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

January 2025

Drugs Health Technologies Health Systems

Provisional Funding Algorithm

Indication: Anaplastic lymphoma kinase–positive non–small cell lung cancer

This report supersedes the provisional funding algorithm report for anaplastic lymphoma kinase–positive non–small cell lung cancer dated May 2022.
Please always check provisional funding algorithms to ensure you are reading the most recent algorithm report.

Background

Following a request from jurisdictions, Canada's Drug Agency (CDA-AMC) may design or update an algorithm depicting the sequence of funded treatments for a particular tumour type. These algorithms are proposals for the jurisdictions to implement and adapt to the local context. As such, they are termed "provisional." Publishing of provisional algorithms is meant to improve the transparency of the oncology drug funding process and promote consistency across jurisdictions.

Provisional funding algorithms are based on 3 principal sources of information:

- pan-Canadian Oncology Drug Review Expert Review Committee (pERC) reimbursement recommendations and/or implementation guidance regarding the place in therapy and sequencing of drugs
- implementation advice from panels of clinicians convened by CDA-AMC concerning the sequencing of drugs in the therapeutic space of interest
- existing oncology drug reimbursement criteria and legacy funding algorithms adopted by jurisdictional drug plans and cancer agencies.

Note that provisional funding algorithms are not treatment algorithms; they are neither meant to detail the full clinical management of each patient nor the provision of each drug regimen. The diagrams may not contain a comprehensive list of all available treatments, and some drugs may not be funded in certain jurisdictions. All drugs are subject to explicit funding criteria, which may also vary between jurisdictions. Readers are invited to refer to the cited sources of information on the CDA-AMC website for more details.

Provisional funding algorithms also delineate treatment sequences available to patients who were never treated for the condition of interest (i.e., incident population). Time-limited funding of new options for previously or currently treated patients (i.e., prevalent population) is not detailed in the algorithm.

Provisional funding algorithms may contain drugs that are under consideration for funding. Algorithms will not be dynamically updated by CDA-AMC following changes to drug funding status. Revisions and updates will occur only upon request by jurisdictions.

Jurisdictional cancer drug programs requested a CDA-AMC provisional funding algorithm on anaplastic lymphoma kinase (*ALK*)–positive non–small cell lung cancer. However, no outstanding implementation issues were identified, and no additional implementation advice is provided in this report. The algorithm depicted herein is meant to reflect the current and anticipated funding landscape based on the previously mentioned sources of information.

History and Development of the Provisional Funding Algorithm

We published the first rapid provisional funding algorithm report for *ALK*-positive non–small cell lung cancer in May 2022. The funding of the following drugs in the advanced or metastatic settings was discussed in this report: alectinib, brigatinib, ceritinib, crizotinib, lorlatinib, atezolizumab, pembrolizumab, nivolumab, and other therapies that have been reviewed by CDA-AMC (e.g., pemetrexed).

The update for this rapid provisional funding algorithm report is to incorporate the latest reimbursement recommendation of alectinib for adjuvant treatment following resection for patients with *ALK*-positive non–small cell lung cancer.

Table 1: Relevant Recommendations

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing

Lorlatinib (Lorbrena)	April 4, 2022	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 if all conditions pertaining to initiation, renewal, discontinuation, prescribing, pricing, and feasibility of adoption are met.
		• Treatment with lorlatinib should only be initiated in adult patients (≥ 18 years) with NSCLC and confirmed *ALK*-positive status who meet the following criteria:
		  ◦ Locally advanced (stage IIIB not amenable for multimodality treatment) or metastatic (stage IV) NSCLC (per AJCC 7th edition);
		  ◦ No prior systemic treatment for advanced or metastatic NSCLC;
		• Patients must have good performance status.
		• Lorlatinib should not be used in patients with the following conditions or comorbidities:
		  ◦ severe acute or chronic medical or psychiatric conditions
		• 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.
		• Treatment with lorlatinib should be discontinued upon occurrence of any of the following:
		  ◦ documented disease progression per RECIST (version 1.1) criteria or clinical progression
		  ◦ toxicity that cannot be managed by dose reduction.
		• 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.
		• 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.
		• The feasibility of adoption of lorlatinib must be addressed.
		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.
		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.
		In clinical practice, some patients who have oligometastatic progression may continue their first-line TKI therapy after completion of treatment for the

