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CADTH Reimbursement Recommendation

Nivolumab (Opdivo)

Indication: In combination with platinum-doublet chemotherapy for the neoadjuvant treatment of adult patients with resectable non–small cell lung cancer (tumours ≥ 4 cm or node positive)

Sponsor: Bristol-Myers Squibb (BMS)

Final recommendation: Reimburse with conditions

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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.

Summary

What Is the CADTH Reimbursement Recommendation for Opdivo?

CADTH recommends that Opdivo, in combination with platinum-doublet chemotherapy, be reimbursed for the neoadjuvant (early-stage) treatment of adult patients with resectable non–small cell lung cancer (NSCLC) (tumours ≥ 4 cm or node positive) if certain conditions are met.

Which Patients Are Eligible for Coverage?

Opdivo used with chemotherapy should only be covered when used to treat adult patients with operable early-stage NSCLC whose tumours are 4 cm or more in size or are considered node positive. Opdivo used with chemotherapy should be given before surgery. Patients receiving Opdivo should be in relatively good health (i.e., have a good performance status, as determined by a specialist).

What Are the Conditions for Reimbursement?

Opdivo used with chemotherapy should only be reimbursed if prescribed by specialists with experience in managing NSCLC. Opdivo used with chemotherapy should not be reimbursed if used to treat patients who have *EGFR* or *ALK* gene abnormalities, patients whose tumour histology is considered large cell neuroendocrine carcinoma, or patients for whom chemotherapy before surgery is inadvisable. The cost of Opdivo must be lowered to be cost-effective and affordable.

Why Did CADTH Make This Recommendation?

- Evidence from 1 clinical trial demonstrated that adding Opdivo to chemotherapy before surgery in patients with early-stage NSCLC lowered the chances of cancer returning compared with chemotherapy before surgery alone.
- Opdivo used with chemotherapy has the potential to address an unmet need for patients.
- Based on CADTH's assessment of the sponsor's economic submission, Opdivo may represent good value at the public listed price. Price reductions would reduce the uncertainty of this assessment.
- Based on the public listed price, Opdivo in combination with platinum-doublet chemotherapy is estimated to cost the public drug plans more than $27 million across the next 3 years.

Summary

Additional Information

What Is Early-Stage Non–Small Cell Lung Cancer?

NSCLC is the most common type of lung cancer in which unusual growth of cells takes place inside the lungs or lining of the airways and can form into tumours. Cancer is considered early stage when the tumour has not spread to other parts of the body.

Unmet Needs in Non–Small Cell Lung Cancer

The intention of surgery for early-stage NSCLC is to cure patients. However, for some patients who had surgery, their cancer may return. Therefore, there is a need for treatment options that can prevent cancer from returning.

How Much Does Opdivo Cost?

Treatment with Opdivo in the neoadjuvant setting is expected to cost approximately $9,908 per 28 days (when using a fixed dose of 360 mg every 21 days).

Recommendation

The CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (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) (tumours ≥ 4 cm or node positive) only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One phase III, multicentre, randomized study (CheckMate 816) demonstrated that the addition of nivolumab to neoadjuvant platinum-doublet chemotherapy compared with neoadjuvant platinum-doublet chemotherapy alone resulted in added clinical benefit for adult patients with resectable NSCLC (tumours ≥ 4 cm or node positive). CheckMate 816 showed that, compared with neoadjuvant platinum-doublet chemotherapy alone, the addition of nivolumab to neoadjuvant platinum-doublet chemotherapy led to a statistically significant and clinically meaningful improvement in event-free survival (EFS) (hazard ratio [HR] = 0.63; 97.38% confidence interval [CI], 0.43 to 0.91; P = 0.0052). As well, the addition of nivolumab to neoadjuvant platinum-doublet chemotherapy demonstrated a significant improvement in pathological complete response (pCR) (24.0% versus 2.2%; odds ratio [OR] = 13.94; 99% CI, 3.49 to 55.75; P < 0.0001) compared with neoadjuvant platinum-doublet chemotherapy alone. Nivolumab was also associated with a manageable toxicity profile with no new safety signals observed.

Nivolumab has the potential to address an unmet need for this patient population with poor prognosis and high risk of disease recurrence. Patients identified a need for additional treatment options that maintain or improve quality of life, delay onset of symptoms, prolong life, provide a cure, and minimize travel time and burden on caregivers. pERC concluded that nivolumab met some of the needs identified by patients, such as improved EFS, which would likely delay onset of symptoms from recurrent disease; no detriment in quality of life was observed with the addition of nivolumab to neoadjuvant platinum-doublet chemotherapy.

