Reimbursement Review

Provisional Funding Algorithm

Indication: *RET* fusion-positive non–small cell lung cancer

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Publication date: June 2023

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

Key Messages

- For patients with confirmed *RET* fusion-positive non–small cell lung cancer, *RET* inhibitors, including selpercatinib or pralsetinib, should be used as first-line therapy.
- Regardless of previous therapies, *RET* inhibitors, including selpercatinib or pralsetinib, should be used as the next line of therapy in patients with non–small cell lung cancer who are subsequently confirmed to be *RET* fusion positive.

Background

The provisional funding algorithm process is used to provide advice when the drug programs have indicated that there is need to establish an appropriate place in therapy for the drug under review relative to alternative treatments that are currently reimbursed by the drug programs, including the impact on the appropriate sequencing of treatments for the purposes of reimbursement. The creation of a new provisional funding algorithm or update of an existing provisional funding algorithm is typically initiated following the issuance of a new pERC recommendation when there are potential implications regarding the funding sequence of drugs within a therapeutic area. CADTH will only initiate work on a provisional funding algorithm at the request of its Provincial Advisory Group (PAG).

The following items are considered by the expert panels when advising the jurisdictions on the provisional algorithm for the relevant indication:

- unmet therapeutic need for patients (particularly those in understudied populations)
- evidence supporting a particular sequence of therapies (if available)
- clinical experience and opinion that support a particular sequence of therapies
- clinical practice guidelines
- variability across jurisdictions regarding the reimbursement status of existing treatment options
- affordability and sustainability of the health care system
- implementation considerations at the jurisdictional level.

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. Most 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. Also note that as per process, implementation advice from panellists and the resulting algorithms cannot contradict prior pERC recommendations or expand target populations beyond what was recommended.

Provisional funding algorithms 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 statuses. Revisions and updates will occur only upon request by jurisdictions.

Cancer drug programs from federal and provincial jurisdictions requested supplemental implementation advice along with a CADTH provisional funding algorithm on *RET* fusion-positive non–small cell lung cancer (NSCLC). See Appendix 1 for a list all past CADTH advice and recommendations relevant for this therapeutic area.

Implementation Issues

At the request of the participating drug programs, CADTH convened a panel of clinical experts in Canada to provide advice for addressing the outstanding implementation issues as follows:

- sequencing and use of the following in *RET* fusion-positive NSCLC: targeted therapies, immunotherapies, immunotherapies with chemotherapies, and chemotherapies.

Consultation Process and Objectives

The implementation advice panel comprised 8 clinical specialists in Canada with expertise in the diagnosis and management of patients with NSCLC, a representative from a public drug program, and a panel chair. The objective of the panel was to provide advice to the participating drug programs regarding the implementation issues noted in the Background section. A consensus-based approach was used, and input from stakeholders was solicited using questionnaires. Stakeholders, including patient and clinician groups and pharmaceutical manufacturers, and public drug programs were invited to provide input in advance of the meeting.

The advice presented in this report has been developed based on the experience and expertise of the implementation advice panel members and, as such, represents experience-informed opinion; it is not necessarily based on evidence.

Advice on Funding Algorithm

Summary of Implementation Advice

Implementation advice regarding the optimal sequencing of treatments is summarized in Table 1. For each implementation issue, a summary of the relevant panel discussion is provided for additional context.

Table 1: Summary of Advice for Addressing Implementation Issues

Issue	Advice	Rationale
Sequencing of therapies for *RET* fusion-positive NSCLC	For patients with confirmed *RET* fusion-positive NSCLC, the panel advises that the *RET* inhibitors selpercatinib and pralsetinib should be used as first-line therapy for this population, with cytotoxic chemotherapy used as second-line therapy. Immunotherapy can be used in subsequent lines of therapy, after exhausting all appropriate options for chemotherapy.	Although this recommendation is based on expert consensus because of a lack of evidence for the sequencing of therapies in this population, it is consistent with the ASCO and CCO[1] joint guidelines and the ESMO guidelines.[2] Based on results from the ARROW[3] (pralsetinib) and LIBRETTO-001[4] (selpercatinib) trials, there is clear evidence of a robust response to *RET* inhibitors in this population. Due to the aggressive nature of NSCLC, the optimal approach is to use the best therapies upfront, as there is considerable attrition from first line to second line of therapy. Although there is limited evidence for the use of immunotherapy in this specific population, the available evidence suggests that response to immunotherapy monotherapy is quite low; therefore, it is advisable to exhaust all available chemotherapy options before proceeding to immunotherapy.
Sequencing of therapies for patients with unknown *RET* status at the time of initial diagnosis	Regardless of previous therapies, the panel advises that the *RET* inhibitors selpercatinib or pralsetinib should be used as the next line of therapy in patients who are subsequently confirmed to be *RET* fusion positive.	It is recognized that there is variation across the country in terms of access to testing, as well as the turnaround time for results. Some patients may be initially started with other therapies. Once the mutation status is confirmed to be positive for *RET* fusion, the panel advises that *RET* inhibitors should be used as the next line of therapy. There was a discussion among the panellists about whether the patient should complete the course of the current therapy, or whether the patient should be switched to *RET* inhibitors immediately upon receiving the result. There was a disagreement among the panellists' approaches, and it was felt that