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		localized progression. pERC agreed this treatment approach would also be reasonable for patients treated with lorlatinib.
	January 30, 2020	pERC does not recommend reimbursement of lorlatinib for the treatment of adult patients with *ALK*-positive metastatic NSCLC who have progressed on: crizotinib and at least one other *ALK* inhibitor, or patients who have progressed on ceritinib or alectinib.
Brigatinib (Alunbrig)	April 21, 2021	pERC conditionally recommends reimbursement of brigatinib for the treatment of adult patients with *ALK*-positive locally advanced (not amenable to curative therapy) or metastatic NSCLC previously untreated with an *ALK* inhibitor if the following conditions are met: • cost-effectiveness is improved to an acceptable level • the public drug plan costs of treatment with brigatinib should not exceed the public drug plan price of alectinib, which is currently reimbursed for *ALK* inhibitor–naïve locally advanced or metastatic NSCLC. pERC was unable to make an informed recommendation on the optimal sequencing of available treatments following progression on treatment with brigatinib. pERC noted that it did not review evidence to inform this clinical situation. However, pERC recognized that provinces would need to address this issue upon implementation of reimbursement of brigatinib and noted that a national approach to developing clinical practice guidelines addressing sequencing of treatments would be of value. pERC discussed treatment options that would be available to patients who discontinued brigatinib in the case of toxicity. In the absence of sufficient evidence to inform this situation pERC agreed with the CGP that intolerance to any *ALK* inhibitor in the first-line setting (crizotinib or alectinib) would be reasonable grounds for consideration of brigatinib and vice versa. It is recognized that the *ALK* inhibitors have differences in their toxicity profiles and patients may have better side effect profiles with an alternate to allow ongoing disease control. pERC discussed preference for brigatinib or alectinib in the first-line setting and under what circumstances would first-line brigatinib be preferred over first-line alectinib if brigatinib is reimbursed. pERC agreed with the CGP that given the absence of a direct comparison, there is no robust evidence to ascertain which of the drugs (i.e., brigatinib or alectinib) has superior efficacy or a better safety profile. pERC and the CGP anticipated that some clinicians may prefer using alectinib as the trial evidence for alectinib has longer follow-up time (median follow-up time in the ALEX trial was 37.8 months) than the trial evidence for brigatinib (median follow-up time in the ALTA-1L trial was 24.9 months). In addition, Canadian clinicians are generally more experienced with alectinib than with brigatinib. Situations in which there would be preference to use alectinib may include patients who have baseline dyspnea or hypoxia (given the rare complication of an early onset pulmonary event), or poorly controlled hypertension. Alternatively, there may be a preference to use brigatinib if there are concerns about the development of weight gain, peripheral edema, myalgia, constipation, or blurry vision.
	August 1, 2019	pERC does not recommend reimbursement of brigatinib (Alunbrig) for the treatment of adult patients with *ALK*-positive locally advanced or metastatic NSCLC who have progressed on or who were intolerant to an *ALK* inhibitor (crizotinib).

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
Atezolizumab (Tecentriq)	June 20, 2018	pERC recommends reimbursement of atezolizumab (Tecentriq) for patients with locally advanced or metastatic NSCLC and who have disease progression on or after cytotoxic chemotherapy only if the following conditions are met: • cost-effectiveness being improved to an acceptable level • the drug plan cost of treatment with atezolizumab should not exceed the public drug plan cost of treatment with the least costly alternative immunotherapy. Patients with genomic tumour driver aberrations (e.g., epidermal growth factor receptor or *ALK*) should first be treated with targeted agents followed by cytotoxic chemotherapy prior to receiving atezolizumab. Treatment with atezolizumab should continue until confirmed disease progression or unacceptable toxicity. pERC concluded that optimal sequencing of atezolizumab and other treatments now available for advanced or metastatic NSCLC is currently unknown. pERC was, therefore, unable to make an evidence-informed recommendation on sequencing following treatment with atezolizumab. pERC also noted that there is no direct evidence to inform the comparative efficacy of atezolizumab with PD-1 inhibitors (nivolumab and pembrolizumab). Thus, with their overlapping indications, there is no evidence to inform the choice of atezolizumab over the other available agents, or vice versa. There is also no evidence to support using PD-L1/PD-1 inhibitors in sequence (e.g., atezolizumab then nivolumab or pembrolizumab, or vice versa).
Alectinib (Alecensaro)	November 18, 2024	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 NSCLC only if the following conditions are met: **Initiation** 1. Alectinib should be reimbursed in adults with stage IB (tumours ≥ 4 cm) – stage IIIA (as per the AJCC seventh edition) *ALK*-positive NSCLC who have undergone tumour resection. 2. Patients must have good performance status. **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 **Prescribing** 4. Alectinib should be prescribed by clinicians with expertise in managing NSCLC. **Pricing** 5. A reduction in price **Guidance on Sequencing** 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 than from the last dose of adjuvant alectinib.

