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 December 2022.

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

Key Messages

- 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 supported by available evidence.
- Patients who have completed neoadjuvant nivolumab in combination with platinum-doublet chemotherapy and require adjuvant therapy (e.g., have residual disease on pathology), may receive adjuvant chemotherapy and/or radiation.
- Patients with stage IIA to IIIB NSCLC (per AJCC 8th edition) who are found to be epidermal growth factor receptor (EGFR) positive following neoadjuvant treatment with nivolumab, may be considered for adjuvant osimertinib adjuvant therapy.

Background

The provisional funding algorithm process is used to provide advice when the drug programs have indicated that there is a 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,

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 status. 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 non–small cell lung cancer without actionable oncogenic alterations. See Appendix 1 for a list all past CADTH advice and recommendations relevant for this therapeutic area.

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).

A second provisional funding algorithm report was released in November 2022, 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 the adjuvant setting, durvalumab is also incorporated into this algorithm. Durvalumab and atezolizumab were added to the algorithms for clarity, as PD-L1 inhibitors are now used upstream of first-line metastatic options in this algorithm.

Jurisdictional cancer drug programs have recently 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 report specifically focuses on providing implementation advice for this new recommendation.

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 guidance postneoadjuvant 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+, anaplastic lymphoma kinase (ALK)+, and others).

Consultation Process and Objectives

The implementation advice panel comprised 9 specialists in Canada with expertise in the diagnosis and management of patients with non–small cell lung cancer without actionable oncogenic alterations, 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 guidance postneoadjuvant 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.	The evidence for both neoadjuvant nivolumab combined with platinum-based chemotherapy and adjuvant atezolizumab following platinum-based chemotherapy is compelling. When feasible, clinicians are more likely to use immunotherapy in the preoperative setting. However, there are currently no funded adjuvant immunotherapy regimens with well-established evidence supporting sequential adjuvant immunotherapy following neoadjuvant immunotherapy. Therefore, further immunotherapy (e.g., with atezolizumab) will not be offered in the adjuvant setting to patients who have received neoadjuvant nivolumab.

Issue	Advice	Rationale
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.	A considerable proportion of patients (75%)[1] do not have a pCR after neoadjuvant chemoimmunotherapy and are at higher risk of recurrence. Although many clinicians would be inclined to offer adjuvant therapy to these patients, there is a lack of direct clinical evidence to guide these decisions. Adjuvant chemotherapy could be considered based on evidence from the CheckMate 816 Study in which patients were allowed to receive adjuvant chemotherapy.[2]
Guidance for adjuvant downstream therapies for patients who received neoadjuvant nivolumab and who are subsequently found to be positive for driver mutations (e.g., EGFR+, ALK+, and others).	Patients with stage IIA to IIIB NSCLC (per AJCC 8th edition) who are found to be EGFR positive following neoadjuvant treatment with nivolumab, may be considered for adjuvant osimertinib therapy.	Assessment of EGFR status is often a requirement for initiating neoadjuvant chemotherapy+ IO. However, in rare situations where EGFR status is unknown (e.g., as a result of inadequate tissue) or when the patient is subsequently found to have cancer harbouring an EGFR mutation, the information should be considered in future treatment decisions. There is strong evidence to support targeted therapy with adjuvant osimertinib in patients with stage IIA to IIIB disease (per AJCC 8th edition) and common EGFR mutations as demonstrated through the ADAURA study.[3,4] These patients are good candidates for upfront resection followed by adjuvant therapy with osimertinib. There is a concern regarding the risk of toxicity, especially with pneumonitis post immunotherapy use. Therefore, for patients treated with neoadjuvant immunotherapy, an adequate washout period from immunotherapy is preferred to minimize or avoid combined toxicity.

AJCC = American Joint Committee on Cancer; ALK = anaplastic lymphoma kinase; EGFR = epidermal growth factor receptor; IO = immune-oncology; pCR = pathological complete response.

