Canadian Journal of Health Technologies

Canada's Drug Agency
L'Agence des médicaments du Canada

November 2024 Volume 4 Issue 11

Drugs Health Technologies Health Systems

Reimbursement Recommendation

Alectinib (Alecensaro)

Indication: For adjuvant treatment following tumour resection for patients with stage IB (tumour ≥ 4 cm) to IIIA *ALK*-positive non–small cell lung cancer

Sponsor: Hoffmann-La Roche Limited

Final recommendation: Reimburse with conditions

Summary

What Is the Reimbursement Recommendation for Alecensaro?

Canada's Drug Agency (CDA-AMC) recommends that Alecensaro should be reimbursed by public drug plans for adjuvant treatment following tumour resection for patients with stage IB (tumours ≥ 4 cm) to IIIA (according to American Joint Committee on Cancer [AJCC] *Cancer Staging Manual*, seventh edition) *ALK*-positive non–small cell lung cancer (NSCLC) if certain conditions are met.

Which Patients Are Eligible for Coverage?

Alecensaro should only be covered to treat adult patients (≥ 18 years) who have stage IB (tumour ≥ 4 cm) to stage IIIA (per the AJCC seventh edition) *ALK*-positive NSCLC, have had complete tumour resection, and are in relatively good health.

What Are the Conditions for Reimbursement?

Alecensaro should only be reimbursed if it is prescribed by clinicians with expertise in managing NSCLC and the cost of Alecensaro is reduced. Alecensaro should be discontinued if a patient's cancer grows or spreads, if treatment is unacceptably toxic to the patient, or the patient has completed 2 years of therapy with Alecensaro.

Why Did CDA-AMC Make This Recommendation?

- Evidence from a clinical trial demonstrated that adjuvant treatment with Alecensaro was better than adjuvant chemotherapy in prolonging life without disease recurrence and delaying the spread of cancer to the brain in adult patients who had complete resection of their stage IB (tumour ≥ 4 cm) to stage IIIA *ALK*-positive NSCLC (stages per AJCC seventh edition).
- Based on the CDA-AMC assessment of the health economic evidence, Alecensaro may represent good value to the health care system at the public list price. Price reductions would reduce the uncertainty of this assessment.
- Based on public list prices, Alecensaro is estimated to cost the public drug plans approximately $36 million over the next 3 years.

Additional Information

What Is *ALK*-Positive NSCLC?

Lung cancer is the most commonly diagnosed cancer and the leading cause of cancer deaths in Canada. Approximately 88% of lung cancer

Summary

cases in Canada are NSCLC. Patients with *ALK*-positive NSCLC (i.e., tumours with *ALK* gene rearrangement) are at a higher risk of the cancer spreading to the brain or spinal cord compared to those with *ALK*-negative NSCLC.

Unmet Needs in *ALK*-Positive NSCLC

There is a need for an effective treatment following tumour resection that can prolong survival, delay recurrent disease, and is less toxic than chemotherapy.

How Much Does Alecensaro Cost?

Treatment with Alecensaro is expected to cost approximately $9,918 per patient per 28-day cycle.

Recommendation

The pan-Canadian Oncology Drug Review Expert Review Committee (pERC) recommends that alectinib be reimbursed for adjuvant treatment following tumour resection for patients with stage IB (tumours ≥ 4 cm) to IIIA (according to American Joint Committee on Cancer [AJCC] *Cancer Staging Manual* seventh edition) *ALK*-positive non–small cell lung cancer (NSCLC) only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One phase III, open-label, randomized controlled trial (RCT) (ALINA) demonstrated that adjuvant treatment with alectinib resulted in added clinical benefit in the primary end point — disease-free survival (DFS) — compared to adjuvant platinum-based chemotherapy in adult patients who had complete resection of their histologically confirmed stage IB (tumour ≥ 4 cm) to stage IIIA *ALK*-positive NSCLC (stages per AJCC seventh edition). As of the data cut-off date, median DFS by investigator assessment was not reached in the alectinib group versus 41.3 months (95% confidence interval [CI], 28.5 months to not evaluable [NE]) in the chemotherapy group, and the stratified hazard ratio (HR) was 0.24 (95% CI, 0.13 to 0.43, P < 0.0001). The difference in the probability of being disease-free and alive between alectinib and chemotherapy was [redacted] at 2 years and [redacted] at 4 years. Results were consistent with the sensitivity analysis of DFS per blinded independent central review (BICR). Furthermore, there was a benefit in central nervous system (CNS) DFS by investigator assessment. Median CNS DFS was not reached for either group, but the stratified HR was 0.22 (95% CI, 0.08 to 0.58) favouring alectinib. The between-group difference in the probability of being CNS disease-free and alive was [redacted] at 2 years and [redacted] at 4 years in favour of alectinib.

Patients identified a need for treatments that prolong life, stop or delay disease recurrence, prevent brain metastases, and improve quality of life. pERC concluded that alectinib may meet some of these needs, such as improving DFS and CNS DFS. pERC was uncertain whether alectinib would prolong overall survival (OS) because there were only 2 (1.5%) deaths in the alectinib group and 4 (3.1%) deaths in the chemotherapy group as of the data cut-off date (median follow-up of 27.8 months; [redacted]).

Using the sponsor-submitted price for alectinib and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for alectinib was $37,154 per quality-adjusted life-year (QALY) gained compared with platinum-based chemotherapy. Due to limitations related to the sponsor's inflexible modelling approach, results from this analysis were considered highly uncertain. pERC assessed scenarios with varying assumptions regarding long-term effects of treatment, which generated ICER estimates for alectinib ranging from $7,988 to $107,457 per QALY gained. Alectinib might be cost-effective at a willingness-to-pay (WTP) threshold of $50,000 per QALY gained for adult patients with completely resected stage IB (tumour size ≥ 4 cm) to IIIA (according to AJCC seventh edition) *ALK*-positive NSCLC. Price reductions would decrease the uncertainty associated with this recommendation.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Alectinib should be reimbursed in adults with stage IB (tumour ≥ 4 cm) to stage IIIA (per the AJCC seventh edition) *ALK*-positive NSCLC who have undergone tumour resection.	The ALINA trial demonstrated that adjuvant treatment with alectinib has a clinical benefit compared to platinum-based chemotherapy in patients with these characteristics.	pERC acknowledged that while the Health Canada–approved indication is according to the AJCC seventh edition, the eighth edition staging system is currently used in clinical practice in Canada. Based on clinical expert opinion and input from the sponsor, patients with stage II or III disease per the eighth edition staging system should be eligible. Although patients with stage IB disease (eighth edition staging system) were included in the ALINA trial, evidence is based on the results from 9 patients. As such, pERC advised that eligibility for those with stage IB disease (eighth edition staging system) and a tumour size equal to 4 cm be considered.
2. Patients must have good performance status.	Patients enrolled in the ALINA trial had an ECOG performance status of 0 or 1.	Based on clinical expert input, selected patients with an ECOG PS of 2 could be considered for treatment at the discretion of the treating physician.
Discontinuation		
3. Reimbursement of alectinib should be discontinued upon occurrence of any of the following: 3.1. disease recurrence 3.2. unacceptable toxicity 3.3. completion of 2 years of therapy.	In the ALINA trial, treatment with alectinib continued until completion of the 24-month treatment period, disease recurrence, unacceptable toxicity, withdrawal of consent, or death, whichever occurred first.	—
Prescribing		
4. Alectinib should be prescribed by clinicians with expertise in managing NSCLC.	This is meant to ensure that alectinib is prescribed for appropriate patients and that adverse effects are managed in an optimized and timely manner.	—
Pricing		
5. A reduction in price.	The committee noted that although the economic analysis suggested alectinib may be cost-effective at a WTP threshold of $50,000 per QALY gained, this conclusion was highly uncertain due to several key assumptions. Main sources of uncertainty included assumptions about the long-term treatment effects, treatment waning, and the potential for cure among patients who remain disease-free. Definitive evidence	—

