CADTH Reimbursement Review

Provisional Funding Algorithm

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

This report supersedes the CADTH Provisional Funding Algorithm report for non–small cell lung cancer without actionable oncogenic alterations dated August 2023.

Please always check CADTH Provisional Funding Algorithms | CADTH to ensure you are reading the most recent algorithm report.

June 2024

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:

- pan-Canadian Oncology Drug Review 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., the incident population). Time-limited funding of new options for previously or currently treated patients (i.e., the 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 update 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 rapid provisional funding algorithm for non–small cell lung cancer (NSCLC) without actionable oncogenic alterations in July 2022, incorporating the recommendation for cemiplimab (Libtayo) for the first-line treatment of adult patients with NSCLC expressing programmed cell death 1 ligand 1 (PD-L1) with a tumour proportion score (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.

A second provisional funding algorithm report was later released in November 2022, to incorporate the 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 the adjuvant setting, durvalumab 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 metastatic options in this algorithm.

In December 2022, jurisdictional cancer drug programs requested a panel algorithm to incorporate the CADTH recommendation for nivolumab (Opdivo) in combination with platinum-doublet chemotherapy for the neoadjuvant treatment of adult patients with resectable NSCLC. This panel addressed the following implementation issues, which have been summarized in Table 2:

- sequencing guidance following neoadjuvant use of nivolumab in combination with platinum-doublet chemotherapy
- treatment guidance for patients who have completed the full course of neoadjuvant nivolumab with residual disease on pathology
- guidance for adjuvant downstream therapies for patients who received neoadjuvant nivolumab and found to be positive for driver mutations (e.g., *EGFR*-positive, *ALK*-positive, and others).

Jurisdictional cancer drug programs have most recently requested an update to this algorithm report to incorporate the latest CADTH recommendations for cemiplimab in combination with platinum-based chemotherapy for the first-line treatment of adult patients with NSCLC whose tumours have no *EGFR*, *ALK*, or *ROS1* aberrations and is locally advanced where patients are not candidates for surgical resection or definitive chemoradiation, or metastatic NSCLC.

Table 1: Relevant CADTH Recommendations

Generic name (brand name)	Date of recommendation	Recommendation
Cemiplimab (Libtayo)	May 21, 2024	pERC recommends that cemiplimab in combination with platinum-based chemotherapy (cemiplimab plus PBC) be reimbursed for the first-line treatment of adults with NSCLC whose tumours have no *EGFR*, *ALK*, or *ROS1* aberrations and is locally advanced where patients are not candidates for surgical resection or definitive chemoradiation, or metastatic NSCLC, only if the following conditions are met: 1. Treatment with cemiplimab + PBC should be reimbursed in adults with squamous or nonsquamous NSCLC who meet the following criteria: 1.1. have stage IIIB or IIIC NSCLC and are not suitable for curative surgery or definitive chemoradiation, or have stage IV NSCLC 1.2. have had no prior systemic treatment. 2. Patients should have good performance status.