Issue	Advice	Rationale
		this decision should be left at the discretion of the treating clinician.

ASCO = American Society for Clinical Oncology; CCO = Cancer Care Ontario; ESMO = European Society for Medical Oncology; NSCLC = non–small cell lung cancer.

In addition to the previously outlined advice, the panel indicated that because an improvement in cost-effectiveness was a condition for reimbursement in each of the recommendations related to the drugs in scope, implementation of any advice herein should be contingent upon ensuring that the relevant treatments are affordable to public payers.

Panel Discussion

What is the Optimal Sequence of Therapies for *RET* Fusion-Positive NSCLC?

The panel was unanimous in recommending that targeted therapies (i.e., the *RET* inhibitors selpercatinib or pralsetinib) should be used as first-line therapy in this population. The panellists noted that the recommendation is based on expert consensus because there are no randomized controlled trials that have studied the sequencing of therapies for *RET* fusion-positive NSCLC. This recommendation is consistent with the American Society of Clinical Oncology (ASCO) and Ontario Health-Cancer Care Ontario (OH-CCO)[1] joint guidelines and the European Society for Medical Oncology (ESMO) guidelines.[2] The panel emphasized the importance of using the most efficacious therapies in the first-line setting in this population due to high attrition rates and indicated that the *RET* inhibitors are the best option because of their enhanced efficacy (i.e., higher response rates and longer progression-free survival), better toxicity profiles, oral route of administration, and central nervous system activity. The panellists noted that evidence of efficacy for selpercatinib comes from the LIBRETTO-001[4] trial and for pralsetinib comes from the ARROW trial.[3]

In addition to recommending targeted therapies (i.e., the *RET* inhibitors selpercatinib or pralsetinib) be used in the first line in this population, the panel was generally in agreement that cytotoxic chemotherapy should be used as second-line therapy or used before considerations of immunotherapy (again based on expert consensus). A panellist noted that they would suggest platinum plus pemetrexed for patients with lung adenocarcinoma and nonpemetrexed platinum doublet for patients with squamous cell lung cancer. A panellist noted that *RET* fusions are almost always found on nonsquamous NSCLC, and these patients tend to respond well to platinum plus pemetrexed.

The panel was less confident in the use of single-drug immunotherapy in subsequent lines of therapy; however, there was general agreement that it was appropriate to use it after chemotherapy. For example, some panellists emphasized that it would be best to exhaust all chemotherapy options before moving on to immunotherapy in this population. One panellist noted that patients who are *RET* fusion positive tend to have minimal to no tobacco use in their history, and this population of patients tends to respond

poorly to immunotherapy as a single drug. There is also some limited, poor quality evidence that there is reduced efficacy of single-drug immunotherapy in patients who are *RET* fusion positive. For example, 1 of the panellists referenced that patients in the LIBRETTO-001 trial who had received single-drug immunotherapy before targeted therapy had an overall response rate of 3%.[5]

The panellists agreed that due to different side effect profiles, patients who are intolerant to one *RET* inhibitor should be allowed to try the other one. However, failure on 1 *RET* inhibitor (e.g., disease progression while on 1 *RET* inhibitor) should preclude them from trying the other *RET* inhibitor.