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		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 other *ALK* inhibitors may be considered for patients who experience disease recurrence 6 months or longer after the last dose of 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 of evidence to either support or oppose the 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 the 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.
	July 25, 2018	pERC recommends the reimbursement of alectinib for the first line treatment of patients with *ALK*-positive, locally advanced or metastatic NSCLC only if the following condition is met: • cost-effectiveness is improved to an acceptable level. pERC noted that there is currently no clinical trial evidence to inform the optimal sequencing of alectinib and other available treatments for *ALK*-positive, locally advanced or metastatic NSCLC. pERC also noted that patients progressing on alectinib are unlikely to be treated with another targeted agent and may instead be offered chemotherapy followed by immunotherapy or be enrolled in a clinical trial.
	March 29, 2018	pERC recommends the reimbursement of alectinib for the treatment of patients with *ALK*-positive, locally advanced (not amenable to curative therapy), or metastatic NSCLC who have disease progression on or intolerance to crizotinib conditional on the cost-effectiveness being improved to an acceptable level. Reimbursement should be for patients with good performance status. Treatment should continue until disease progression or unacceptable toxicity. pERC noted that there is currently no clinical trial evidence to inform the optimal sequencing of alectinib and other available treatments for *ALK*-positive, locally advanced, or metastatic NSCLC. Although the ALUR trial included patients who had been treated with crizotinib and a platinum-based doublet chemotherapy, pERC agreed that treatment with alectinib is likely to be used as a second-line option, after progression on crizotinib, followed by platinum-based doublet chemotherapy as a third-line treatment and subsequently with single-agent chemotherapy or immune checkpoint inhibitors. However, the Committee acknowledged that there is no direct evidence investigating head-to-head efficacy and safety nor for the appropriate sequence for alectinib