Generic name (brand name)	Date of recommendation	Recommendation
		3. Patients must not have any of the following: 3.1. tumours with *EGFR*, *ALK*, or *ROS1* aberrations 3.2. active or untreated brain metastases 3.3. prior neoadjuvant or adjuvant anti–PD-1 or anti–PD-L1 therapy within 6 months of treatment start or any prior anti–PD-1 or anti–PD-L1 therapy in the advanced disease setting. 4. Reimbursement of cemiplimab should be renewed for patients who demonstrate a continued response to treatment defined as absence of disease progression. 4.1. Assessment for renewal should be based on clinical and radiographic evaluation every 3 to 4 months. 5. Cemiplimab treatment should be reimbursed for a maximum of 108 weeks. 6. Treatment with cemiplimab + PBC should be prescribed by clinicians with expertise and experience treating NSCLC. The treatment should be supervised and delivered in outpatient specialized oncology clinics with expertise in systemic therapy delivery and management of immunotherapy-related side effects. 7. Cemiplimab + PBC should only be reimbursed when started in combination. 8. The cost of cemiplimab should be negotiated so that it does not exceed the drug program cost of treatment with the least costly immunotherapy reimbursed for first-line treatment of adults with NSCLC whose tumours have no *EGFR*, *ALK*, or *ROS1* aberrations and who have locally advanced NSCLC who are not candidates for surgical resection or definitive chemoradiation, or those who have metastatic NSCLC. **Optimal sequencing guidance:** pERC noted that patients who progress at least 6 months after their last dose of adjuvant or neoadjuvant platinum-doublet chemotherapy and PD-1 or PD-L1 inhibitor should be eligible to receive cemiplimab + PBC, in line with the EMPOWER-Lung 3 trial criteria. Treating patients with an ECOG performance status of 2 may be at the discretion of the treating clinician. pERC agreed with the clinical expert that patients with an ECOG PS of 2 are likely to benefit from cemiplimab + PBC and should be considered. Cemiplimab can continue as monotherapy after 4 cycles of PBC. If a patient experiences a toxicity that is known to be associated with chemotherapy, chemotherapy treatment may be discontinued but cemiplimab may be continued. pERC noted that patients who completed 2 years of cemiplimab treatment and progressed after the end of treatment should be eligible for re-treatment for up to

Generic name (brand name)	Date of recommendation	Recommendation
		17 cycles (1 year). pERC agreed that patients who start re-treatment with cemiplimab may receive chemotherapy treatment at the discretion of the treating physician. pERC agreed with the clinical experts that cemiplimab + PBC may be a valuable addition to the treatment landscape but may not drastically change the current standard of care. Cemiplimab + PBC may expand the options available to patients who are not suitable candidates for other treatments and have disease that has progressed on other PD-1 or PD-L1 therapies in the advanced setting.
Nivolumab (Opdivo)	April 18, 2023	pERC recommends that nivolumab, in combination with platinum-doublet chemotherapy, be reimbursed for the neoadjuvant treatment of adult patients with resectable non–small cell lung cancer (NSCLC) (tumour ≥ 4 cm or node positive) only if the following conditions are met: **Initiation:** 1. Neoadjuvant treatment with nivolumab in combination with platinum-doublet chemotherapy should only be initiated in adult patients with NSCLC whose tumours are both: 1.1. are resectable, 1.2. ≥ 4 cm or node positive (M0). 2. Patients must have good performance status. 3. Patients are ineligible for neoadjuvant treatment with nivolumab in combination with platinum-doublet chemotherapy if they have any of the following: 3.1. contraindications to neoadjuvant platinum-doublet chemotherapy or nivolumab as per clinical judgment 3.2. unresectable or metastatic disease 3.3. known *EGFR* mutations or *ALK* translocations, 3.4. large-cell neuroendocrine carcinoma tumour histology. **Discontinuation:** 4. Treatment with nivolumab, in combination with platinum-doublet chemotherapy, should be discontinued upon the occurrence of any of the following: 4.1. disease progression 4.1.1. patients should be assessed for evidence of disease progression during the 3 cycles of neoadjuvant therapy as per local standard practice 4.2. unacceptable toxicity 4.3. completion of 3 cycles of neoadjuvant therapy. **Prescribing:** 5. Nivolumab in combination with platinum-doublet chemotherapy should be prescribed by clinicians with expertise in managing NSCLC.

