Canada's Drug and
Health Technology Agency

Provisional Funding Algorithm

Indication: Non-small cell lung cancer without actionable oncogenic alterations

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 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 non-small cell lung cancer without actionable oncogenic alterations. 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

CADTH first published a provisional funding algorithm report for non-small cell lung cancer without actionable oncogenic alterations in July 2022. This was a rapid algorithm with the aim to incorporate the CADTH recommendation for cemiplimab (Libtayo).

Jurisdictional cancer drug programs have recently requested to update this rapid algorithm to incorporate the CADTH recommendation for atezolizumab(Tecentriq) as a monotherapy for adjuvant treatment following resection and platinum-based chemotherapy. Because there is also a CADTH recommendation for another PD-L1 inhibitor durvalumab in this setting, this drug is also incorporated into this algorithm. Durvalumab and atezolizumab were added to the algorithms for clarity as they are PD-L1 inhibitors now used upstream of first-line options in this algorithm.

Table 1: Relevant CADTH Recommendations

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

Atezolizumab (Tecentriq)	Sept 20, 2022	The CADTH pCODR Expert Review Committee (pERC) recommends that atezolizumab be reimbursed as monotherapy for adjuvant treatment following complete resection and no progression after platinum-based adjuvant chemotherapy for adult patients with stage II to IIIA (per the American Joint Committee on Cancer [7th edition]) non-small cell lung cancer (NSCLC) whose tumours have PD-L1 expression on 50% or more of tumour cells and do not have epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumour aberrations only if the following conditions are met:
		• Patients must have good performance status
		• A reduction in price
		• Patients are ineligible for atezolizumab if they are:
		  ○ Not eligible for surgical resection
		  ○ Not eligible for initiation of cisplatin-based adjuvant chemotherapy
		Treatment should be:
		• Renewed for patients who tolerate treatment and have no evidence of disease recurrence
		• Discontinued upon the occurrence of any of the following:
		  ○ Disease recurrence
		  ○ Unacceptable toxicity
		  ○ Up to 48 weeks
		Patients should be assessed for evidence of disease recurrence based on standard care.
		Optimal sequencing guidance (based on clinical expert opinion):
		• Chemotherapy should be initiated within 12 weeks of surgical resection. Starting atezolizumab within 3 to 8 weeks from the completion of chemotherapy is reasonable in the real world. It is reasonable on a time limited basis to offer

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		atezolizumab to patients who had received platinum chemotherapy up to 12 weeks but where atezolizumab was not accessible. • Patients who become ineligible for cisplatin after 1 cycle due to toxicities should be eligible to receive atezolizumab.
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 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: o tumours with *EGFR, ALK, or ROS1* aberrations. o a contraindication to immunotherapy. o 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 (Opdivo) -Ipilimumab (Yervoy)	March 4, 2021	pERC conditionally recommends the reimbursement of nivolumab plus ipilimumab (nivolumab/ipilimumab) and 2 cycles of PDC, for the first-line treatment of adult patients with metastatic or recurrent NSCLC with no known EGFR or ALK genomic tumour aberrations, if the following condition is met: • cost-effectiveness being improved to an acceptable level. Eligible patients include those with non-squamous or squamous NSCLC, any PD-L1 expression level including patients with unknown PD-L1 expression, and good

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		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 non-squamous 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 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 or unacceptable toxicity to a maximum of 2 years, whichever comes first. **Optimal sequencing guidance:** • pERC noted that patients who receive pembrolizumab in the first-line setting would not be eligible to receive subsequent PD-1 (e.g., nivolumab) or PD-L1 (e.g., atezolizumab) inhibitors in the second-line setting. • pERC acknowledged that for patients with PD-L1 TPS equal to or greater than 50%, pembrolizumab monotherapy represents the standard first-line therapy and that based on Keynote 407, pembrolizumab in combination with carboplatin and paclitaxel is an alternative first-line therapy. pERC supports having both options available to patients as these regimens have not been directly compared and an indirect comparison as part of this review shows no clear regimen that is superior in OS.

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		pERC noted that patients who completed two years of pembrolizumab and discontinue therapy without progression, should have an option of re-treatment with pembrolizumab.
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 non-squamous 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 two years, whichever comes first. **Optimal sequencing guidance:** • pERC noted that patients receiving pembrolizumab plus chemotherapy in the first-line setting would not receive subsequent PD-1 (e.g., nivolumab) or PD-L1 inhibitors (e.g., atezolizumab) in the second-line setting. • pERC noted that patients who are unable to tolerate pemetrexed would likely not be administered pembrolizumab. However, in this unlikely setting, it would be reasonable to continue single-agent pembrolizumab. • pERC considered the CGP's expert opinion and agreed that for patients who received prior adjuvant or consolidation durvalumab and remain candidates for platinum-pemetrexed chemotherapy, it would be reasonable to consider treatment with platinum-pemetrexed plus pembrolizumab. In general, for such patients, it should be more than 12 months since they last received platinum-based therapy. For patients progressing during adjuvant or consolidation immune checkpoint inhibitor therapy there is limited data at this time to support further immune checkpoint inhibitor therapy. pERC felt it is reasonable that patients who complete two years of pembrolizumab and discontinue therapy without progression, should have the option for re-treatment with pembrolizumab, if there is at least six months between completion of therapy and documented disease progression.
Durvalumab (Imfinzi)	May 3, 2019	pERC conditionally recommends the reimbursement of durvalumab for the treatment of patients with locally advanced, unresectable stage III non-small cell lung cancer (NSCLC) following curative intent platinum-based concurrent chemoradiation therapy 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 who are deemed fit following curative intent platinum-based concurrent chemoradiation therapy. Treatment should continue until unacceptable toxicity or disease progression to a maximum of 12 months.

