFS, ORR, DOR). However, it is possible that the open-label design posed a greater risk of bias for end points involving subjective reporting such as HRQoL and safety (e.g., CNS effects).

PFS and OS were the primary and secondary end points of the CROWN trial. Both end points were considered in power calculations, and OS was tested hierarchically at the time of the data cut-off date dependent on the statistical significance of PFS. Other secondary and exploratory end points were not included in the statistical hierarchy. The statistically significant findings on subgroup analyses were likely subject to multiplicity and inflated type I error rate. At the time of the data cut-off date, the interim analysis of PFS had crossed the prespecified efficacy boundary and showed a statistically significant difference in PFS in favour of lorlatinib, therefore the analysis was considered final by the sponsor. However, OS data were deemed immature as only 26% of the 198 OS events required for the final analysis of OS had occurred. It is worthy of highlighting that an improvement in PFS may not always correlate to a difference in OS in the assessment of oncology treatment benefit. Therefore, further evidence is required to confirm the superiority of lorlatinib over crizotinib in treatment efficacy in terms of OS.

Most patients included in the CROWN trial had an ECOG Performance Status of 0 or 1. The generalizability of the results in terms of a PFS benefit to patients with poor ECOG Performance Status remains unknown. Moreover, the study excluded patients with potential vascular or cardiac diseases, or patients with unfavourable laboratory test results with regards to renal, liver, pancreatic, or bone marrow function. In reality, the safety profile of lorlatinib for patients with those comorbidities or abnormal testing may be even worse, especially considering that lorlatinib increased the risk of hypercholesterolemia and hypertriglyceridemia. The CROWN trial allowed for enrolment of patients with brain metastases; these patients accounted for 25.5% of patients in the lorlatinib group and 27.2% of patients in the crizotinib group. Inclusion of patients with brain metastases is

highly relevant because many patients with *ALK*-positive metastatic NSCLC develop brain metastases. The results for IC efficacy end points assessed consistently showed numerically improved outcomes in the lorlatinib group over the crizotinib group. Despite the limitations associated with prespecified exploratory secondary end points, the clinical experts consulted by CADTH recognized the results of patients with brain metastases as clinically meaningful.

Indirect Comparisons

Description of Studies

Four ITCs were summarized and critically appraised, including 1 from the sponsor and 3 published ITCs from Chuang et al. (2021), Wang et al. (2021), and Ando et al. (2021).

The ITCs compared the safety and efficacy of lorlatinib to alectinib (600 mg and 300 mg), brigatinib, crizotinib, ceritinib, chemotherapy, and ensartinib as first-line treatment among patients with *ALK*-positive metastatic NSCLC. Although not all ITCs included comparisons to each of these treatments, all ITCs compared lorlatinib to alectinib, brigatinib, and crizotinib.

The sponsor's ITC compared lorlatinib to alectinib (600 mg and 300 mg), brigatinib, ceritinib (450 mg, 600 mg, 750 mg), crizotinib, chemotherapy, and ensartinib. Ando et al. (2021) compared lorlatinib to alectinib, brigatinib, ceritinib, crizotinib, and chemotherapy. Wang et al. (2021) compared lorlatinib to alectinib and brigatinib. Chuang et al. (2021) compared lorlatinib to alectinib (600 mg and 300 mg), brigatinib, crizotinib, and ensartinib.

Efficacy Results

Efficacy results reported here focus on PFS because this was the primary end point of all trials included in the ITCs.

Results of the sponsor's ITC favoured lorlatinib over all comparators, including alectinib at 600 mg (HR = 0.61; 95% credible interval [CrI], 0.38 to 0.99), brigatinib (HR = 0.57; 95% CrI, 0.34 to 0.95), ceritinib at 750 mg (HR = 0.22; 95% CrI, 0.13 to 0.37), ceritinib at 450 mg (HR = 0.31; 95% CrI, 0.15 to 0.66), ceritinib at 600 mg (HR = 0.25; 95% CrI, 0.12 to 0.54), crizotinib (HR = 0.28; 95% CrI, 0.19 to 0.41), ensartinib (HR = 0.55; 95% CrI, 0.32 to 0.93), and chemotherapy (HR = 0.12; CrI, 0.08 to 0.19) except for alectinib at 300 mg (HR = 0.83; 95% CrI, 0.36 to 1.85).

The results in the ITC by Ando et al. (2021) favoured lorlatinib over all comparators, including brigatinib (HR = 0.572; 95% CrI, 0.326 to 0.997), ceritinib (HR = 0.220; 95% CrI, 0.131 to 0.367), crizotinib (HR = 0.280; 95% CrI, 0.191 to 0.411), and chemotherapy (HR = 0.121; 95% CrI, 0.078 to 0.187), except for alectinib (HR = 0.742; 95% CrI, 0.4666 to 1.180).