Reimbursement condition	Reason	Implementation guidance
	to support these assumptions was lacking. The degree of uncertainty could not be fully addressed in the economic analysis given the inflexible structure of the model submitted by the sponsor. A price reduction would reduce the uncertainty regarding the cost-effectiveness of alectinib in this setting.	

AJCC = American Joint Committee on Cancer; ICER = incremental cost-effectiveness ratio; pERC = pan-Canadian Oncology Drug Review Expert Review Committee; QALY = quality-adjusted life-year; WTP = willingness to pay.

Discussion Points

- **Overall survival:** Patients identified a need for treatments that can prolong survival; however, pERC was unable to definitively conclude that adjuvant treatment with alectinib would meet this need due to uncertainty in the OS results from the small number of deaths that occurred during the follow-up period. Of note, alectinib is indicated for early-stage *ALK*-positive NSCLC; therefore, mature data for OS is unlikely to be available in this setting, and outcomes such as DFS and CNS DFS are considered clinically important.
- **Health-related quality of life:** Patients identified a need for treatments that improve quality of life. In the ALINA trial, HRQoL was evaluated using a generic outcome measure, Short Form (36) Health Survey version 2 (SF-36 v2), which may lack condition specificity for NSCLC. The results of the ALINA trial suggest that, compared to adjuvant chemotherapy, alectinib may improve the SF-36 v2 mental component summary score but evidence for the SF-36 v2 physical component summary is uncertain. Further, the certainty of evidence was determined to be low for an improvement in the SF-36 v2 mental component summary score and very low for the SF-36 v2 physical component summary score.
- **Side effects:** pERC discussed the safety profile of alectinib and noted that alectinib does not appear to be associated with a more favourable toxicity profile than chemotherapy, but rather it is associated with a different toxicity profile that is consistent with the expectations of the drug based on the mechanism of action. pERC concluded that these adverse events (AEs) were expected, and that side effects can be managed.
- **Testing considerations:** pERC discussed the requirement for *ALK* gene rearrangement testing when determining eligibility for alectinib. Overall, this is not anticipated to be an implementation issue as reflex testing for *ALK* gene rearrangement upon diagnosis of NSCLC has been recommended as the standard of care in Canada. Further, clinical experts consulted by the review team noted that *ALK* gene rearrangement testing following surgery is currently part of routine care for NSCLC. pERC also discussed the turnaround time for testing, which is estimated to be between 2 and 4 weeks. In consultation with the clinical experts, pERC agreed that patients should still be eligible

for alectinib if they had been started on chemotherapy while waiting for the results of the *ALK* gene rearrangement testing.

- **Economic analysis:** pERC highlighted that the cost-effectiveness of alectinib is sensitive to assumptions regarding long-term effects of treatment. Given the limited duration of trial data, pERC emphasized the importance of exploring various assumptions about the continued effect of alectinib on event rates after discontinuation. To address this, pERC assessed 2 scenario analyses: the first assumed no waning of treatment effect, implying indefinite relative effectiveness, and the second assumed that the treatment effect would wane after 24 months. These analyses produced a wide range of ICER estimates for alectinib, from $7,988 to $107,457 per QALY gained, reflecting the variability associated with these assumptions. pERC observed that while the base case ICER estimate remains less than the WTP threshold of $50,000 per QALY gained, results from scenario analyses point to the need for a price reduction.
- **Inflexibility of the submitted economic model introduces a high degree of uncertainty:** pERC raised concerns about the inflexible modelling approach used by the sponsor, particularly the exclusion of independently fitted parametric distributions to extrapolate long-term DFS. pERC additionally notes that requests from CDA-AMC to the sponsor to amend the model were not heeded. Concerns with the modelling approach, coupled with the uncertainty associated with the long-term comparative clinical effectiveness, led to uncertainty associated with the incremental cost-effectiveness estimates of alectinib. pERC acknowledged that alectinib may be cost-effective at the sponsor-submitted list price based on the clinical evidence provided. However, the results could not be fully verified by reviewers. The committee emphasized that price reductions would reduce some of the unresolved uncertainty resulting from the inflexibility of the sponsor's modelling approach.

Background

Lung cancer is a leading cause of cancer-associated mortality for both males and females in Canada. NSCLC accounts for approximately 85% of lung cancer cases. Staging is used to identify the extent of disease according to the AJCC–Union for International Cancer Control (UICC) tumour, node, and metastasis (TNM) staging system. In Canada, approximately half of all lung cancer cases are stages I to III (per the AJCC seventh edition) at diagnosis. Some patients with NSCLC may possess an underlying pathogenic driver mutation, such as an *ALK* gene rearrangement. Patients with *ALK*-positive disease are at a higher risk for developing brain metastases compared to those with *ALK*-negative disease.

According to the clinical experts consulted by the review team, the goal of treatment for adult patients with early-stage *ALK*-positive NSCLC is cure. Therefore, the first-line treatment option for these patients is typically surgery with the goal of complete resection. Currently, after tumour resection, most patients are treated with 4 cycles or months of adjuvant platinum-based chemotherapy depending on what regimen is used. After adjuvant chemotherapy is complete, patients receive routine surveillance and are observed for signs of disease progression.