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

Use of Immunotherapy in the Neoadjuvant Versus Adjuvant Setting

The panellists agreed that there are benefits to the use of immunotherapy in both the neoadjuvant and adjuvant settings. Both settings have demonstrated clinical evidence for reduction in the risk of relapse

in resectable NSCLC. The panellists stated that there is a role for both options in nonoverlapping patients; some cases would be appropriate for neoadjuvant chemotherapy with immunotherapy and surgery, while others would be suitable for surgery followed by adjuvant atezolizumab. There is a lack of evidence comparing neoadjuvant immunotherapy alone versus neoadjuvant plus adjuvant immunotherapy and there are no funded immunotherapy regimens in the adjuvant setting postneoadjuvant immunotherapy.

Treatment guidance for patients who have completed a full course of neoadjuvant nivolumab in combination with platinum-doublet chemotherapy with residual disease on pathology

Although there is appeal to only requiring 3 cycles of chemoimmunotherapy in the neoadjuvant setting, there is concern that patients who do not achieve a pCR, about 75%[1] of patients as 1 panellist noted, have been undertreated. For these patients, although clinicians may be inclined to offer additional immunotherapy (including with atezolizumab if PD-L1 expression is high) there is only indirect evidence to support this approach. However, panellists have noted that emerging evidence is forthcoming.[5] However, funding across most jurisdictions for further immunotherapy in the adjuvant setting is restricted.

One panellist noted that they may consider adjuvant chemotherapy for these patients or combination chemotherapy and radiation for gross residual disease but would not offer atezolizumab for patients with nonpCR. The panellists cited the CheckMate 816 Study in which patients who received nivolumab in the neoadjuvant setting were allowed to receive adjuvant chemotherapy and/or radiation after surgery.[6] Another panellist agreed that there was little reason to offer adjuvant immunotherapy to patients who have shown no or little response to immunotherapy in the neoadjuvant setting for whom immunotherapy may be deemed ineffective.

The panellists have deliberated on potential treatment approaches in the following clinical scenarios.

For patients who have not completed a full course of nivolumab (i.e., received ≤ 2 of 3 full cycles)

For patients who have not completed a full course of nivolumab (i.e., received ≤ 2 cycles) in the neoadjuvant setting due to toxicity or other reasons, subsequent systemic treatment decisions depend on various factors, including the reason for an inability to complete the full course of neoadjuvant nivolumab (e.g., immune toxicity, chemo toxicity, change in medical condition unrelated to therapy such as a heart attack or COVID-19 infection, or organizational reasons unrelated to patient), pathological response, PDL1 status and other patient-specific factors. Given the complexity of potential scenarios, the panellists agree that this may require a case-by-case assessment to determine the best downstream treatment strategies.

For patients who have achieved a pCR, additional therapy is not recommended, but for patients who do not achieve a pCR, adjuvant chemotherapy and/or radiation would be considered. Adjuvant immunotherapy may be considered on a case-by-case basis. Some panellists noted that they might be inclined to use adjuvant atezolizumab in some cases, but currently, there are no funded adjuvant immunotherapy regimens for these patients due to a lack of well-established evidence for a benefit of both neoadjuvant and adjuvant immunotherapy in patients with resectable early-stage NSCLC. However, the evidence is evolving, with recent

results of phase III randomized trials showing a benefit of further adjuvant immunotherapy in patients with early-stage NSCLC who received immunotherapy plus chemotherapy in the neoadjuvant setting.[5,7,8]

For patients who do not proceed with surgery

For up to 20% of patients who have received neoadjuvant nivolumab and do not proceed with surgery, there are competing treatment strategies all supported by good quality evidence from randomized controlled trials (RCTs). Treatment choice would be guided by patient characteristics and reason for no surgery. For patients that still have localized disease, there should be an opportunity for curative intent treatment.

Patients who cannot proceed to surgery (e.g., have unresectable stage III NSCLC), should be treated with concurrent chemoradiation and subsequent durvalumab given the compelling survival benefits with curative intent as demonstrated by the PACIFIC trial.[9]

For patients with stage IV disease (i.e., brain metastases, or incidental metastases discovered), a switch to chemoimmunotherapy with palliative intent (or palliative alone) would be a reasonable approach as discovery of metastases does not always equal clinical progression and 3 cycles of nivolumab is insufficient to consider a patient immunotherapy refractory.