Generic name (brand name)	Date of recommendation	Recommendation
		Pricing: 6. A reduction in price. **Optimal sequencing guidance:** pERC and the clinical experts noted that docetaxel and vinorelbine were only allowed in the chemotherapy arm, and not in the nivolumab arm. At the time nivolumab plus chemotherapy was added to the CheckMate 816 study protocol, safety data were not available for nivolumab in combination with cisplatin and docetaxel, nor nivolumab in combination with cisplatin plus vinorelbine. pERC agreed with the clinical experts in that it would be appropriate to apply the chemotherapy agents that were used in the nivolumab plus chemotherapy arm for patients in real-world practice. Patients who had a known *EGFR* mutations or *ALK* translocation were excluded from CheckMate 816; therefore, the clinical benefit of nivolumab in combination with neoadjuvant chemotherapy is unknown. As a result, patients with known *EGFR* mutations or *ALK* translocation would not be eligible for nivolumab in combination with neoadjuvant chemotherapy for resectable NSCLC. The clinical experts highlighted that knowledge of driver mutations such as *EGFR* and *ALK* would be important; however, testing for these may not be routinely performed at all centres for early-stage disease. pERC concluded that *EGFR* and *ALK* testing at diagnosis is recommended. Patients were included in CheckMate 816 regardless of PD-L1 status. While there were potential differences in the clinical benefit observed by PD-L1 status, pERC acknowledged that the efficacy results in these subgroup analyses should be interpreted with caution, as the study was not statistically powered to assess PD-L1 subgroups. A clinical benefit was observed in the overall study population. Therefore, PD-L1 status is not required to be eligible for nivolumab in combination with neoadjuvant chemotherapy for resectable NSCLC.
Atezolizumab (Tecentriq)	September 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 [Seventh Edition]) non–small cell lung cancer (NSCLC) whose tumours have PD-L1 expression on 50% or more of tumour cells (TCs) and do not have *EGFR* or *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

Generic name (brand name)	Date of recommendation	Recommendation
		◦ 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 ◦ treatment 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 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 cell death 1 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: ◦ 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

Generic name (brand name)	Date of recommendation	Recommendation
		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) plus 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 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 nonplatinum 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

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		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 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. pERC noted that patients who completed 2 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 nonsquamous NSCLC, in adults with no *EGFR* or *ALK* genomic tumour aberrations and no prior systemic

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		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 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 2 years of pembrolizumab and discontinue therapy without progression, should have the option for re-treatment with pembrolizumab, if there is at least 6 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
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 before 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 or 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 2 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

Generic name (brand name)	Date of recommendation	Recommendation
		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 cytotoxic chemotherapy before 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 2 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

Generic name (brand name)	Date of recommendation	Recommendation
		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; NSCLC = non–small cell lung cancer; PBC = platinum-based chemotherapy; PD-1 = programmed cell death 1 protein; PDC = platinum-doublet chemotherapy; PD-L1 = programmed cell death 1 ligand 1; pERC = pan-Canadian Oncology Drug Review Expert Review Committee; TPS = Tumour Proportion Score.