Alectinib has been approved by Health Canada for adjuvant treatment following tumour resection for patients with stage IB (tumour ≥ 4 cm) to IIIA (according to AJCC seventh edition) *ALK*-positive NSCLC. Alectinib is a tyrosine kinase inhibitor. It is available as a 150-mg capsule, and the dosage recommended in the product monograph is 600 mg, given orally twice daily with food (total daily dose of 1,200 mg).

Sources of Information Used by the Committee

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

- a review of 1 pivotal, phase III, open-label, RCT (ALINA) in adult patients who had complete resection of histologically confirmed stage IB (tumour ≥ 4 cm) to stage IIIA *ALK*-positive NSCLC (per AJCC-UICC seventh edition)
- patients' perspectives gathered by 2 patient groups, Lung Cancer Canada (LCC) and the Lung Health Foundation
- input from public drug plans that participate in the CDA-AMC review process
- input from 2 clinical specialists with expertise diagnosing and treating patients with *ALK*-positive NSCLC
- input from 2 clinician groups, the LCC Medical Advisory Committee and the Ontario Health–Cancer Care Ontario (OH-CCO) Lung Cancer Drug Advisory Committees
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

Patient Input

Two patient groups, LCC and the Lung Health Foundation, submitted patient group input for this review. LCC gathered data through interviews with 17 patients and/or caregivers living in Canada or internationally who had experience with alectinib, either in the early stage (stages I to IIIB) setting or stage IV *ALK*-positive setting. As of April 2024, 14 of 17 patients interviewed for this submission were still being treated with alectinib. The Lung Health Foundation obtained input from patients with lung cancer via an online survey conducted in April 2024 (9 respondents, location not stated) and via interviews (3 respondents, living in Canada). Seven patients surveyed by the Lung Health Foundation had experience with alectinib.

Input from LCC noted that patients with *ALK*-positive NSCLC were most concerned about CNS disease because this type of lung cancer can be aggressive in spreading to the brain and current treatments with chemotherapy or radiation might not prevent metastases in the brain. Because the primary treatment goal in the current treatment paradigm is cure, LCC emphasized that this might be particularly important for patients with early-stage resectable disease. The LCC input reported that patients in the early-stage setting prefer a treatment that may effectively treat their disease and manage the symptoms of lung cancer, delay disease progression and get patients into long-term remission for improved survivorship, allow patients to

live longer and maintain their independence and functionality to minimize the burden on their caregivers and loved ones, allow patients to have a fulfilling and worthwhile quality of life, and have manageable side effects. Similarly, input from the Lung Health Foundation indicated that desired treatment outcomes included stopping or slowing the progression of the disease with minimal side effects.

Clinician Input

Input From Clinical Experts Consulted by the Review Team

According to the clinical experts consulted by the review team, for patients with early-stage *ALK*-positive NSCLC there is a need for effective treatments following tumour resection that are less toxic than adjuvant chemotherapy, can improve OS, and can decrease the risk of recurrence more than surgery alone or surgery plus adjuvant chemotherapy.

According to the clinical experts consulted by the review team, alectinib may replace chemotherapy in the adjuvant setting for some adult patients with stage IB (≥ 4 cm) to IIIA (staging per AJCC-UICC seventh edition) *ALK*-positive NSCLC. According to the clinical experts consulted by the review team, chemotherapy should remain available in the adjuvant setting, and adjuvant alectinib could be used following adjuvant chemotherapy.

Both clinical experts consulted by the review team noted that patients with completely resected stage II to IIIA *ALK*-positive NSCLC (staging per AJCC-UICC seventh edition) would be best suited for alectinib. For patients with completely resected stage IB (≥ 4 cm) *ALK*-positive NSCLC, 1 clinical expert noted that these patients would be best suited for alectinib, whereas the other clinical expert noted that these patients may not be as suitable. Both clinical experts consulted by the review team noted that patients with Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 to 2 could be eligible for alectinib. In terms of patients who are least suitable for alectinib, the clinical experts consulted by the review team noted that patients who are least suitable for alectinib could be those who do not have a demonstrated *ALK* translocation. According to the clinical experts consulted by the review team, OS, DFS, and time to recurrence are meaningful outcomes in adult patients with stage IB (≥ 4 cm) to IIIA (staging per AJCC-UICC seventh edition) *ALK*-positive NSCLC and need to be assessed with regular imaging. According to the clinical experts, alectinib should be discontinued due to unacceptable toxicity despite appropriate dose modifications, evidence of treatment failure (i.e., disease progression) or disease recurrence, or patient's withdrawal of consent.

According to the clinical experts, treatment with alectinib should occur in a medical oncology clinic and be supervised by a medical oncologist or pulmonary oncologist who is experienced in treating patients with lung cancer.

Clinician Group Input

Clinician group input on the review of alectinib was received from 2 clinician groups: the LCC Medical Advisory Committee and the OH-CCO Lung Cancer Drug Advisory Committees. A total of 36 clinicians (30 from LCC and 6 from the OH-CCO Lung Cancer Drug Advisory Committees) provided input for this submission.

Similar to the clinical experts consulted by the review team, the OH-CCO Lung Cancer Drug Advisory Committees indicated that the treatment goals include improved survival, quality of life, and prevention of recurrence. LCC noted that the primary goal for treatment for stages IB to IIIA (seventh edition) NSCLC is cure (i.e., to improve 5-year OS).

The OH-CCO Lung Cancer Drug Advisory Committees highlighted that there is an unmet need due to poor outcomes with adjuvant chemotherapy alone among patients with lung cancer who are often young and healthy and who may have a very high degree of brain tropism, with no known modifiable risk factors. The group noted that there is a need to improve CNS DFS.

Similar to the clinical experts consulted by the review team, both the OH-CCO Lung Cancer Drug Advisory Committees and LCC indicated that, in practice, adjuvant alectinib would be expected to be either used alone or used following adjuvant chemotherapy. In response to the patients best suited for treatment with alectinib, the OH-CCO Lung Cancer Drug Advisory Committees noted that patients would be selected based on the presence of *ALK* rearrangement, which is applicable for patients with resected tumour that is stage IIA or higher, or any node positive, T3/T4, or T2 of 4.0 cm or larger. However, LCC stated that all patients with resected stage IB to IIIA *ALK*-positive NSCLC may benefit from adjuvant alectinib irrespective of clinical characteristics.

Per LCC, prevention of disease recurrence would be the only truly meaningful end point in the early-stage setting when determining whether a patient is responding to treatment in clinical practice. Both clinician groups agreed that treatment discontinuation would be determined based on disease progression or recurrence, drug intolerance, or severe complications.