The ITC by Wang et al. (2021) conducted comparisons among patients who were ALK inhibitor and chemotherapy-naive, and patients who were ALK inhibitor–naive. Results favoured lorlatinib compared with alectinib (ALK inhibitor- and chemotherapy-naive patients: HR = 0.59; 95% CrI, 0.37 to 0.94; ALK inhibitor–naive: HR = 0.65; 95% CrI, 0.42 to 1.01) and brigatinib (ALK inhibitor- chemotherapy-naive patients: HR = 0.54; 95% CrI, 0.31 to 0.94; ALK inhibitor–naive: HR = 0.57; 95% CrI, 0.34 to 0.95) in both groups of patients.

In the ITC by Chuang et al. (2021), lorlatinib was favoured over crizotinib (HR = 0.28; 95% CrI, 0.19 to 0.41), ensartinib (HR = 0.54; 95% CrI, 0.32 to 0.92), and brigatinib (HR = 0.57; 95% CrI, 0.32 to 0.95), but not over alectinib at 600 mg (HR = 0.68; 95% CrI, 0.42 to 1.08) or 300 mg (HR = 0.76; 95% CrI, 0.34 to 1.28).

Harms Results

The sponsor's ITC conducted a safety analysis for grade 3 and grade 4 AEs. Grade 3 and grade 4 AEs were [redacted] reported in the lorlatinib group compared with alectinib at 300 mg (odds ratio [OR] = [redacted]; 95% CrI, [redacted]) or 600 mg (OR = [redacted]; 95% CrI, [redacted]) and crizotinib (OR = [redacted]; 95% CrI, [redacted]). [redacted] were observed between lorlatinib and brigatinib (OR = [redacted]; 95% CrI, [redacted]), ceritinib (750 mg) (OR = [redacted]; 95% CrI, [redacted]), ensartinib (OR = [redacted]; 95% CrI, [redacted]), and chemotherapy (OR = [redacted]; 95% CrI, [redacted]).

Ando et al. (2021) conducted analyses of safety outcomes that included any-grade AEs, SAEs, grade 3 or higher SAEs, and specific AEs including nausea, diarrhea, increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST), and pneumonitis. A different number of trials were included in the analysis of each safety end point; therefore, the comparators were different for each safety end point. In general, lorlatinib was not favoured over comparators. For any-grade AEs, no treatments were favoured between lorlatinib and alectinib (relative risk [RR] = 1.018; 95% CrI, 0.985 to 1.051), lorlatinib and brigatinib (RR = 1.041; 95% CrI, 1.001 to 1.083), or lorlatinib and crizotinib (RR = 1.010; 95% CrI, 0.985 to 1.035). Regarding SAEs, no treatments were favoured between lorlatinib and alectinib (RR = 1.614; 95% CrI, 1.041 to 2.503) or lorlatinib and crizotinib (RR = 1.249; 95% CrI, 0.881 to 1.768). For grade 3 or higher AEs, no treatments were favoured between lorlatinib and alectinib (RR = 1.255; 95% CrI, 0.737 to 2.146) or lorlatinib and crizotinib (RR = 1.219; 95% CrI, 0.816 to 1.818). Regarding specific AEs (nausea, diarrhea, ALT or AST increase, and pneumonitis), lorlatinib was generally favoured over chemotherapy, crizotinib, or ceritinib, but not over alectinib or brigatinib.

Wang et al. (2021) conducted safety analyses involving assessments of AEs, AEs leading to treatment discontinuation, and AEs leading to dose reduction. In all cases, no treatments, between lorlatinib, alectinib, and brigatinib, were favoured over another.

Chuang et al. (2021) conducted a safety analysis for grade 3 or higher AEs. Lorlatinib had a greater risk of grade 3 or higher AEs compared with crizotinib (RR = 1.27; CrI 1.07 to 1.52), and alectinib at 600 mg (RR = 1.62; 95% CrI, 1.24 to 2.12) and 300 mg (RR = 2.09; 95% CrI, 1.48 to 2.95), but not brigatinib (RR = 1.07; 95% CrI, 0.84 to 1.37).

Critical Appraisal

Among all ITCs, there were issues related to heterogeneity. Specifically, there were differences in baseline characteristics which may limit the comparability of patients across trials. For example, there were differences in the proportions of patients with brain metastases, the enrolment of patients from Asian and non-Asian countries, and the inclusion of patients who may have received prior treatment with an ALK inhibitor and/or chemotherapy. These characteristics may serve as treatment effect modifiers affecting the comparisons of efficacy and safety in the ITCs. In some cases, the ITCs conducted subgroup or sensitivity analyses that accounted for differences in some but not all of these characteristics. The sponsor's ITC included the ASCEND-8 trial, which was a phase I, dose-ranging, active-controlled trial. The inclusion of this trial is likely to have introduced bias into the comparisons with ceritinib, although it is possible that the evidence base of the ITC was broadened with the inclusion of this trial. In addition, some studies included in the ITCs assessed treatment at different doses; specifically, alectinib was assessed at 300 mg and 600 mg. Although some ITCs considered the 2 doses to be different nodes in the overall networks of comparisons, 2 of the ITCs combined data from trials that assessed alectinib at different doses and included only 1 node for alectinib. The 2 doses of alectinib may not be considered equivalent in efficacy or safety,

and comparisons against alectinib that include data from both doses (600 mg and 300 mg) may have introduced uncertainty. The efficacy end points of PFS, OS, and ORR were assessed in the ITCs, but all the included trials were only powered for PFS; therefore, interpretation of evidence should be limited to this end point. Overall, due to limitations of the ITCs, it is not possible to know the true magnitude and direction of comparative treatment effects between lorlatinib, alectinib, and brigatinib.