For patients who may present with progression within 6 months following completed neoadjuvant nivolumab

There may be scenarios where patients who have completed 3 cycles of neoadjuvant nivolumab may be suspected to have progression within 6 months to the metastatic setting without an opportunity to receive any adjuvant treatment. One panellist has noted that patients who are treated with immunotherapy often show a pseudoprogression after the first 3 to 4 cycles and may go on to have deep and durable responses to immunotherapy.

In these scenarios where patients have only completed 3 cycles of immunotherapy, there is currently insufficient evidence for them to be deemed resistant to immunotherapy. There is also a lack of pharmacokinetic and pharmacodynamic data to support a decision on the re-treatment interval. For these patients, they may be considered on a case-by-case basis to access immunotherapy in the metastatic setting based on PDL1 scores and other patient-specific factors.

For patients subsequently found to be positive for driver mutations

For patients who have received neoadjuvant nivolumab but subsequently found to be positive for driver mutations (e.g., EGFR + NSCLC) the approach downstream therapies depend on the driver mutation. For stage II to IIIB NSCLC patients subsequently found to have common EGFR mutations (exon 19 del and exon 21 L858R), the panellists stated that adjuvant osimertinib would be a treatment option, based on strong data supporting its use in these EGFR positive patients. It was noted that an adequate washout time from neoadjuvant immunotherapy was needed to avoid combined toxicity such as pneumonitis. There are no other adjuvant treatments indicated for these patients.

The panellists emphasized that determining EGFR/ALK mutation status is important before embarking on neoadjuvant chemoimmunotherapy. It was noted that there are some variations in testing and turnaround

time in different cancer centres. In some centres reflex next generation sequencing (NGS) testing regardless of stage is performed with a good turnaround time. The paradigm shift to neoadjuvant treatment was noted as a reason to advocate for equitable access to timely NGS biomarker testing for all lung cancer patients in Canada regardless of where they are treated.

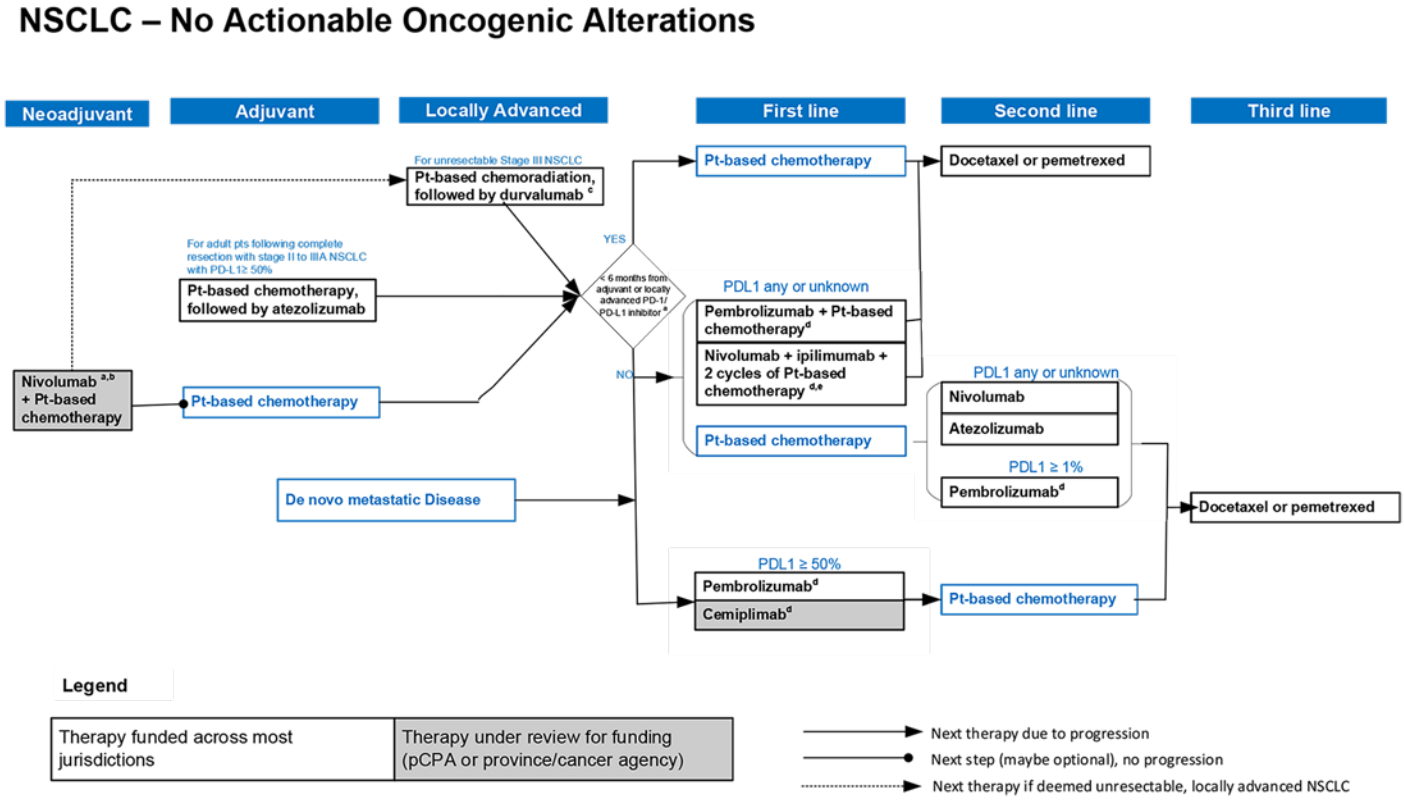
Re-Treatment Interval for Disease Progression