Drug Program Input

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

Table 2: Responses to Questions From the Drug Programs

Implementation issues	Response
Relevant comparators	
The ALINA trial compared adjuvant alectinib versus platinum-based chemotherapy (cisplatin-vinorelbine, cisplatin-gemcitabine, cisplatin-pemetrexed, or if intolerant to cisplatin, then carboplatin-vinorelbine, carboplatin-gemcitabine, carboplatin-pemetrexed). Do you have any comment on another relevant comparator that may be used in this setting: carboplatin-paclitaxel?	Both clinical experts consulted by the review team noted that, in their own clinical practice, they would not offer carboplatin-paclitaxel in the adjuvant setting. Chemotherapy would be used alone. pERC agreed with the clinical experts. pERC noted that the comparator regimens used in the ALINA trial were appropriate based on information from relevant guidelines and input from the clinical experts.

Implementation issues	Response
Considerations for initiation of therapy	
Who will be the eligible patient population based on the AJCC eighth edition staging system?	The clinical experts consulted by the review team noted that the ALINA trial included patients with stage IB (tumour ≥ 4 cm) to stage IIIA *ALK*-positive NSCLC (per AJCC-UICC seventh edition), which could be converted to resected stage II and III NSCLC per the AJCC eighth edition staging system. The sponsor indicated that patients with stage IB (tumour ≥ 4 cm) to stage IIIA *ALK*-positive NSCLC (per AJCC-UICC seventh edition) could be converted to resected stage IB to IIIA and select IIIB NSCLC per the AJCC eighth edition staging system. According to the sponsor, the ALINA study eligibility based on the AJCC seventh edition staging would be classified according to the AJCC eighth edition as: • stage IB = T2a with tumour size equal to 4 cm or T2a with endobronchial involvement or atelectasis (3 cm to 4 cm) • stage IIA • stage IIB • stage IIIA • stage IIIB = T3N2 OR T4N2 only for tumours > 7 cm or with diaphragmatic invasion. According to the sponsor, when the staging classification was changed from the seventh to the eighth edition, patients with IB disease > 4 cm per seventh edition became stage IIB per eighth edition. However, because ALINA enrolled some patients with stage IB ≥ 4 cm, there are still some patients with stage IB per eighth edition taking part in the study. In ALINA, there were 11 patients with stage IB disease (per eighth edition). Nine patients had tumour size = 4 cm; the remaining 2 patients had tumours < 4 cm (major protocol deviations reported). When patients were restaged using the AJCC eighth edition, there were 13 stage IIIB (per eighth edition) patients. pERC agreed with the proposed conversions from the AJCC seventh edition staging system to the eighth edition staging system and refers to the implementation guidance for initiation criteria (condition 1), which was included to align with the ALINA trial population.
Can patients be re-treated with downstream *ALK* inhibitors provided that disease recurrence occurs 6 months or more from the last dose of adjuvant alectinib? Are there preferences on re-treatment with alectinib versus other *ALK* inhibitors?	Both clinical experts consulted by the review team agreed that patients can be re-treated with *ALK* inhibitors if disease recurrence occurs 6 months or more from the last dose of adjuvant alectinib. According to the clinical experts consulted by the review team, there are 3 *ALK* inhibitors funded as first-line therapy for metastatic disease (alectinib, brigatinib, and lorlatinib), and there are no data to facilitate the selection of drug for the metastatic setting in patients who have received adjuvant alectinib. Both clinical experts consulted by the review team agreed that clinicians might choose a different drug rather than administration of alectinib again. pERC agreed with the clinical experts, noting that re-treatment with *ALK* inhibitors may be considered for patients who experience

Implementation issues	Response
	disease recurrence 6 months or longer after the last dose of adjuvant alectinib.
Considerations for discontinuation of therapy	
In the trial, alectinib was given for 24 months or until the occurrence of disease recurrence or unacceptable toxicity, whichever occurred first.	This is a comment from the drug plans to inform pERC deliberations. pERC noted that early discontinuation of alectinib due to toxicity was considered in the economic model, but not in the BIA.
Generalizability	
The following patients were excluded from the ALINA trial. Should they be considered for alectinib: • patients with ECOG PS > 1 • patients who are not eligible to receive platinum-based chemotherapy?	The clinical experts consulted by the review team noted that patients with ECOG PS of 2 could be considered for alectinib. However, the clinical experts consulted by the review team would not consider patients with ECOG PS of 3 or 4 to be eligible for alectinib. The clinical experts consulted by the review team noted that patients who are not eligible to receive platinum-based chemotherapy could still be eligible for alectinib. pERC agreed with the clinical experts.
On a time-limited basis, should patients who are currently receiving adjuvant chemotherapy be eligible to switch to adjuvant alectinib?	Both clinical experts consulted by the review team agreed that patients who are currently receiving adjuvant chemotherapy could switch to adjuvant alectinib. The clinical experts consulted by the review team further noted that sequentially adding alectinib after completing adjuvant chemotherapy could also be an option, although there is a lack evidence to either support or oppose sequential use. pERC agreed with the clinical experts, noting that for patients who are currently on adjuvant chemotherapy, a time-limited transition period should be implemented to allow for switching. For sequential use (i.e., adjuvant chemotherapy followed by adjuvant alectinib), it is reasonable to start chemotherapy before test results are available and consider switching to alectinib once results are available. pERC also noted that sequential use was not considered in the economic model and BIA.
Funding algorithm (oncology only)	
Drug may change place in therapy of comparator drugs.	This is a comment from the drug plans to inform pERC deliberations.
Drug may change place in therapy of drugs reimbursed in subsequent lines.	This is a comment from the drug plans to inform pERC deliberations.
Care provision issues	
Reflex testing must be in place. If adjuvant chemotherapy had to be started before *ALK* status is confirmed, should patients be given the option to switch to adjuvant alectinib once *ALK* positivity is confirmed?	The clinical experts consulted by the review team agreed that patients who start adjuvant chemotherapy before *ALK* status is confirmed could switch to adjuvant alectinib once *ALK* positivity is confirmed. However, the clinical experts consulted by the review team noted that this situation would be rare because, in current clinical practice, reflex testing results should be available at time of medical oncology consultation. According to the clinical experts, patients in Canada would normally not start adjuvant therapy

Implementation issues	Response
	before approximately 6 weeks after surgery, and testing results should be available by that time. pERC agreed with the clinical experts.
Should patients who have intolerable toxicities to platinum-based chemotherapy be switched to alectinib?	Both clinical experts consulted by the review team agreed that patients who have intolerable toxicities to platinum-based chemotherapy could be switched to alectinib as long as the patients meet other eligibility criteria (e.g., *ALK* positive). pERC agreed with the clinical experts.