Using the sponsor-submitted price for nivolumab and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for neoadjuvant nivolumab plus platinum-doublet chemotherapy before surgery was $32,846 per quality-adjusted life-year (QALY) gained compared with surgery alone. Due to uncertainty in the evidence and limitations in the modelling approach, results from this analysis were considered uncertain. Nivolumab may be cost-effective at a willingness-to-pay threshold of $50,000 per QALY gained for adult patients newly diagnosed with resectable stage IB (≥ 4 cm), stage II, and stage IIIA NSCLC; price reductions would reduce the uncertainty with this conclusion.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Neoadjuvant treatment with nivolumab in combination with	Evidence from the CheckMate 816 study demonstrated that the addition of nivolumab to	—

Reimbursement condition	Reason	Implementation guidance
platinum-doublet chemotherapy should only be initiated in adult patients with NSCLC whose tumours are both: 1.1. resectable 1.2. ≥ 4 cm or node positive, M0.	neoadjuvant platinum-doublet chemotherapy compared with neoadjuvant platinum-doublet chemotherapy alone resulted in added clinical benefit for adult patients with resectable NSCLC (tumours ≥ 4 cm or node positive). The population outlined reflects the patient population of the CheckMate 816 study, and this aligns with clinical expert opinion.	
2. Patients must have good performance status.	The clinical experts emphasized the need for patients to have robust performance status to be eligible to receive the treatment given that patients with less clinical reserve will be susceptible to adverse events that may render them ineligible for curative-intent surgery.	–
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.	Based on clinical expert opinion, the patients for whom neoadjuvant treatment with nivolumab in combination with platinum-doublet chemotherapy would be least suitable are those with a contraindication to chemotherapy and immunotherapy treatments. Patients who have unresectable or metastatic disease, known *EGFR* mutations or *ALK* translocations, or large cell neuroendocrine carcinoma tumour histology were excluded from the CheckMate 816 study.	According to clinical experts, *EGFR* and *ALK* testing may not be routinely performed at all centres for early-stage disease. *EGFR* and *ALK* testing at diagnosis is recommended as targeted therapies are available for patients with *EGFR* mutations or *ALK* translocations.
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	Based on clinical expert opinion, intolerable toxicity and clinically obvious disease progression are factors to consider when deciding to discontinue nivolumab treatment. According to clinical experts, clinical and biological evaluations are performed at every cycle of therapy as per standard practice in oncology similarly as patients undergoing chemotherapy immunotherapy in the advanced disease setting. In the CheckMate 816 study, nivolumab, in combination with platinum-doublet chemotherapy was administered every 3 weeks for 3 cycles as neoadjuvant treatment, which aligns with the Health Canada product monograph.	pERC agreed with the clinical experts that if the adverse event is attributable to chemotherapy only, then the patients may receive the remainder of the treatment with nivolumab monotherapy up to the 3 cycles of neoadjuvant therapy before surgery.

Reimbursement condition	Reason	Implementation guidance
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.	To ensure that nivolumab is prescribed only for appropriate patients and adverse effects are managed in an optimized and timely manner.	—
Pricing		
6. A reduction in price.	The committee noted that although the economic analysis suggested that nivolumab was cost-effective at a threshold of $50,000 per QALY gained, this conclusion was uncertain due to several assumptions made in the analysis. The main uncertainties included treatment effects and long-term outcomes based on cancer stage, long-term OS benefits with nivolumab, and reliance on uncertain indirect comparisons vs. surgery alone and adjuvant therapy. Not all these uncertainties could be fully explored in the economic analysis due to the inflexible model structure. A reduction in price would reduce the uncertainty regarding the cost-effectiveness of nivolumab in this setting.	—

NSCLC = non–small cell lung cancer; pERC = CADTH pan-Canadian Oncology Drug Review Expert Review Committee; QALY = quality-adjusted life-year.

Discussion Points

- pERC discussed that many patients receiving current standard of care (i.e., surgery followed by adjuvant chemotherapy) still experience disease relapse and, according to clinical experts, the benefit of adjuvant chemotherapy is modest and is associated with a toxicity burden. As a result, pERC concluded there is an unmet need for new treatment for patients with resectable NSCLC.
- pERC acknowledged that the rationale for neoadjuvant chemotherapy is to reduce tumour size, increase resectability, treat micrometastases and tumour cells in lymph nodes, thereby reducing the risk of recurrence from tumour cells that are not removed by surgery. pERC noted that neoadjuvant chemotherapy is seldomly used in Canada and may render some patients ineligible for surgery due to disease progression or treatment-related toxicity.
- Given the risk of rendering some patients ineligible for surgery due to disease progression or treatment-related toxicity and the complexity of staging and treatment, pERC acknowledged the importance of discussing the eligibility of patients to neoadjuvant treatment of nivolumab in combination with platinum-doublet chemotherapy with a multidisciplinary board before initiating treatment.