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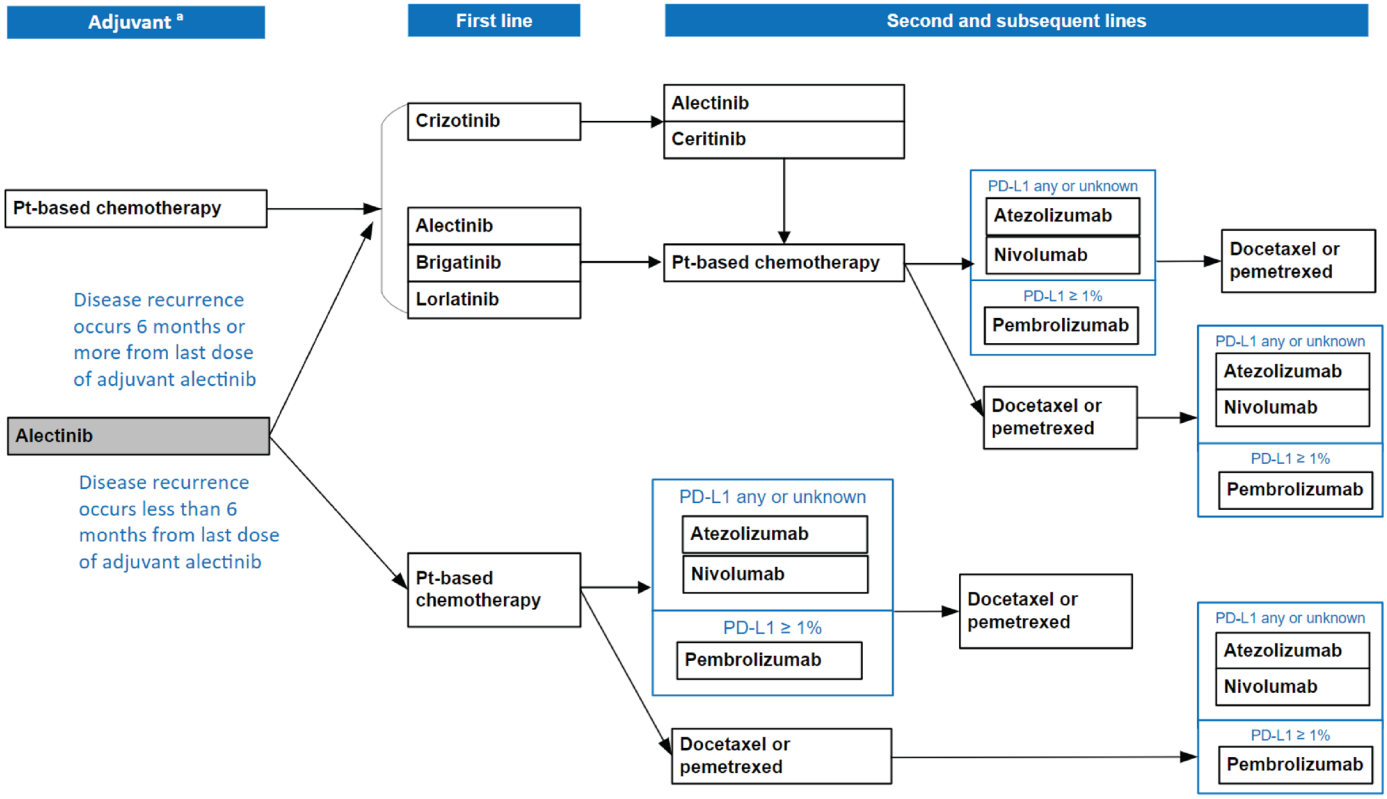
		with other available therapies (e.g., ceritinib) for the treatment of *ALK*-positive NSCLC patients who have progressed on crizotinib. Upon implementation of reimbursement of alectinib, pERC recognized that collaboration among provinces to develop a national, uniform approach to optimal sequencing would be of value.
Pembrolizumab (Keytruda)	November 3, 2016	pERC recommends reimbursement of pembrolizumab (Keytruda) conditional on the cost-effectiveness being improved to an acceptable level. Funding should be for the treatment of patients with metastatic NSCLC whose tumours express PD-L1 (as determined by a validated test) and who have disease progression on or after cytotoxic chemotherapy. Patients with epidermal growth factor receptor (EGFR) or *ALK* genomic tumour aberrations should have disease progression on authorized therapy for these aberrations and cytotoxic chemotherapy prior to receiving pembrolizumab. Funding should be for patients with a Tumour Proportion Score (TPS) of PD-L1 ≥ 1% and who have good performance status. Treatment should continue until confirmed disease progression, unacceptable toxicity, or to a maximum of two years, whichever comes first. pERC concluded that the optimal sequencing of pembrolizumab and other treatments now available for the treatment of advanced or metastatic NSCLC is currently unknown. pERC was, therefore, unable to make an evidence-informed recommendation on sequencing following pembrolizumab. pERC also noted that there is no direct evidence to inform the comparative efficacy of pembrolizumab with other PD-L1 inhibitors. Thus, with their overlapping indications, there is no evidence to inform the choice of pembrolizumab over nivolumab, or vice versa. There is also no evidence to support using PD-L1 inhibitors in sequence (e.g., pembrolizumab then nivolumab, or vice versa). However, pERC recognized that provinces will need to address this issue upon implementation of reimbursement of pembrolizumab and noted that collaboration among provinces to develop a common approach would be of value, as would the development and implementation of an evidence-based clinical practice guideline.
Nivolumab (Opdivo)	June 3, 2016	pERC recommends funding nivolumab (Opdivo) conditional on the cost-effectiveness being improved to an acceptable level. Funding should be for the treatment of adult patients with advanced or metastatic NSCLC with disease progression on or after cytotoxic chemotherapy for advanced disease and have a good performance status. Treatment should continue until confirmed disease progression or unacceptable toxicity. pERC concluded that the optimal sequencing of nivolumab and other treatments now available for the treatment of advanced or metastatic NSCLC is currently unknown. pERC was, therefore, unable to make an evidence-informed recommendation on sequencing. However, pERC recognized that provinces will need to address this issue upon implementation of an evidence-based clinical practice guideline.
Ceritinib (Zykadia)	March 21, 2017	pERC recommends reimbursement of ceritinib (Zykadia) monotherapy for patients with *ALK*-positive locally advanced (not amenable to curative therapy) or metastatic NSCLC who have disease progression on or intolerance to crizotinib conditional on the cost-effectiveness being improved to an acceptable level. pERC noted that there is no clinical trial evidence to inform the optimal