AJCC = American Joint Committee on Cancer; BIA = budget impact analysis; ECOG PS = Eastern Cooperative Oncology Group performance status; NSCLC = non–small cell lung cancer; pERC = pan-Canadian Oncology Drug Review Expert Review Committee.

Clinical Evidence

Systematic Review

Description of Studies

One ongoing phase III, open-label, randomized active-controlled trial (ALINA, N = 257) was included in the sponsor-submitted systematic literature review. The ALINA trial enrolled adult patients who had complete resection of histologically confirmed stage IB (tumour ≥ 4 cm) to stage IIIA *ALK*-positive NSCLC (per AJCC-UICC seventh edition). Patients were randomized to the alectinib group (n = 130) or the platinum-based chemotherapy group (n = 127), stratified by disease stage (stage IB [tumours ≥ 4 cm] versus stage II versus stage IIIA) and race (Asian versus non-Asian). The primary objective of the ALINA trial was to compare the efficacy of alectinib and chemotherapy, measured by DFS per investigator assessment. Other efficacy and safety outcomes included OS, CNS DFS, SF-36 v2 mental and physical component scores, as well as harms, including AEs, serious AE (SAEs), withdrawal, and deaths.

The median age of the intention-to-treat (ITT) population in the ALINA trial was 56 years (range, 26 to 87 years), and most were younger than 65 years (196 of 257; 76.3%). Of the 257 patients enrolled, 47.9% were male and 52.1% were female, 55.6% were Asian, and 41.6% were white. There were 10.1% (26 of 257) of patients with stage IB disease, 31.1% (80 of 257) with stage IIA disease, 3.9% (10 of 257) with stage IIB disease, and 54.9% (141 of 257) with stage IIIA disease. Most of the ITT population had nonsquamous histology (248 of 257; 96.5%), of which 96% (238 of 248) were adenocarcinoma.

Efficacy Results

The data cut-off date for efficacy results was June 26, 2023.

Overall Survival

In the ALINA ITT population, the median duration of survival follow-up was 27.8 months ([redacted]). As of the data cut-off date (June 26, 2023), OS was immature. There were 2 OS events (1.5%) in the alectinib group and 4 OS events (3.1%) in the chemotherapy group. The stratified HR for OS was 0.46 (95% CI, 0.08 to 2.52).

DFS per Investigator Assessment

In the ALINA ITT population, the median duration of follow-up for DFS was [redacted]. As of June 26, 2023, 11.5% (15 of 130) of the patients in the alectinib group and 39.4% (50 of 127) in the chemotherapy group had DFS events. The stratified HR was 0.24 (95% CI, 0.13 to 0.43, [redacted]), which met the prespecified stopping boundary (P ≤ 0.0077) in favour of alectinib. The difference in the probability of being disease-free between alectinib and chemotherapy was [redacted] at 2 years, [redacted] at 3 years, and [redacted] at 4 years. Median DFS was not reached in the alectinib group and was 41.3 months (95% CI, 28.5 months to NE) in the chemotherapy group. The results in the subgroup classified by disease stage appeared consistent with the results in the ITT population in direction and magnitude, although there were few patients in the stage IB subgroup (n = 26), resulting in a wide 95% CI.

DFS per BICR was assessed as a sensitivity analysis in the ITT population. The stratified HR was 0.30 (95% CI, 0.17 to 0.54, [redacted]. Additional sensitivity analyses assessing the impact of missing disease assessments, stratification errors, and the Ukraine-Russia conflict has similar results as the primary analysis.

CNS DFS per Investigator Assessment

In the ALINA ITT population, the median duration of follow-up for CNS DFS was [redacted]. As of June 26, 2023, 3.8% (5 of 130) of the patients in the alectinib group and 14.2% (18 of 127) in the chemotherapy group had CNS DFS events. The stratified HR was 0.22 (95% CI, 0.08 to 0.58), favouring the alectinib group. The difference in the probability of being CNS disease-free between alectinib and chemotherapy was [redacted] at 2 years, [redacted] at 3 years, and [redacted] at 4 years. Median CNS DFS was not reached for either group.

SF-36 v2 Mental Component Summary Score

The SF-36 v2 mental component summary score ranges from 0 to 100 in which a higher score indicates better HRQoL. In the alectinib group, the mean change from baseline at week 12 was 3.65 (95% CI, 1.96 to 5.35), indicating an improvement. However, no improvement was observed in the chemotherapy group at week 12 (mean change from baseline = −2.24; 95% CI, −4.05 to −0.43). At week 12, the difference in

mean change from baseline between the alectinib group and the chemotherapy group was 5.89 (95% CI, 3.41 to 8.37).

SF-36 v2 Physical Component Summary Score

The SF-36 v2 physical component summary score ranges from 0 to 100 in which a higher score indicates better HRQoL. In the alectinib group, the mean change from baseline at week 12 was 1.10 (95% CI, −0.02 to 2.21), indicating an improvement. However, no improvement was observed in the chemotherapy group at week 12 (mean change from baseline = −0.40; 95% CI, −1.59 to 0.78). At week 12, the difference in mean change from baseline between the alectinib group and the chemotherapy group was 1.50 (95% CI, −0.13 to 3.13).

Harms Results

The data cut-off date for harms outcomes was June 26, 2023. For the patients included in the safety evaluation, the median duration of safety follow-up was 24.8 months (range, 1.1 to 26.2 months) in the alectinib group and 3.7 months (range, 1.6 to 5.3 months) in the chemotherapy group.

The proportion of patients who had at least 1 AE in the alectinib group was slightly higher than that of patients in the chemotherapy group (98.4% versus 93.3%). Blood creatine phosphokinase increased (43.0% of patients), constipation (42.2% of patients), aspartate aminotransferase increased (41.4% of patients), alanine aminotransferase (ALT) increased (33.6% of patients), and blood bilirubin increased (33.6% of patients) were among the most common AEs in the alectinib group. The proportions of patients who had at least 1 grade 3 to 5 AE were similar between the alectinib and chemotherapy groups (29.7% versus 30.8%). The most common grade 3 to 5 AEs in the alectinib group were increased blood creatine phosphokinase (6.3%) and appendicitis (3.1%). There was a higher percentage of patients in the alectinib group who experienced SAEs compared to patients in the chemotherapy group (13.3% versus 8.3%). The most common SAE in the alectinib group was appendicitis (3.1%). Discontinuation of alectinib occurred in 5.5% of patients in the alectinib group and 12.5% in the chemotherapy group. There were 2 deaths in the alectinib group (1.6%) versus 5 deaths in the chemotherapy group (4.2%).