Rare Considerations for Alternative Sequencing

In response to a question about whether alternative sequencing should ever be considered, the panellists noted that *RET* inhibitors would always be considered in the first line, except in rare cases where patients were unable or unwilling to take an oral therapy, were nonadherent, or had a contraindication to both *RET* inhibitors. The panellists added that *RET* inhibitors should be allowed in later lines of therapy in cases where patients were placed on chemotherapy while waiting for next-generation sequencing test results, especially if that entailed getting another tissue biopsy because of inadequate initial tissue to complete molecular testing, and the lack of efficacy of circulating DNA blood tests to detect *RET* fusions. Panellists emphasized that due to the aggressive nature of NSCLC, many patients are simply unable to wait for next-generation sequencing results, as that can take weeks to months, depending on the jurisdiction. They also noted that as *RET* mutations are relatively uncommon, it would be unwise to hold chemotherapy in this situation. Some panellists added that if the patient were responding to chemotherapy, they would be reluctant to stop the chemotherapy to switch them to a *RET* inhibitor, but would instead wait until the patient stopped responding to the chemotherapy. Other panellists would switch their patients to the *RET* inhibitors as soon as results were available. This was felt to be an area best left at the discretion of the treating clinicians. Panellists were also in agreement with *RET* inhibitors being offered as the next line of therapy for any patients who were on another intervention (chemotherapy and/or immunotherapy) at the time of publication of this algorithm. One panellist noted that the use of *RET* inhibitors immediately after immunotherapy may lead to potential pneumonitis and this should be taken into account when physicians are considering switching.

Other Discussion Points

- A panellist noted that not all driver mutations behave and respond similarly to immunotherapy. In addition, many trials evaluating the use of first-line immunotherapy (alone or with chemotherapy) have excluded driver mutations such as EGFR and ALK. Although patients positive for *RET* fusion were included in various trials that evaluated the first-line use of immunotherapy (e.g., KEYNOTE-024[6] and EMPOWER-Lung 1[7]), the evidence cannot be generalized to this very small population (approximately 1% to 2%). Additionally, there is currently no strong evidence to support or refute the use of chemotherapy with immunotherapy for patients with *RET* fusion-positive NSCLC. A

panellist noted, and others agreed, that an issue with combining immunotherapy with chemotherapy in this population is that if a benefit is seen, it will not be clear whether this is mainly due to the chemotherapy, or the immunotherapy, which is more expensive. However, the ongoing trial of LIBRETTO-431[8] will help address these evidence gaps. LIBRETTO-431 is a phase III study of selpercatinib versus chemotherapy with or without pembrolizumab in untreated *RET* fusion-positive NSCLC with a built-in crossover design.

- A panellist also noted that evidence from other tyrosine kinase inhibitors like EGFR inhibitors and KRAS G12C oral inhibitors suggests that there may be increased toxicity from tyrosine kinase inhibitors if given after immunotherapy, and this would potentially be another argument for using *RET* inhibitors before immunotherapy.

Figure 1 depicts the provisional funding algorithm proposed by the panel. Note that this diagram is a summary representation of the drug funding options for the condition of interest. It is not a treatment algorithm; it is neither meant to detail the full clinical management of each patient nor the provision of each drug regimen. The diagram may not contain a comprehensive list of all available treatments, and some drugs may not be funded in certain provinces. All drugs are subject to explicit funding criteria, which may also vary between provinces. Readers are invited to refer to the individual drug entries on the CADTH website for more details.