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 and • 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., EGFR 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. **Optimal sequencing guidance:** pERC concluded that the optimal sequencing of atezolizumab 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 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).
Pembrolizumab (Keytruda)	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 metastatic NSCLC in patients whose tumours express PD-L1 (TPS ≥ 50%) as determined by a validated test and who do not harbour a sensitizing EGFR mutation or 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 two years (35 cycles), whichever comes first. **Optimal sequencing guidance:** In the trial patients could receive re-treatment for up to 17 cycles if patients stopped receiving pembrolizumab after receiving 35 cycles for reasons other than disease progression of intolerability, or if patients attained a complete response and stopped treatment with pembrolizumab, they may be eligible for re-treatment with pembrolizumab upon experiencing disease progression. pERC noted that in the trial, if pembrolizumab was withheld for toxicity, patients were able to resume pembrolizumab if appropriate and when toxicity had improved. pERC felt that these criteria for re-treatment with pembrolizumab following a progression-free time period and toxicity interruption were reasonable.
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 EGFR or ALK genomic tumour aberrations should have disease progression on authorized therapy for these aberrations and

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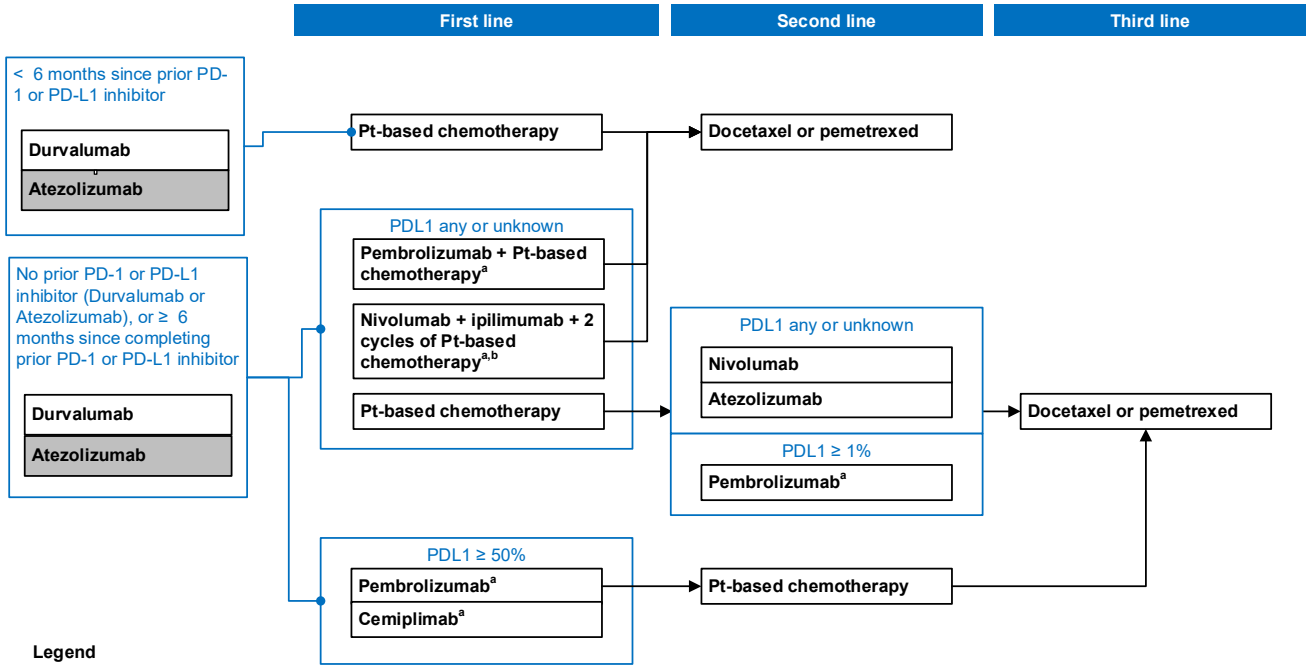
		cytotoxic chemotherapy prior to receiving pembrolizumab. Patients could receive up to 12 months of pembrolizumab if they experienced an investigator-determined confirmed radiographic disease progression, according to immune-related response criteria after stopping their initial treatment with pembrolizumab due to achievement of a confirmed complete response or having experienced 35 administrations of pembrolizumab. Funding should be for patients with a TPS of PD-L1 ≥ 1% and who have good performance status. Treatment should continue until confirmed disease progression or unacceptable toxicity, or to a maximum of two years, whichever comes first. **Optimal sequencing guidance:** 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-1 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-1 inhibitors in sequence (e.g., pembrolizumab then nivolumab, or vice versa).
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. **Optimal sequencing guidance:** 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.