Critical Appraisal

In the ALINA trial, a higher percentage of patients in the alectinib group were younger, female, had better performance status, and did not have a history of smoking at baseline. These could indicate a possibly better prognosis of patients in the alectinib group compared with the chemotherapy group. The review team, in consultation with the clinical experts, determined that the bias introduced by the imbalance was likely trivial. DFS per investigator assessment (primary end point) could be impacted by detection bias due to the open-label design; however, the review team determined that the risk was low because the results of DFS per investigator assessment were relatively consistent with those of DFS per BICR and the analysis of concordance showed a relatively good agreement between the ways of assessment. The risk of performance bias due to the open-label study design could not be ruled out for SF-36 v2, a self-reported HRQoL outcome, as well as subjective harms outcomes. OS was immature at the current data cut-off time. The ALINA trial reported OS data up to 48 months. However, according to the clinical experts consulted by the review team, a follow-up of at least 60 months will likely be needed to allow for further understanding the treatment effects

of alectinib on OS. DFS was adjusted for multiplicity, but CNS DFS was not. Additionally, DFS and CNS DFS were assessed at an interim analysis, resulting in a potential risk of overestimation of the true magnitude of the difference between alectinib and chemotherapy. Nonetheless, there were minor concerns with the internal validity of the results of DFS and CNS DFS. However, the impact of missing data on DFS estimates due to loss to follow-up or dropout remained unclear because relevant information for the review team to make the judgment was not provided. Based on the patient disposition information, discontinuation of the study for lost to follow-up and withdrawal by patients occurred among [redacted] of the alectinib group and [redacted] of the chemotherapy group. There was an imbalance between the 2 groups [redacted]. The review team determined that the potential bias due to missing outcome data could not be ruled out but might be small due to the small imbalance. The missing data issue was also identified in HRQoL outcomes. Data were assumed to be missing at random, but this might not be plausible, and sensitivity analyses using different assumptions were not presented.

There are several considerations related to the generalizability of the ALINA trial. The clinical experts consulted by the review team noted that using adjuvant platinum-based chemotherapy as the comparator in the ALINA trial was appropriate because adjuvant chemotherapy is the standard of care in the Canadian setting in adult patients. The clinical experts consulted by the review team generally considered the patient eligibility criteria used in the ALINA trial appropriate and reflective of the criteria they would use to select patients in Canada. However, the clinical experts consulted by the review team also commented that the eligibility criteria are restrictive, and patients who could benefit from alectinib were excluded from the trial (e.g., patients with a ECOG PS of 2, patients who are not eligible to receive a platinum-based chemotherapy regimen, patients who had prior adjuvant radiotherapy, patients who had prior systemic anticancer therapy, patients with stage IIIA NSCLC who received postoperative radiation therapy, patients with prior malignancies, patients who had a history of organ transplant, and patients who are HIV positive).

GRADE Summary of Findings and Certainty of the Evidence

For pivotal studies and RCTs identified in the sponsor's systematic review, Grading of Recommendations Assessment, Development and Evaluation (GRADE) was used to assess the certainty of the evidence for outcomes considered most relevant to inform the expert committee deliberations, and a final certainty rating was determined as outlined by the GRADE Working Group:

Following the GRADE approach, evidence from RCTs started as high-certainty evidence and could be rated down for concerns related to study limitations (which refers to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias.

When possible, certainty was rated in the context of the presence of an important (nontrivial) treatment effect; if this was not possible, certainty was rated in the context of the presence of any treatment effect (i.e., the clinical importance is unclear). In all cases, the target of the certainty of evidence assessment was based on the point estimate and where it was located relative to the threshold for a clinically important effect (when a threshold was available) or to the null.

The reference points for the certainty of evidence assessment for OS, DFS per investigator assessment, and CNS DFS were set according to the presence of an important effect based on thresholds agreed upon

by clinical experts consulted by the review team for this review. The reference points for the certainty of evidence assessment for SF-36 v2 mental component summary score and SF-36 v2 physical component summary score were set according to the presence of an important effect based on thresholds identified from the literature by the sponsor. For harm events, the certainty of evidence was summarized narratively.

The selection of outcomes for GRADE assessment was based on the sponsor's Summary of Clinical Evidence, consultation with clinical experts, and input received from patient and clinician groups and public drug plans. The following list of outcomes was finalized in consultation with expert committee members:

- survival outcomes (OS, DFS)
- HRQoL outcome (SF-36 v2 mental component summary score, SF-36 v2 physical component summary score)
- harms (AEs of grade 3 or higher).

Results of GRADE Assessments

Table 3 presents the GRADE summary of findings for alectinib versus platinum-based chemotherapy in adult patients with stage IB (≥ 4 cm) to IIIA (staging per AJCC-UICC seventh edition) *ALK*-positive NSCLC.

Table 3: Summary of Findings for Alectinib Versus Platinum-Based Chemotherapy for Adult Patients With Stage IB (≥ 4 cm) to IIIA (Staging per AJCC-UICC Seventh Edition) *ALK*-Positive NSCLC

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Chemotherapy	Alectinib	Difference		
OS – ITT (data cut-off date: June 26, 2023)							
Probability of being alive at 48 months Median follow-up duration (months): 27.8 for alectinib group; 28.4 for chemotherapy group	257 (1 RCT)	NR	[redacted] per 1,000	[redacted] per 1,000 ([redacted] to [redacted] per 1,000)	[redacted] per 1,000 ([redacted] to [redacted] per 1,000)	Moderate[a]	Alectinib likely results in little or no difference in the probability of being alive at 48 months, compared to chemotherapy.
Probability of being alive at 60 months or more	NR	NR	NR	NR	NR	NA	There is no evidence about the effect of alectinib on the probability of being alive at 60 months or more (at present, OS data are immature).
DFS per investigator assessment – ITT (data cut-off date: June 26, 2023)							
Probability of being disease-free at 24 months Median follow-up duration (months [redacted] for alectinib group; [redacted] for chemotherapy group	257 (1 RCT)	NR	637 per 1,000	936 per 1,000 (894 per 1,000 to 979 per 1,000)	[redacted] per 1,000 ([redacted] to [redacted] per 1,000)	Moderate[b]	Alectinib likely results in a clinically important increase in the probability of being disease-free at 24 months compared to chemotherapy.
Probability of being disease-free at 48 months Median follow-up duration (months): [redacted] for alectinib group; [redacted] for chemotherapy group	257 (1 RCT)	NR	462 per 1,000	[redacted] per 1,000 ([redacted] to [redacted] per 1,000)	[redacted] per 1,000 ([redacted] to [redacted] per 1,000)	Moderate[c]	Alectinib likely results in a clinically important increase in the probability of being disease-free at 48 months compared to chemotherapy.
CNS DFS – ITT (data cut-off date: June 26, 2023)							
Probability of being CNS disease-free at 24 months	257 (1 RCT)	NR	858 per 1,000	984 per 1,000 (961 per 1,000 to	[redacted] per 1,000 ([redacted]	Moderate[d]	Alectinib likely results in a clinically important increase in the probability of being CNS