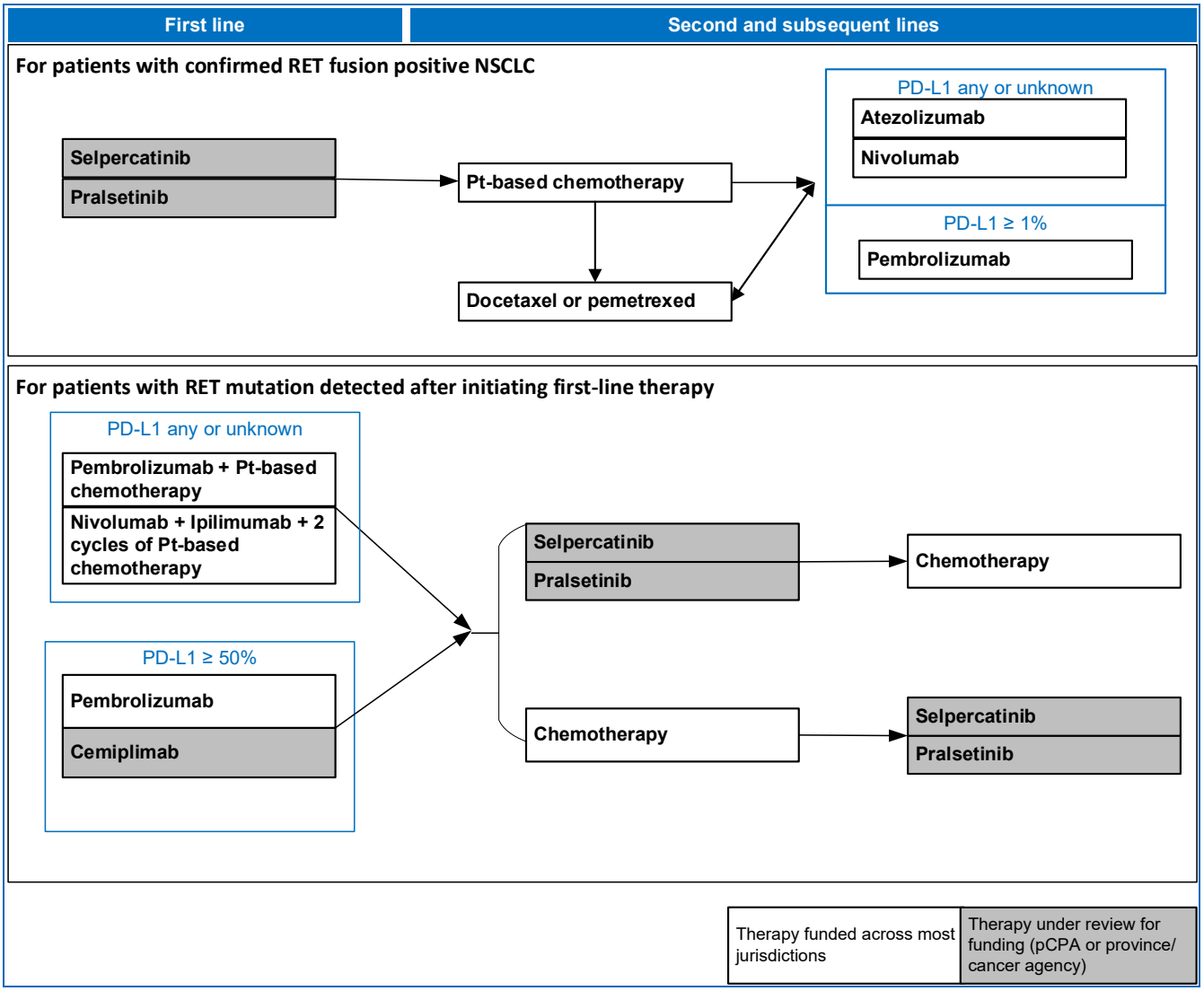
First-Line Setting

For patients with confirmed *RET* fusion-positive NSCLC, *RET* inhibitors should be used as first-line therapy. Current options include pralsetinib or selpercatinib. The panellists did not suggest a preference for 1 *RET* inhibitor over another. However, they did note that given that each *RET* inhibitor has a unique toxicity profile, patients may switch to a different *RET* inhibitor if they develop intolerance without disease progression.

Patients without confirmation of their driver mutation status, may be started on other first-line options. As 98% to 99% of patients awaiting testing will be negative for *RET* fusion mutation, it is appropriate to start standard first-line therapy, which may include immunotherapy with or without chemotherapy. During the panel discussion, some panellists have suggested initiating chemotherapy when *RET* status is pending. It is noted that options may differ in this setting for different jurisdictions.

Provisional Funding Algorithm

Figure 1: Provisional Funding Algorithm Diagram for *RET* Fusion-Positive NSCLC



NSCLC = non–small cell lung cancer; pCPA = pan-Canadian Pharmaceutical Alliance; PD-L1= programmed cell death 1 ligand 1; Pt = platinum.

Notes: *RET* inhibitors should be funded as first-line therapy for patients with confirmed results or *RET* inhibitors should be funded as the next line of therapy once *RET* status is confirmed.

Pralsetinib and selpercatinib may be given after prior systemic therapy.

Switching between pralsetinib and selpercatinib is an option if the patient develops intolerance without disease progression.

Chemotherapy options should be exhausted where possible due to better response rate for patients with *RET* fusion-positive NSCLC before treatment with single-drug immunotherapy. There is limited evidence to support the use of single-drug immunotherapy at this time.