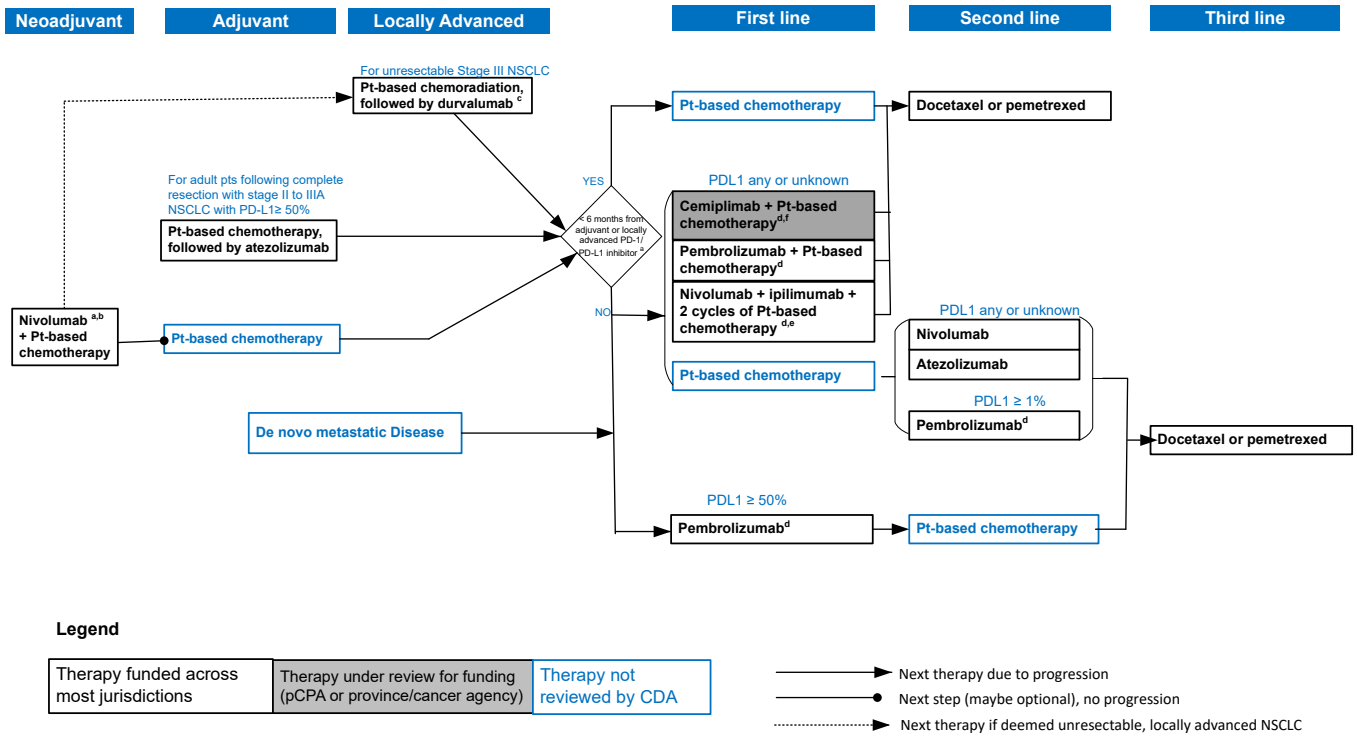
Table 2: CADTH Implementation Advice Panels on NSCLC Without Actionable Oncogenic Alterations

Date of publication	Implementation advice
December 2022	**Sequencing guidance following neoadjuvant use of nivolumab in combination with platinum-doublet chemotherapy:** For patients who have received a full course of treatment with nivolumab (i.e., 3 cycles) in combination with platinum-doublet chemotherapy in the neoadjuvant setting, the panel acknowledges that further immunotherapy (e.g., atezolizumab) in the adjuvant setting is not yet supported by available evidence. **Treatment guidance for patients who have completed a full course of neoadjuvant nivolumab in combination with platinum-doublet chemotherapy with residual disease on pathology:** Patients who have completed neoadjuvant nivolumab in combination with platinum-doublet chemotherapy and require adjuvant therapy (e.g., have residual disease on pathology) may be considered for adjuvant chemotherapy and/or radiation. **Guidance for adjuvant downstream therapies for patients who have received neoadjuvant nivolumab and who are subsequently found to be positive for driver mutations (e.g., *EGFR*-positive, *ALK*-positive, and others):** Patients with stage IIA to IIIB NSCLC (per AJCC Eighth Edition) who are found to be *EGFR* positive following neoadjuvant treatment with nivolumab may be considered for adjuvant osimertinib therapy.

AJCC = American Joint Committee on Cancer; NSCLC = non–small cell lung cancer.

Provisional Funding Algorithm

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



Legend

Therapy funded across most jurisdictions	Therapy under review for funding (pCPA or province/cancer agency)	Therapy not reviewed by CDA

Next therapy due to progression
Next step (maybe optional), no progression
Next therapy if deemed unresectable, locally advanced NSCLC

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

[a] For patients with resectable disease who have completed neoadjuvant nivolumab and may require adjuvant therapy (e.g., have residual disease on pathology), they may receive adjuvant chemotherapy. For patients who have completed neoadjuvant nivolumab (3 cycles) and if there is concern for rapid progression (e.g., pseudoprogression) to the metastatic setting, they may be considered on a case-by-case basis for immunotherapy within 6 months in the metastatic setting. Refer to the Discussion section of the full report for details.

[b] For patients who have not completed neoadjuvant nivolumab (≤ 2 cycles), they may be considered on a case-by-case basis for adjuvant chemoimmunotherapy (e.g., atezolizumab), depending on PD-L1 status and other patient specific factors.