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Chemotherapy	Alectinib	Difference		
Median follow-up duration (months): [redacted] for alectinib group; [redacted] for chemotherapy group				1,000 per 1,000)	to [redacted] per 1,000)		disease-free at 24 months compared to chemotherapy.
Probability of being CNS disease-free at 48 months Median follow-up duration (months): [redacted] for alectinib group; [redacted] for chemotherapy group	257 (1 RCT)	NR	[redacted] per 1,000	[redacted] per 1,000 ([redacted] to [redacted] per 1,000)	[redacted] per 1,000 ([redacted] to [redacted] per 1,000)	Moderate[e]	Alectinib likely results in a clinically important increase in the probability of being CNS disease-free at 48 months compared to chemotherapy.
HRQoL – ITT (data cut-off date: June 26, 2023)							
SF-36 v2 mental component summary score (0 [worst] to 100 [best]) Follow-up: week 12	257 (1 RCT)	NR	−2.24	3.65 (NR)	5.89 (3.41 to 8.37)	Low[f]	Alectinib may result in a clinically important improvement in the SF-36 v2 mental component summary score at 12 weeks compared to chemotherapy.
SF-36 v2 physical component summary score (0 [worst] to 100 [best]) Follow-up: week 12	257 (1 RCT)	NR	−0.40	1.10 (NR)	1.50 (−0.13 to 3.13)	Very low[g]	The evidence is uncertain about the effect of alectinib on the SF-36 v2 physical component summary score at 12 weeks compared to chemotherapy.
Harms, safety-evaluable population (data cut-off date: June 26, 2023)							
AEs of grade 3 or higher	248 (1 RCT)	RR = 0.963 (0.621 to 1.393)	308 per 1,000 (NR)	297 per 1,000 (NR)	12 fewer per 1,000 (126 fewer to 103 more per 1,000)	Low[h]	Alectinib may result in little or no difference in AEs of grade 3 or higher compared to chemotherapy.

AE = adverse event; AJCC = American Joint Committee on Cancer; BICR = blinded independent central review; CI = confidence interval; CNS = central nervous system; DFS = disease-free survival; HRQoL = health-related quality of life; MID = minimal important difference; NA = not applicable; NR = not reported; NSCLC = non–small cell lung cancer; RCT = randomized controlled trial; SF-36 v2 = Short Form (36) Health Survey version 2; UICC = Union for International Cancer Control.

Notes: The start point for the study design of ALINA (i.e., RCT) was high certainty. Study limitations (which refer to internal validity or risk of bias), indirectness, imprecision of effects, and publication bias were considered when assessing the certainty of the evidence. All serious concerns in these domains that led to the rating down of the level of certainty are documented in the table footnotes.

The between-group differences for SF-36 v2 mental and physical component summary scores and AEs of grade 3 or higher were not part of the sponsor's statistical analysis plan and were requested by the review team to inform the interpretation of the findings.

[a]Certainty was not rated down for risk of bias. Compared with the chemotherapy group, a higher percentage of patients in the alectinib group were younger, female, with better performance status, and without a history of smoking at baseline, which indicated a possibly better prognosis of patients in the alectinib group. However, these imbalances in patient characteristics at baseline might have been the result of the relatively small sample size, which challenged achieving prognostic balance; as such, we did not rate down for risk of bias. Indirectness was not rated down although the clinical experts consulted by the review team noted that year 5 was the earliest time point at which a meaningful between-group difference in probability of being alive would be expected. Rated down 1 level for imprecision. The point estimate suggests little to no difference while the upper bound of the 95% CI indicates benefits based on a clinical importance threshold of 5% to 10% suggested by clinical experts.

[b]Certainty was not rated down for risk of bias. Although the assessment of DFS per investigator was prone to detection bias due to the open-label design, the risk was considered low because relatively consistent results were found using DFS per BICR, although absolute between-group differences by BICR were smaller in magnitude, they remained clinically important. Rated down 1 level for imprecision. The clinical experts consulted by the review team suggested that the effect estimate and lower bound of the 95% CI were clinically important, but the result was informed by an interim analysis with a small number of events resulting in potential for overestimation of the true effect.

[c]Certainty was not rated down for risk of bias. Although the assessment of DFS per investigator was prone to detection bias due to the open-label design, the risk was considered low because relatively consistent results were found using DFS per BICR, although absolute between-group differences by BICR were smaller in magnitude but remained clinically important. Rated down 1 level for imprecision. The clinical experts consulted by the review team suggested that the effect estimate and lower bound of the 95% CI were clinically important, but the result was informed by an interim analysis with a small number of events resulting in potential for overestimation of the true effect.

[d]Certainty was not rated down for risk of bias. Although the assessment of CNS DFS was prone to detection bias due to the open-label design, the risk was considered relatively low (may be some potential for overestimation, similar to DFS per investigator). Rated down 1 level for imprecision. The point estimate suggests benefit while the lower bound of the 95% CI suggests little to no difference based on a clinical importance threshold of 10% suggested by clinical experts.

[e]Certainty was not rated down for risk of bias. Although the assessment of CNS DFS was prone to detection bias due to the open-label design, the risk was considered relatively low. Indirectness was not rated down (may be some potential for overestimation, similar to DFS per investigator). Rated down 1 level for imprecision. The point estimate suggests benefit while the lower bound of the 95% CI suggests little to no difference based on a clinical importance threshold of 10% suggested by clinical experts.

[f]Certainty was rated down 2 levels for risk of bias due to imbalanced missing outcome data and a risk of performance bias associated with the open-label design and the subjective nature of the measure. Certainty was not rated down for imprecision. The 95% CI excludes the MID estimate of 3 provided by the sponsor.

[g]Certainty was rated down 2 levels for risk of bias due to imbalanced missing outcome data and a risk of performance bias associated with the open-label design and the subjective nature of the measure. Certainty was rated down 1 level for imprecision. The point estimate suggests little to no important difference, but the upper bound of the 95% CI suggests potential for benefit based on the MID estimate of 2 points provided by the sponsor.

[h]Rated down 2 levels for imprecision. The null was used as the threshold for clinical relevance. The point estimate suggested little to no important difference, but the 95% CI includes potential for both benefit and harm.