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

Second-Line and Beyond Setting

For patients with confirmed *RET* fusion-positive NSCLC treated with first-line *RET* inhibitors, chemotherapy should be used in the second line, with platinum-based chemotherapy followed by maintenance treatment with pemetrexed for nonsquamous histology. It is preferred to exhaust all available chemotherapies before proceeding with immunotherapy. For patients with any or unknown programmed cell death 1 ligand 1 (PD-L1) status, subsequent lines of immunotherapy include atezolizumab or nivolumab. For patients with a PD-L1 of 1% or greater, the subsequent line of immunotherapy includes pembrolizumab.

For patients with NSCLC who are subsequently confirmed to be *RET* fusion positive, the next lines of therapy should be *RET* inhibitors, which include pralsetinib or selpercatinib. Chemotherapy is also an option in this setting.

Appendix 1: Past CADTH Advice and Recommendations

Note that this appendix has not been copy-edited.

Table 2: Relevant CADTH Recommendations

Generic name (brand name)	Date of recommendation	Recommendation

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

Generic name (brand name)	Date of recommendation	Recommendation
		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 pretreated 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 the 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.

Generic name (brand name)	Date of recommendation	Recommendation
		• 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 selpercatinib 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 lung 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.

Cemiplimab (Libtayo)	June 20, 2022	pERC recommends that cemiplimab be reimbursed for the first-line treatment of adult patients with NSCLC expressing PD-L1 (programmed death-ligand 1) with a TPS of 50% or greater, as

Generic name (brand name)	Date of recommendation	Recommendation

		determined by a validated test, with no *EGFR*, *ALK*, or *ROS1* aberrations, who have locally advanced NSCLC who are not candidates for surgical resection or definitive chemoradiation, or metastatic NSCLC only if the following conditions are met:
		• Previously untreated stage IV NSCLC or stage IIIB or IIIC NSCLC not amenable to curative therapy.
		• PD-L1 strongly positive tumours (TPS ≥ 50%).
		• Good performance status.
		• Patients should not have any of the following:
		  ○ tumours with *EGFR*, *ALK*, or *ROS1* aberrations.
		  ○ a contraindication to immunotherapy.
		  ○ uncontrolled and symptomatic CNS metastases.
		Treatment should be:
		• renewed for patients who demonstrate a continued response to treatment defined as absence of disease progression, based on clinical and radiographic evaluation every 3 to 4 months.
		• reimbursed for a maximum of 108 weeks.
		Cemiplimab should be negotiated so that it does not exceed the drug program cost of treatment with pembrolizumab.
		Optimal sequencing guidance:
		• pERC agreed with the clinical experts and considered that patients who received previous adjuvant or neoadjuvant chemotherapy should be eligible to receive cemiplimab. In addition, patients who progress at least 6 months after their last dose of immunotherapy should be eligible to receive cemiplimab.
		• pERC noted that the addition of chemotherapy to cemiplimab at disease progression should not be funded as there is insufficient evidence to recommend this practice.
		• pERC agreed with the clinical experts that patients who completed 2 years of cemiplimab treatment and subsequently progressed and patients who discontinued cemiplimab after less than 2 years due to complete response should be eligible for re-treatment for up to 17 cycles (1 year).

Nivolumab-Ipilimumab (Opdivo-Yervoy)	March 4, 2021	pERC conditionally recommends the reimbursement of nivolumab plus ipilimumab (nivolumab/ipilimumab) and 2 cycles of platinum-doublet chemotherapy (PDC), for the first-line treatment of adult patients with metastatic or recurrent non–small cell lung cancer (NSCLC) with no known epidermal growth factor receptor (*EGFR*) or anaplastic lymphoma kinase (*ALK*) genomic tumour aberrations, if the following condition is met: • Cost-effectiveness being improved to an acceptable level.

