CADTH Reimbursement Review

Provisional Funding Algorithm

Indication: Rearranged during Transfection (RET) Fusion Positive Non-Small Cell Lung Cancer

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CADTH

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Background

Following a request from jurisdictions, CADTH will 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 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 RET Fusion 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

This rapid algorithm report for RET-fusion Positive Non-Small Cell Lung Cancer aims to incorporate CADTH recommendation for Pralsetinib (Gavreto) for the treatment of adult patients with rearranged during transfection (RET) fusion-positive locally advanced unresectable or metastatic non-small cell lung cancer.

In this report, it will also incorporate CADTH recommendation for Selpercatinib (Retevmo) as a monotherapy for the treatment of metastatic RET fusion-positive non-small cell lung cancer.

Table 1: Relevant CADTH Recommendations

Generic name (brand name)	Date of recommendation	Recommendation and Guidance on Treatment Sequencing

Pralsetinib (Gavreto)	October 18, 2022	The CADTH pCODR Expert Review Committee (pERC) recommends that pralsetinib be reimbursed for the treatment of adult patients with rearranged during transfection (RET) fusion-positive locally advanced unresectable or metastatic non-small cell lung cancer (NSCLC) only if the following conditions are met:
		
		• Treatment with pralsetinib should be reimbursed when initiated in adult patients with RET fusion-positive locally advanced unresectable or metastatic NSCLC who meet 1 of the following criteria:
		  ○ For first-line treatment
		  ○ After prior systemic therapy
		• Patients must have good performance status and clinically stable CNS disease or no brain metastasis.
		• Assessment of renewal of pralsetinib should be based on assessment of:
		  ○ Response using radiographic evaluation (CT or MRI scans) every 8 to 12 weeks or as per physician's discretion to investigate new symptoms or concerns of progression
		  ○ Tolerability every 3 to 4 weeks or as per physician's discretion
		• Pralsetinib should be prescribed by clinicians with expertise in the management of NSCLC.
		• Pralsetinib should not be given or reimbursed in combination with other systemic anticancer drugs.
		• Pralsetinib should not be given to or reimbursed for patients who have previously progressed on selpercatinib.
		• A reduction in price
		• The feasibility of adoption of pralsetinib must be addressed.
		• Organizational feasibility must be addressed so that jurisdictions have the infrastructure in place to implement treatment with pralsetinib.
		
		Guidance on Optimal Sequencing:
		
		• What is the comparative efficacy of pralsetinib vs. selpercatinib? pERC agreed with the clinical expert that there is no evidence to suggest that 1 drug is more efficacious than the other. According to the clinical expert, in practice, the adverse effect profile of either drug would be considered in relation to the medical history of the patient to determine the most suitable option. The clinical expert noted that beyond adverse effect considerations, the 2 drugs are considered equivalent.

		• pERC agreed with the clinical expert that all patients with RET fusion-positive NSCLC should be treated with pralsetinib, regardless of whether they have been pre-treated or not. pERC also agreed with the clinical expert that the 1 exception would be in a patient who had previous treatment with selpercatinib and progressed on selpercatinib, in which case it would not be appropriate to treat them with pralsetinib. According to the clinical expert, pralsetinib is more effective and less toxic than chemotherapy and immunotherapy checkpoint inhibitors. Based on these same principles, it is most appropriate to use pralsetinib in first line or in the next line of therapy after progression on a current line of therapy. • pERC acknowledged that although selpercatinib received a reimburse with conditions recommendation, it is currently not publicly funded. However, should selpercatinib become a funded treatment option, pERC agreed with the clinical expert that the funding criteria of pralsetinib should be aligned to that of selpercatinib. According to the clinical expert, selpercatinib and pralsetinib are highly comparable in terms of both efficacy and incidence of significant toxicity. Both should not be used in a single patient (unless a patient is switched from 1 to another due to toxicity with no progression of disease), but the option should be made to have equal access to both to facilitate choice for patients and oncologists which will enhance the ability to provide best care. pERC also noted the instances in which 1 treatment may be favoured over the other as highlighted by the clinical expert. For instance, there are some differences in adverse effect profiles in which having the option to use either drug would be important; for example, selpercatinib is associated with a risk to develop a prolonged QT interval, whereas pralsetinib had no clinically relevant or significant effect on QT interval prolongation. Therefore, pralsetinib would be a more appropriate choice in a patient with RET fusion-positive NSCLC with a pre-existent prolonged QT interval or who requires the use of concomitant medications that can prolong QT interval. For a second example, pralsetinib can cause pneumonitis. Thus, selpercatinib would be a more appropriate choice in a patient with pre-existing limited pulmonary reserves or who already has pneumonitis from a different cause such as palliative chest radiation. • pERC agreed with the clinical expert that intolerance to selpercatinib, in the absence of disease progression, would not preclude the use of pralsetinib. • Should patients currently receiving systemic therapy but whose disease has not yet progressed switch over to pralsetinib? Based on clinical expert response, patients should not switch over to pralsetinib unless there is an unacceptable toxicity or the patient decides they no longer want to receive treatment with a current line of therapy on which there has not been progression; that line of therapy should continue until progression after which it would be appropriate to switch to pralsetinib.