Economic Evidence

Cost and Cost-Effectiveness

Table 4: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Partitioned survival model
Target population	As first-line treatment for patients with *ALK*-positive NSCLC
Treatment	Lorlatinib, administered orally as 100 mg once daily, until disease progression or unacceptable toxicity
Submitted price	Lorlatinib, 100 mg: $337.33 per tablet Lorlatinib, 25 mg: $112.44 per tablet
Treatment cost	Based on the submitted prices and distribution of doses, the 28-day cycle cost of lorlatinib is $8,982
Comparators	• Crizotinib • Alectinib • Brigatinib
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, life-years
Time horizon	Lifetime (30 years)
Key data sources	• CROWN trial: efficacy estimates (PFS, IC-PFS, OS) and time on treatment for lorlatinib and crizotinib • NMA: hazard ratios for PFS and OS for alectinib and brigatinib compared to crizotinib • Time on treatment for alectinib and brigatinib were derived using estimates for mean treatment duration obtained from literature
Submitted results	• Results from sequential analysis indicated that the 2 optimal treatments (i.e., on the cost-effectiveness frontier) are lorlatinib and crizotinib. • The ICER for lorlatinib was $128,964 per QALY when compared to crizotinib (incremental costs = $338,070; incremental QALYs = 2.62).

Component	Description
Key limitations	• There was substantial uncertainty in the extrapolated long-term OS outcomes for all treatments due to immature OS data reported in the CROWN trial. • Evidence from the NMA were uncertain due to limited number of included studies and heterogeneity across studies in terms of trial design and eligibility criteria. • The sponsor did not consider any potential treatment effect waning that may benefit lorlatinib as the modelled survival benefit for lorlatinib persists over the entire time horizon. • Feedback from clinical experts consulted by CADTH indicated that OS benefit and treatment durations derived for alectinib and brigatinib in the sponsor's model lacked face validity and were expected to be comparable for the 2 treatments. • Estimates for resources required to manage CNS progression, subsequent treatment distributions, and dose intensities did not reflect standard of care in Canada.
CADTH reanalysis results	• CADTH corrected the sponsor's model by applying a 20% variance to parameters without known standard errors and using a gamma distribution for cost data. The CADTH base case assumed equivalence of OS benefit and time on treatment for alectinib and brigatinib, and incorporated revised estimates for resources required to manage CNS progression, subsequent treatment distribution, and dose intensity for alectinib. • In the CADTH base case, crizotinib, brigatinib, and lorlatinib are on the cost-effectiveness frontier. The ICER for brigatinib compared with crizotinib is $116,289 per QALY, and the ICER for lorlatinib compared to brigatinib is $147,368 per QALY. • The probability of lorlatinib being cost-effective at a WTP of $50,000 per QALY is 1.4% compared with crizotinib, brigatinib, and alectinib. A price reduction of at least 42% is required for lorlatinib to be considered an optimal treatment option at a WTP threshold of $50,000 per QALY gained. • The results are highly sensitive to assumptions regarding survival outcomes.

ICER = incremental cost-effectiveness ratio; IC-PFS = intracranial progression-free survival; NMA = network meta-analysis; NSCLC = non–small cell lung cancer; OS = overall survival; PFS = progression-survival; QALYs = quality-adjusted life-years; WTP = willingness to pay.

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis: the treatment duration (i.e., median time on treatment) applied in the model likely underestimated costs associated with treatment, anticipated market uptake of lorlatinib was overestimated, uncertainty around the estimates used to derive the size of the population eligible for treatment with lorlatinib, dosing intensities assumed by the sponsor likely underestimated costs associated with treatment, and the market share estimates for the current standard of care treatments did not reflect Canadian clinical practice. In reanalyses, CADTH adjusted drug costs by changing the median time on treatment for lorlatinib, alectinib, and brigatinib; revised the anticipated market share for lorlatinib in the new drug scenario; changed the incidence rate of lung cancer over the 3-year time horizon; changed the proportion of patients eligible for treatment coverage across Canada; adjusted dosing intensities used to calculate costs associated with treatment; and revised the market share distribution of treatments in the reference scenario. Although the sponsor suggested that lorlatinib would be associated with cost savings ($36,473,898) over the 3-year time horizon, based on the CADTH reanalyses, the budget impact from the introduction of lorlatinib would result in an incremental budget impact of $459,404 in year 1, $1,407,996 in year 2, and $6,246,895 in year 3, for a total budget impact of $8,114,296 over the 3-year time horizon.

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: November 10, 2021

Regrets: None

Conflicts of interest: One expert committee member did not participate due to considerations of conflict of interest.