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CADTH Reimbursement Review

Provisional Funding Algorithm

Indication: Anaplastic Lymphoma Kinase–Positive Non–Small Cell Lung Cancer

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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.

Background

Following a request from jurisdictions, CADTH 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 transparency of the oncology drug funding process and promote consistency across jurisdictions.

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

- CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) reimbursement recommendations and/or implementation guidance regarding drug place in therapy and sequencing
- implementation advice from panels of clinicians convened by CADTH concerning 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 CADTH 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 CADTH following changes to drug funding status. Revisions and updates will occur only upon request by jurisdictions.

Jurisdictional cancer drug programs requested a CADTH provisional funding algorithm on anaplastic lymphoma kinase (ALK)–positive non–small cell lung cancer (NSCLC). 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.

Table 1: Relevant CADTH 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.
		• Patients should not have severe acute or chronic medical or psychiatric conditions and should not have gastrointestinal abnormalities, requirement for IV alimentation or unable to take oral medications.
		• Renewal of lorlatinib should be based on radiographic assessment performed every 2 to 6 months and clinical assessment performed every 2 to 3 months.
		• Treatment with lorlatinib should be discontinued upon occurrence of documented disease progression per RECIST (version 1.1) criteria or clinical progression or 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 tyrosine kinase inhibitors (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 localized progression. pERC agreed this treatment approach would also be reasonable for patients treated with lorlatinib.

	February 14, 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.

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
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 Clinical Guidance Panel (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).
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.

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
		Patients with genomic tumor 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 programmed cell death protein 1 (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 programmed death-ligand 1 (PD-L1)/PD-1 inhibitors in sequence (e.g., atezolizumab then nivolumab or pembrolizumab, or vice versa).
Alectinib (Alecensaro)	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 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

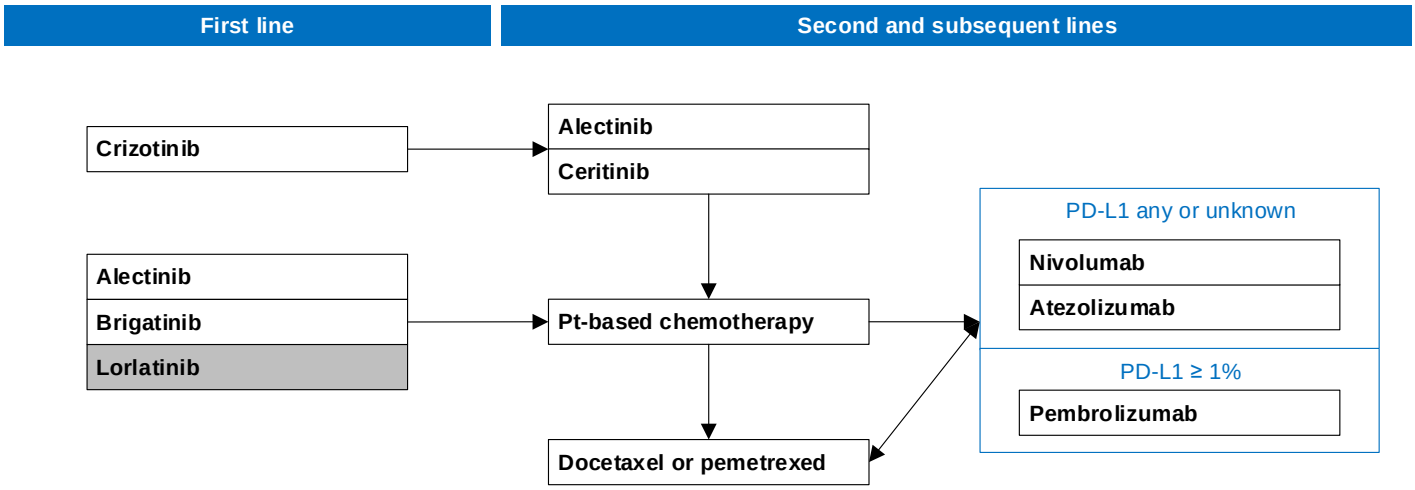
Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
		express PD-L1 (as determined by a validated test) and who have disease progression on or after cytotoxic chemotherapy. Patients with epidermal growth factor receptor (EGFR) or ALK genomic tumour aberrations 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 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 check-point inhibitors. Upon implementation of ceritinib reimbursement, pERC recognized that collaboration among provinces to develop a common approach for treatment sequencing would be of value.

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
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. Funding crizotinib as a first-line therapy for patients with ALK-positive advanced NSCLC was not recommended because the Committee was not confident of the net clinical benefit of crizotinib due to limitations in the evidence currently available from clinical trials.

ALK = anaplastic lymphoma kinase; CGP = Clinical Guidance Panel; CNS = central nervous system; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; ITC = indirect treatment comparison; MAIC = matched-adjusted indirect comparison; NSCLC = non-small cell lung cancer; OS = overall survival; PAG = Provincial Advisory Group; pERC = pCODR expert review committee; PD1 = Programmed cell death protein 1; PD-L1 = Programmed death-ligand 1; PFS = progression-free survival; pCODR = pan-Canadian oncology drug review; RECIST = Response Evaluation Criteria in Solid Tumours; TKI = tyrosine kinase inhibitors; TPS = Tumour Proportion Score.

Provisional Funding Algorithm

Figure 1: Provisional Funding Algorithm Diagram for Advanced ALK-Positive NSCLC



PD-L1 = programmed death-ligand 1; Pt = platinum; pCPA = pan-Canadian Pharmaceutical Alliance.

Notes: Chemotherapy composition depends on histology (squamous versus non-squamous). Pemetrexed maintenance therapy may follow platinum-based chemotherapy if non-squamous histology.

White boxes indicate that therapy was funded across most jurisdictions. Grey boxes indicate that the therapy is under review for funding (pCPA or province or cancer agency).

Description of the Provisional Funding Algorithm

For patients with NSCLC who have a driver mutation (e.g., ALK, EFGR, ROS-1), targeted therapy (e.g., ALK inhibitors) is used upfront, followed by second-line treatment with a platinum doublet, and subsequent treatment with immunotherapy or an alternate chemotherapy.

In the first-line setting, the ALK inhibitors crizotinib, alectinib, and brigatinib are reimbursed; 1 other ALK inhibitor, lorlatinib, is currently under review for funding.

Upon progression on or intolerance to 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., nivolumab, atezolizumab, and pembrolizumab) are available in subsequent lines in any order. Pembrolizumab is funded for patients whose tumours express 1% or more programmed death-ligand 1. Of note, pERC did not recommend reimbursement of lorlatinib or brigatinib for the treatment patients with ALK-positive metastatic NSCLC in the second-line setting.

Chemotherapy composition depends on histology (squamous versus non-squamous). Pemetrexed maintenance therapy may follow platinum-based chemotherapy in non-squamous histology.