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
		sequencing of ceritinib and other treatments now available for the treatment of patients with *ALK*-positive locally advanced or metastatic NSCLC. Although the ASCEND-5 trial included patients who had previously been treated with crizotinib and a platinum doublet, pERC agreed that treatment with ceritinib is likely to be used as a second line option followed by doublet chemotherapy as third line treatment and subsequently with immune checkpoint inhibitors. Upon implementation of ceritinib reimbursement, pERC recognized that collaboration among provinces to develop a common approach for treatment sequencing would be of value.
Crizotinib (Xalkori)	July 21, 2015	pERC recommends funding crizotinib (Xalkori) as a first-line treatment for patients with *ALK*-positive NSCLC with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 - 2, conditional on the cost-effectiveness of crizotinib being improved to an acceptable level. Treatment should be continued until disease progression or unacceptable toxicity. pERC agreed with the CGP that crizotinib is a preferable treatment to platinum-based chemotherapy in the first line setting as patients may not be eligible for crizotinib in the second line setting due to disease progression and declining performance status. pERC was, however, unable to comment on sequencing of other treatments after progression on crizotinib as there was no data available to determine optimal sequencing of subsequent therapies.
	May 2, 2013	pERC recommends funding crizotinib (Xalkori) as a second-line therapy for patients with *ALK*-positive advanced NSCLC with ECOG performance status ≤ 2, only if the following condition is met: • cost-effectiveness of crizotinib being improved to an acceptable level.

ALK = anaplastic lymphoma kinase; BIA = budget impact analysis; CGP = Clinical Guidance Panel; ECOG = Eastern Cooperative Oncology Group; NSCLC = non–small cell lung cancer; pERC = pan-Canadian Oncology Drug Review Expert Review Committee; TKI = tyrosine kinase inhibitors.

Provisional Funding Algorithm

Figure 1: Provisional Funding Algorithm Diagram for *ALK*-Positive Non–Small Cell Lung Cancer



ALK = anaplastic lymphoma kinase; pCPA = pan-Canadian Pharmaceutical Alliance; Pt = platinum.

Note: Chemotherapy composition depends on histology (squamous versus nonsquamous). In patients with nonsquamous histology, pemetrexed maintenance therapy may follow Pt-based chemotherapy.

[a]Note that to align with the provisional funding algorithms for NSCLC without actionable oncogenic alterations, patients who have completed prior PD-1 or PD-L1 inhibitor treatment in the adjuvant or locally advanced setting less than 6 months ago should be offered other non-immunotherapy such as platinum-based chemotherapy.

Description of the Provisional Funding Algorithm

For patients with *ALK*-positive non–small cell lung cancer, adjuvant treatment options include alectinib or platinum-based chemotherapy. Alectinib is under review for funding.

Upon progression to advanced or metastatic disease, patients may be eligible for first-line *ALK* inhibitors alectinib, brigatinib, crizotinib, and lorlatinib if they have not previously received adjuvant treatment with alectinib or it has been 6 months or longer since they completed adjuvant treatment with alectinib.

Upon progression on, or intolerance to, first-line use of crizotinib, alectinib or ceritinib are reimbursed as second-line options.

For patients treated with any prior *ALK* inhibitor, platinum-based doublet chemotherapy is available as next-line treatment, and single-agent chemotherapy (e.g., docetaxel or pemetrexed) and immune checkpoint inhibitors (e.g., atezolizumab, nivolumab, and pembrolizumab) are available in subsequent lines in any order.

Atezolizumab or nivolumab are funded immunotherapy treatment options for patients with unknown or any PD-L1 status, while pembrolizumab is funded for patients whose tumours express 1% or more PD-L1.

Of note, pERC did not recommend the reimbursement of lorlatinib or brigatinib for the treatment of patients with *ALK*-positive metastatic NSCLC in the second-line setting.

Chemotherapy composition depends on histology (squamous versus nonsquamous). In patients with nonsquamous histology, pemetrexed maintenance therapy may follow platinum-based chemotherapy.

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