Generic name (brand name)	Date of recommendation	Recommendation
		Eligible patients include those with nonsquamous or squamous NSCLC, any PD-L1 expression level including patients with unknown PD-L1 expression, and good performance status. Treatment with nivolumab-ipilimumab should continue until confirmed disease progression or unacceptable toxicity to a maximum of 2 years, whichever comes first. Optimal sequencing guidance: • pERC agreed with the CGP that patients progressing on nivolumab-ipilimumab would not be eligible for subsequent immunotherapy. • pERC agreed with the CGP that nivolumab-ipilimumab should not be used in combination with non–platinum doublets or single-agent chemotherapy. However, the CGP noted that platinum and gemcitabine have been combined with durvalumab plus tremelimumab in the CCTG IND 226 and BR342 trials. Given there were no safety concerns identified in those trials, pERC agreed with the CGP that jurisdictions may wish to consider allowing the use of platinum and gemcitabine with nivolumab-ipilimumab. • pERC agreed that patients progressing on nivolumab-ipilimumab plus 2 cycles of PDC would be most appropriately treated with chemotherapy as the next treatment option. For patients progressing more than 6 months from completion of PDC, re-treatment with a histology-appropriate platinum doublet would be recommended. Patients progressing within 6 months would likely be treated with docetaxel. The CGP noted that re-treatment with pemetrexed may pose funding issues in some jurisdictions and this gap should be addressed during implementation. pERC agreed with the CGP that patients with nonsquamous NSCLC who have only received 2 cycles of pemetrexed, should have access to the most effective PDC (i.e., platinum plus pemetrexed). • pERC agreed that re-treatment with nivolumab-ipilimumab for 1 year be an option for patients progressing after completion of 2 years of nivolumab-ipilimumab.
Pembrolizumab (Keytruda)	January 3, 2020	pERC conditionally recommends the reimbursement of pembrolizumab in combination with carboplatin and paclitaxel for the treatment of patients with metastatic squamous non–small cell lung cancer (NSCLC) in adults with no prior systemic chemotherapy treatment for metastatic NSCLC if the following conditions are met: • cost-effectiveness being improved to an acceptable level • feasibility of adoption (budget impact) being addressed. Eligible patients include those with good performance status. Treatment should continue until confirmed disease progression

Generic name (brand name)	Date of recommendation	Recommendation
		or unacceptable toxicity to a maximum of 2 years, whichever comes first.
Pembrolizumab (Keytruda)	May 31, 2019	pERC conditionally recommends the reimbursement of pembrolizumab (Keytruda) in combination with pemetrexed and platinum chemotherapy, for the treatment of metastatic nonsquamous, non–small cell lung cancer (NSCLC), in adults with no *EGFR* or *ALK* genomic tumour aberrations, and no prior systemic chemotherapy treatment for metastatic NSCLC if the following conditions are met: • Cost-effectiveness being improved to an acceptable level • Feasibility of adoption (budget impact) being addressed. Eligible patients include those with good performance status. Treatment should continue until confirmed disease progression or unacceptable toxicity to a maximum of 2 years, whichever comes first.
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 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): First line	August 23, 2017	pERC recommends reimbursement of pembrolizumab (Keytruda) conditional on the cost-effectiveness being substantially improved to an acceptable level. Funding should be for the treatment of locally advanced or previously untreated

Generic name (brand name)	Date of recommendation	Recommendation
		metastatic non–small cell lung cancer (NSCLC) in patients whose tumours express PD-L1 (Tumour Proportion Score [TPS] ≥ 50%) as determined by a validated test and who do not harbour a sensitizing epidermal growth factor receptor (*EGFR*) mutation or anaplastic lymphoma kinase (*ALK*) translocation. Patients with locally advanced disease (stage IIIB) should be eligible for funding if they are not eligible for potentially curative concurrent chemoradiotherapy. Funding should be for patients who have good performance status. Treatment should be administered at a dose of 2 mg/kg up to a total dose amount of 200 mg (dose capped at 200 mg). Treatment should continue until confirmed disease progression or unacceptable toxicity or to a maximum of 2 years (35 cycles), whichever comes first.
Pembrolizumab (Keytruda): Second line and beyond	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 2 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.

Generic name (brand name)	Date of recommendation	Recommendation
		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.
Pemetrexed (Alimta)	November 19, 2013	pERC recommends funding pemetrexed (Alimta) as a maintenance treatment following first-line treatment with pemetrexed plus cisplatin in patients with advanced or metastatic nonsquamous non–small cell lung cancer (NS-NSCLC) conditional on its cost-effectiveness being improved to an acceptable level. Funding should be for patients who achieved stable disease or better with 4 cycles of induction pemetrexed plus cisplatin and with an ECOG performance status of 0 or 1 after induction therapy.

ECOG = Eastern Cooperative Oncology Group; NSCLC = non–small cell lung cancer; PDC = platinum-doublet chemotherapy; PD-L1 = programmed death-ligand 1; pERC = CADTH pan-Canadian Oncology Review Expert Review Committee; TPS = tumour proportion score.

[a] See published recommendation reports for full details, including conditions and criteria.

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