[c] For patients who do not proceed with surgery due to disease (e.g., unresectable NSCLC), they can proceed with locally advanced treatment options within 6 months with platinum-based chemoradiation followed by durvalumab for curative intent. Refer to the Discussion section of the full report for details.

[d] For patients who complete 2 years of therapy and discontinue without progression, re-treatment is allowed.

[e] For patients who progress more than 6 months after completion of platinum-doublet chemotherapy while on this regimen, re-treatment with a histology-appropriate platinum doublet is allowed.

[f] For patients who have stage IIIB or IIIC NSCLC and are not suitable for curative surgery or definitive chemoradiation, or have stage IV NSCLC.

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

PD-L1 expression is determined using the tumour proportion score.

Description of the Provisional Funding Algorithm

Neoadjuvant and Adjuvant Setting

In the neoadjuvant setting, nivolumab in combination with platinum-doublet chemotherapy is available for adult patients with resectable NSCLC (tumours that are ≥ 4 cm or node positive). For individuals who have completed a full course of nivolumab (3 cycles) in combination with chemotherapy, they may be eligible for adjuvant platinum-based chemotherapy if there is residual disease on pathology.

For individuals who have not received any nivolumab in the neoadjuvant setting, other adjuvant immunotherapy options are available. For adult patients with stage II to IIIA (per the American Joint Committee on Cancer [Seventh Edition]) NSCLC whose tumours have PD-L1 expression on 50% or more of the tumour cells, atezolizumab is available as a monotherapy for adjuvant treatment following complete resection and no progression after platinum-based adjuvant chemotherapy.

For individuals deemed to have unresectable stage III NSCLC, durvalumab is funded for the treatment of patients with locally advanced, unresectable NSCLC following curative intent platinum-based chemoradiation.

For individuals who have received neoadjuvant nivolumab and do not proceed with surgery (e.g., those found to have unresectable locally advanced NSCLC), they may be considered for locally advanced treatment options with durvalumab following platinum-based chemoradiation.

Metastatic Setting

Patients who have completed prior PD-1 or PD-L1 inhibitor treatment in the adjuvant or locally advanced setting less than 6 months ago: In the first-line setting, platinum-based chemotherapy is used in patients with NSCLC without actionable oncogenic alterations who have completed prior PD-1 or PD-L1 inhibitor treatment in the adjuvant or locally advanced setting less than 6 months previously. Docetaxel or pemetrexed are available as second-line options upon progression.

Patients who completed prior PD-1 or PD-L1 inhibitor treatment in the adjuvant or locally advanced setting at least 6 months previously or with no prior PD-1 or PD-L1 inhibitor treatment including those with de novo metastatic disease: 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 (which can be nivolumab plus ipilimumab with 2 cycles of platinum-doublet chemotherapy, or pembrolizumab with platinum chemotherapy, or pemetrexed or cemiplimab in combination with platinum-based chemotherapy) or platinum-based chemotherapy alone. Following progression on pembrolizumab plus chemotherapy, or nivolumab plus ipilimumab with 2 cycles of chemotherapy, or cemiplimab in combination with platinum-based chemotherapy, docetaxel or pemetrexed can be offered in the second-line.

Among patients who have disease progression on or after first-line platinum-based chemotherapy, nivolumab or atezolizumab treatment can be considered in those with any PD-L1 status or whose PD-L1 status is unknown, while pembrolizumab can be considered in patients whose tumours express PD-L1 of 1% or more. For all patients, docetaxel or pemetrexed are available in subsequent lines of therapy.

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

Additional Remarks

pERC acknowledges that while the Health Canada–approved indication for atezolizumab is according to the American Joint Committee on Cancer Seventh Edition, the Eighth Edition staging system is currently used in Canadian clinical practice. Based on clinical expert opinion, the eligible population based on the Eighth Edition would be patients with fully resected stage II to IIIA NSCLC who had a primary tumour larger than 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, adjuvant immunotherapy may provide limited, if any, benefit to a patient with resected NSCLC who is *ALK*-positive.

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