ALK = anaplastic lymphoma kinase; CGP = Clinical Guidance Panel; EGFR = epidermal growth factor receptor; NSCLC = non-small cell lung cancer; PD-L1 = programmed death ligand 1; pERC = pCODR Expert Review Committee; PDC = platinum doublet chemotherapy; PD-L1 = programmed death-ligand 1; ROS1 = c-ros oncogene 1 receptor tyrosine kinase; TPS = Tumour Proportion Score.

[a] Summaries of the reimbursement conditions are provided; for the complete recommendations refer to the final recommendations posted on the CADTH website.

Provisional Funding Algorithm

Figure 1: Provisional Funding Algorithm Diagram for NSCLC Without Actionable Oncogenic Alterations



[a] For patients who complete 2 years of therapy and discontinue without progression, retreatment is allowed.
[b] For patients who progress more than 6 months after completion of platinum doublet chemotherapy while on this regimen, retreatment with a histology-appropriate platinum doublet is allowed.

Note: Chemotherapy composition depends on histology (squamous vs. non-squamous). Pemetrexed maintenance therapy may follow platinum-based chemotherapy if non-squamous histology.
Note: PD-L1 expression is determined using Tumour Proportion Score.

pCPA=pan-Canadian Pharmaceutical Alliance; PDL1=programmed death ligand-1; Pt=platinum.

Description of the Provisional Funding Algorithm

Patients Who Completed Prior PD-1 Or PD-L1 Inhibitor Treatment Less Than 6 Months Ago

In the first-line setting, platinum-based chemotherapy is used in patients with NSCLC without actionable oncogenic alterations who completed prior PD-1 or PD-L1 inhibitor

treatment less than 6 months ago. Available options for prior PD-1 or PD-L1 inhibitors include durvalumab or atezolizumab. Atezolizumab is currently under consideration for funding. Docetaxel or pemetrexed are available second-line options upon progression.

Patients Who Completed Prior PD-1 Or PD-L1 Inhibitor Treatment at Least 6 Months Ago or With No Prior PD-1 Or PD-L1 Inhibitor Treatment

Available treatment options for patients who completed prior PD-1 or PD-L1 inhibitor treatment at least 6 months ago or without prior PD-1 or PD-L1 inhibitor treatment depending on the tumour PD-L1 status of the patients, which is assessed using Tumour Proportion Score. Available options for prior PD-1 or PD-L1 inhibitors include durvalumab or atezolizumab. Atezolizumab is currently under consideration for funding.

For patients with any PD-L1 status or whose PD-L1 status is unknown, available first-line treatment options include immunotherapy in combination with chemotherapy (either nivolumab or ipilimumab with 2 cycles of platinum doublet chemotherapy or pembrolizumab with platinum chemotherapy or pemetrexed) or platinum-based chemotherapy alone. Following progression on pembrolizumab plus chemotherapy or nivolumab plus ipilimumab with 2 cycles of chemotherapy, docetaxel or pemetrexed can be offered in second-line. Among patients who have disease progression on or after first-line platinum-based chemotherapy, nivolumab or atezolizumab treatment can be considered in patients with any PD-L1 status or whose PD-L1 status is unknown, while pembrolizumab can be considered in patients whose tumours express PD-L1. For all patients, docetaxel or pemetrexed are available in subsequent lines of therapy.

In patients whose tumours express PD-L1 (tumour proportion score of 50% or greater), pembrolizumab monotherapy can be offered in the first-line setting. Cemiplimab monotherapy is another first-line treatment option. Available treatments in subsequent lines of therapy include platinum-based chemotherapy (as second line) and docetaxel or pemetrexed (as third line).

Additional Remarks

pERC acknowledged that while the Health Canada approved indication for atezolizumab is according to the American Joint Committee on Cancer 7th edition, the 8th edition staging system is currently used in Canadian clinical practice. Based on clinical expert opinion, the eligible population based on the 8th edition would be fully resected stage II to IIIA patients who had a primary tumour > 5 cm regardless of nodal status or who were node positive regardless of primary tumour size.

Based on clinical expert opinion, patients with the common EGFR mutations (exon 19 del and exon 21 L858R) should not be offered adjuvant atezolizumab in favour of adjuvant osimertinib. The clinical experts also noted that immune checkpoint inhibitors do not have significant activity in the advanced setting in patients with ALK fusion; thus, there

may be limited, if any, benefit for a resected ALK-positive patient from adjuvant immunotherapy.