The panellists have also discussed the re-treatment interval for disease progression from neoadjuvant to metastatic setting. Typically, patients may be retreated with immunotherapy in the metastatic setting if the previous immunotherapy was completed more than 6 months ago. This 6-month interval is based on pharmacokinetics and half-lives of immunotherapy after receiving treatment for a longer duration (e.g., up to 2 years). However, with patients receiving a much shorter treatment duration in the neoadjuvant setting (3 cycles of nivolumab), it begs the question if this 6-month interval is appropriate.

During the deliberation, the responses from the panellists were mixed. For patients who receive neoadjuvant chemoimmunotherapy, proceed to surgery and have an R0 resection, some panellists stated that it makes sense to use a 6-month disease free interval in determining eligibility for re-treatment for relapsed disease. They stated that there are competing treatment strategies for this population of patients with stage III disease. If patients are not able to proceed to surgery, or have an incomplete resection, they should have access to the competing treatment strategy (i.e., concurrent chemoradiation followed by a year of consolidation durvalumab). Other panellists disagreed with the 6-month interval and stated that 3 cycles are not sufficient to deem patients immunotherapy resistant. Citing the PACIFIC trial,[10] many of these patients may qualify for chemoradiation therapy followed by durvalumab.

Provisional Funding Algorithm

Figure 1: Provisional Funding Algorithm Diagram for Non–Small Cell Lung Cancer Without Actionable Oncogenic Alterations



NSCLC = non–small cell lung cancer; pCPA = pan-Canadian Pharmaceutical Alliance; PD-L1 = programmed cell death 1 ligand; 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 progression within 6 months (e.g., pseudo-progression) to the metastatic setting, they may be considered on a case-by-case basis for immunotherapy 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), on a case-by-case basis for adjuvant chemoimmunotherapy (e.g., atezolizumab) may be considered depending on PDL1 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 option within 6 months with platinum-based chemoradiation followed by durvalumab for curative intent. See discussion section of the full reports for details.

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

[e]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.

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.

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 ≥ 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. Nivolumab is currently under review for funding.

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 [7th 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 deem to have unresectable stage III NSCLC, durvalumab is funded for the treatment of patients with locally advanced, unresectable non–small cell lung cancer following curative intent platinum-based chemoradiation.

For individuals who have received neoadjuvant nivolumab and do not proceed with surgery (e.g., found to have unresectable locally advanced NSCLC), they may be considered for locally advanced treatment option 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 ago. 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 ago or with no prior PD-1 or PD-L1 inhibitor treatment including those with de novo metastatic disease

Available treatment options for patients who have completed prior PD-1 or PD-L1 inhibitor treatment at least 6 months ago in the adjuvant or locally advanced or without prior PD-1 or PD-L1 inhibitor treatment depend on the tumour PD-L1 status of the patients, which is assessed using Tumour Proportion Score.