Economic Evidence

Cost and Cost-Effectiveness

Table 4: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Semi-Markov model
Target population	Adult patients with stage IB (≥ 4 cm) to IIIA (according to AJCC-UICC seventh edition) *ALK*-positive NSCLC following tumour resection
Treatment	Alectinib as adjuvant treatment
Dose regimen	600 mg twice daily (total daily dose of 1,200 mg) for 24 months
Submitted price	Alectinib: $44.28 per 150 mg capsule
Submitted treatment cost	Annual drug acquisition cost of $129,372 per patient 28-day drug acquisition cost of $9,918 per patient
Comparator	CHT: • Cisplatin or carboplatin plus vinorelbine • Cisplatin or carboplatin plus gemcitabine • Cisplatin or carboplatin plus pemetrexed
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (40 years)
Key data source	ALINA trial; data cut-off date: June 26, 2023 (ITT population)
Submitted results	Alectinib was dominant compared with CHT (incremental costs: –$2,454; incremental QALYs: 3.54).
Key limitations	• The sponsor excluded independently fitted parametric distributions from the submitted model. As a result, all possible extrapolations for DFS assume that the hazard rates for alectinib and CHT remain proportional across the lifetime horizon. CDA-AMC was unable to relax the assumption of proportional hazards owing to the inflexible structure of the model. • The long-term impact of alectinib on DFS is highly uncertain. The sponsor's modelling approach resulted in sustained increases in the DFS benefit for alectinib during the extrapolated period, a concern noted by clinical experts due to the absence of evidence supporting this assumption. The entirety of incremental QALYs predicted by the sponsor's analysis are accrued in the "Disease Free" health state, with 84% of these accrued through extrapolation. • The sponsor assumed that 95% of all patients who remained disease-free after 5 years and 100% of patients who remained disease-free after 10 years were cured of disease. Clinical experts consulted by CDA-AMC, as well as the published literature, suggest that the cure assumption modelled by the sponsor was overly optimistic. • In the submitted model, the treatment effect of alectinib persists for 38 years after discontinuation in patients who are not cured. Clinical experts indicated it is plausible for the effect of alectinib to wane earlier than assumed by the sponsor given the lack of evidence for long-term effectiveness.

Component	Description
	• The sponsor's base case predicts a survival benefit with alectinib compared to CHT (incremental LYs: 5.94) over a 40-year horizon; however, no difference in survival was observed in the ALINA trial (median follow-up: 28 months). Clinical experts consulted by CDA-AMC indicated that it is uncertain whether and to what extent delayed disease progression will translate to gains in OS. • The distribution of nonmetastatic and metastatic recurrences among patients treated with alectinib and CHT remains uncertain because the sponsor's assumptions were based on treatment-specific data from the ALINA trial without formal statistical testing or long-term evidence. Consequently, the sponsor's assumed benefit of a higher proportion of nonmetastatic recurrences in patients treated with alectinib compared to CHT carries significant uncertainty. • The sponsor inappropriately applied treatment-specific utility values for alectinib and CHT. This approach overestimated the **incremental QALYs associated with alectinib** and is counter to best practice guidance, which recommends the use of health state–specific utilities.
CDA-AMC reanalysis results	• The CDA-AMC base case was derived by making changes to the following model parameters: adopting alternative parametric survival extrapolations of DFS, assuming that 90% of patients who are disease-free 5 years after treatment initiation and 95% of patients who are disease-free 10 years after treatment initiation would be considered cured, assuming treatment waning begins at 28 months and ends at 60 months, using pooled trial data to inform the type of first disease recurrence, and applying health state–specific utility values. • In the CDA-AMC base case, alectinib is associated with an ICER of $37,154 per QALY gained compared to CHT (incremental costs: $87,506; incremental QALYs: 2.36). • The cost-effectiveness of alectinib was sensitive to assumptions concerning treatment waning and cure among patients who remain disease-free. When assuming no further effect beyond treatment discontinuation (i.e., 24 months), the ICER for alectinib increased to $107,457 per QALY gained compared to CHT. When assuming a lower proportion of patients would be cured (65%) after remaining disease-free for 10 years, the ICER for alectinib increased to $55,735 per QALY gained relative to CHT.

AJCC = American Joint Committee on Cancer; CHT = platinum-based chemotherapy; DFS = disease-free survival; ICER = incremental cost-effectiveness ratio; ITT = intention to treat; LY = life-year; NSCLC = non–small cell lung cancer; OS = overall survival; QALY = quality-adjusted life-year; UICC = Union for International Cancer Control; WTP = willingness to pay.

Budget Impact

CDA-AMC identified the following key limitations with the sponsor's analysis: the target population size is associated with uncertainty, the *ALK* positivity rate in NSCLC is uncertain in the Canadian context and was found to have notable impact on the total patients eligible for treatment, the market uptake of alectinib is uncertain, and the proportion of patients with public coverage is uncertain. CDA-AMC did not undertake a reanalysis of the sponsor's BIA because the issues related to uncertainty in parameters used to derive the target population and market shares could not be adequately addressed with the available information. The sponsor's base case estimated the budget impact of alectinib to be $6,022,741 in year 1, $13,292,716 in year 2, and $14,343,161 in year 3, for a 3-year total of $33,658,618. CDA-AMC presented a series of scenario analyses to test the impact of alternative assumptions on the estimated population size and budget impact. Assuming a higher *ALK* positivity rate of 7% resulted in a 3-year total budget impact of $58,902,582. Assuming higher market uptake for alectinib reaching 80% in year 1, 85% in year 2, and 90% in year 3

resulted in a 3-year total budget impact of $35,789,849. Assuming 100% public coverage resulted in a 3-year total budget impact of $48,083,741.

pERC Information

Members of the Committee

Dr. Maureen Trudeau (Chair), Mr. Daryl Bell, Dr. Philip Blanchette, Dr. Kelvin Chan, Dr. Matthew Cheung; Dr. Michael Crump, Dr. Jennifer Fishman, Mr. Terry Hawrysh, Dr. Yoo-Joung Ko, Dr. Christian Kollmannsberger, 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: September 11, 2024

Regrets: None

Conflicts of interest: None

Canada's Drug Agency
L'Agence des médicaments du Canada
Drugs. Health Technologies and Systems. Médicaments, technologies de la santé et systèmes.

ISSN: 2563-6596

Canada's Drug Agency (CDA-AMC) is a pan-Canadian health organization. Created and funded by Canada's federal, provincial, and territorial governments, we're responsible for driving better coordination, alignment, and public value within Canada's drug and health technology landscape. We provide Canada's health system leaders with independent evidence and advice so they can make informed drug, health technology, and health system decisions, and we collaborate with national and international partners to enhance our collective impact.

Questions or requests for information about this report can be directed to Requests@CDA-AMC.ca.