		• pERC agreed with the clinical expert that there should be no sequencing of pralsetinib and selpercatinib. Pralsetinib, if funded, would be an alternative to selpercatinib if selpercatnib is also funded.

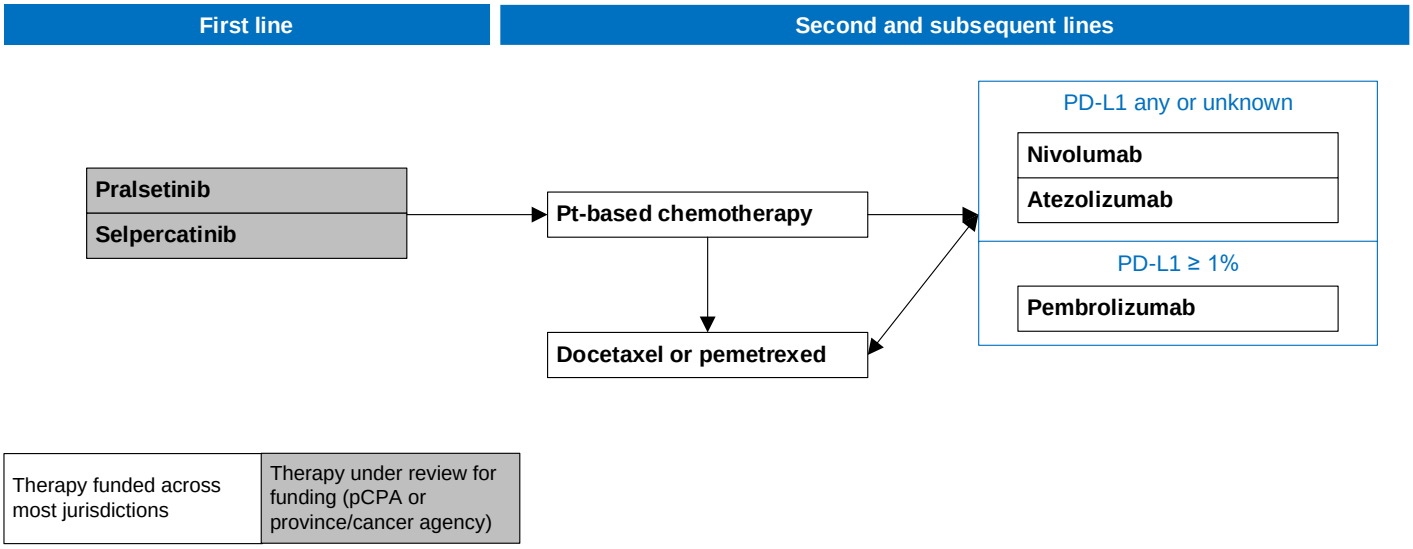
Selpercatinib (Retevmo)	May 16, 2022	pERC recommends that selpercatinib be reimbursed for the treatment of metastatic RET fusion positive non-small cell ung cancer (NSCLC) in adult patients only if the following conditions are met:
		• Treatment with selpercatinib should be reimbursed when initiated in adult (≥18 years) patients with metastatic RET fusion-positive NSCLC who meet 1 of the following criteria:
		  ○ For first-line treatment
		  ○ After prior systemic therapy
		• Patients must have good performance status and clinically stable CNS disease or no brain metastases.
		• Assessment of renewal of selpercatinib should be based on assessment of:
		  ○ Response using radiographic evaluation (CT or MRI scans) every 8 to 12 weeks or as per physician discretion to investigate new symptoms or concerns of progression
		  ○ Tolerability every 3 to 4 weeks or as per physician discretion
		• Selpercatinib should be prescribed by clinicians with expertise in the management of NSCLC.
		• Selpercatinib should not be given or reimbursed in combination with other systemic anti-cancer drugs.
		• A reduction in price
		• The feasibility of adoption of selpercatinib must be addressed.
		• Access to RET testing

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 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).
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.

Provisional Funding Algorithm

Figure 1: Provisional Funding Algorithm Diagram for RET fusion-positive NSCLC



pCPA = pan-Canadian Pharmaceutical Alliance; PD-L1 = programmed death-ligand 1; Pt = Platinum
Note#1: Chemotherapy composition depends on histology (squamous vs. non-squamous). Pemetrexed maintenance therapy may follow platinum-based chemotherapy if non-squamous histology.
Note#2: Pralsetinib and selpercatinib may be given after prior systemic therapy.

Alt text: See description of the algorithm in the text.

Description of the Provisional Funding Algorithm

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

In the first-line setting, RET inhibitors include pralsetinib and selpercatinib. Both pralsetinib and selpercatinib are currently under review for funding. Any patient initiated on either RET inhibitor who experiences intolerance without progression would be able to switch therapies.

For patients treated with any prior RET inhibitors, 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 PD-L1 (PD-L1 ≥ 1%).

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