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 plus 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 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 or cemiplimab monotherapy can be offered in the first-line setting. Available treatments in subsequent lines of therapy include platinum-based chemotherapy as second-line and docetaxel or pemetrexed as third-line.

Additional Remarks

pERC acknowledge 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 clinical practice in Canada. 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 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, there may be limited, if any, benefit for a resected *ALK*-positive patient from adjuvant immunotherapy.

References

1. Hu Y, Ren SY, Wang RY, et al. Surgical Outcomes After Neoadjuvant Chemoimmunotherapy for Resectable Non-Small Cell Lung Cancer. *Front Oncol.* 2021;11:684070. PubMed
2. Forde PM, Spicer J, Lu S, et al. Neoadjuvant Nivolumab plus Chemotherapy in Resectable Lung Cancer. *N Engl J Med.* 2022;386(21):1973-1985. PubMed
3. Wu YL, Tsuboi M, He J, et al. Osimertinib in Resected EGFR-Mutated Non-Small-Cell Lung Cancer. *N Engl J Med.* 2020;383(18):1711-1723. PubMed
4. CADTH Drug Reimbursement Expert Review Committee final recommendation: osimertinib (Tagrisso -AstraZeneca Canada Inc.). *Can J Health Technol.* 2022;2(3). https://www.cadth.ca/sites/default/files/DRR/2022/PC0246-Tagrisso.pdf. Accessed 2023 Jun 13.
5. Coyle L. AEGEAN trial demonstrates improved OS for durvalumab NSCLC treatment arm. *OncologyCentral.* 2023: https://www.oncology-central.com/aacr-2023-aegean-trial-demonstrates-improved-os-for-durvalumab-nsclc-treatment-arm/. Accessed 2023 Jun 26.
6. CADTH Drug Reimbursement Expert Review Committee final recommendation: Nivolumab (Opdivo - Bristol-Myers Squibb). *Can J Health Technol.* 2023;3(4). https://www.cadth.ca/sites/default/files/DRR/2023/PC0303%20Opdivo%20NSCLC%20-%20Final%20CADTH%20Recommendation.pdf. Accessed 2023 Jun 13.
7. Lu S, Wu L, Zhang P, et al. Perioperative toripalimab + platinum-doublet chemotherapy vs chemotherapy in resectable stage II/III non-small cell lung cancer (NSCLC): Interim event-free survival (EFS) analysis of the phase III NEOTORCH study. *J Clin Oncol.* 2023;41(16 Suppl):8501-8501.
8. Wakelee H, Liberman M, Kato T, et al. Perioperative Pembrolizumab for Early-Stage Non-Small-Cell Lung Cancer. *N Engl J Med.* 2023. PubMed
9. Antonia SJ, Villegas A, Daniel D, et al. Overall Survival with Durvalumab after Chemoradiotherapy in Stage III NSCLC. *N Engl J Med.* 2018;379(24):2342-2350. PubMed
10. Antonia SJ, Villegas A, Daniel D, et al. Durvalumab after Chemoradiotherapy in Stage III Non-Small-Cell Lung Cancer. *N Engl J Med.* 2017;377(20):1919-1929. PubMed

Appendix 1: Past CADTH Advice and Recommendations

Table 2: Relevant CADTH Recommendations

Generic name (brand name)	Date of recommendation	Recommendation
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: 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: 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. **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

Generic name (brand name)	Date of recommendation	Recommendation
		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 like the *EGFR* and *ALK* would be important, however 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 [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 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
		  ◦ 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

Generic name (brand name)	Date of recommendation	Recommendation
		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 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: ◦ 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).

Generic name (brand name)	Date of recommendation	Recommendation
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 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 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

Generic name (brand name)	Date of recommendation	Recommendation
		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 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.

Generic name (brand name)	Date of recommendation	Recommendation
		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 (Infinzi)	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.
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., 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/PD-1 inhibitors in sequence (e.g., atezolizumab then nivolumab or pembrolizumab, or vice versa).

Generic name (brand name)	Date of recommendation	Recommendation
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 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

Generic name (brand name)	Date of recommendation	Recommendation
		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.

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