- pERC discussed the impact of neoadjuvant treatment with nivolumab in combination with platinum-doublet chemotherapy on survival. Although pERC acknowledged the CheckMate 816 study is still ongoing and overall survival (OS) data were immature, pERC noted a trend to improved OS.
- pERC also discussed the sponsor-submitted indirect treatment comparison (ITC) in the form of a network meta-analysis which assessed the efficacy and safety of neoadjuvant nivolumab with chemotherapy compared with other relevant treatments: neoadjuvant chemotherapy, neoadjuvant chemoradiotherapy, adjuvant chemotherapy, and surgery alone in patients with resectable NSCLC. Given the limitations of the ITC and the lack of direct comparative evidence, there remains uncertainty in the magnitude of benefit of neoadjuvant nivolumab in combination with platinum-doublet chemotherapy compared with neoadjuvant chemoradiotherapy, adjuvant chemotherapy, and surgery alone.
- pERC discussed the uncertainty with the economic analysis regarding both limitations with the modelling approach and the clinical evidence presented. Although the analysis indicated that nivolumab was cost-effective in this setting at a threshold of $50,000 per QALY gained, pERC noted concerns with the inflexible model approach. Combined with clinical uncertainty regarding OS and limitations with indirect evidence, results from the analysis were considered uncertain. Overall, given the evidence presented and the small number of cycles needed in the neoadjuvant setting, the committee felt that nivolumab may be cost-effective at the sponsor-submitted list price but noted that price reductions would decrease the uncertainty of this assessment and account for unresolved uncertainty in the analysis.

Background

Lung cancer is the most frequently diagnosed cancer in Canada and the leading cause of cancer-related deaths. Approximately 30,000 new diagnoses (50% males and 50% females) and 20,700 cancer-related deaths were projected in Canada in 2022, with an anticipated 98% of all cases in people aged 50 years and older. The adjusted 5-year net survival for all forms of lung cancers (based on 2015 to 2017 estimates) is only 22% (19% in males and 26% in females in Canada). NSCLC is the most common form of lung cancer, accounting for more than 80% of all lung cancers in Canada. Approximately 47.1% of all new NSCLC cases are diagnosed at stage IV, 19.0% at stage III, 9.1% at stage II, and only 23.1% at stage I.

The primary goals of treating patients with resectable NSCLC disease is to cure, improve the 5-year OS, and prevent disease recurrence. Surgery with curative intent is the current gold standard for clinical stage I to stage IIIA NSCLC amenable to resection. The standard of care according to the American Society of Clinical Oncology (ASCO) and Cancer Care Ontario (CCO) guidelines for completely resectable stage IIA or stage B and IIIA NSCLC (7th edition of the *AJCC Cancer Staging Manual* [*AJCC* 7th edition]) is surgical resection followed by adjuvant cisplatin-based chemotherapy. Cisplatin-based chemotherapy is not recommended for patients with stage IA NSCLC and not routinely for stage IB disease; however, postoperative evaluations are recommended. Stereotactic ablative radiation with curative intent is available for some patients with early-stage disease who are ineligible for surgery (e.g., due to significant comorbidities that make them high

risk for a general anesthetic, or who refuse surgery), whereas patients with resectable stage III cancer may be offered chemotherapy and or radiation before surgery in current practice. Neoadjuvant chemotherapy is seldom used in Canada because it has not been shown to provide survival benefit over adjuvant therapy and, in the process of pursuing neoadjuvant chemotherapy, some patients may become ineligible for surgery (due to disease progression or treatment-related toxicity) according to the clinical experts consulted. Notwithstanding, neoadjuvant therapy has several advantages: it can reduce tumour size, increase resectability, and remove micrometastases and tumour cells in more distant lymph nodes, thereby reducing the risk of recurrence resulting from tumour cells that are not removed by surgery.

Nivolumab has been approved by Health Canada in combination with platinum-doublet chemotherapy for the neoadjuvant treatment of adult patients with resectable NSCLC (tumours ≥ 4 cm or node positive). Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody that binds to the programmed cell death protein 1 (PD-1) receptor and blocks its interaction with programmed cell death ligands 1 and 2 (PD-L1 and PD-L2). The dosage recommended in the product monograph 360 mg nivolumab administered intravenously over 30 minutes in combination with platinum-doublet chemotherapy every 3 weeks for 3 cycles as neoadjuvant treatment.

Sources of Information Used by the Committee

To make their recommendation, the committee considered the following information:

- a review of 1 phase III clinical trial in adult patients with resectable NSCLC (tumours ≥ 4 cm or node positive)
- a review of 1 sponsor-submitted ITC, 1 meta-analysis, and 1 real-world evidence study
- patient perspectives gathered by a patient group (Lung Cancer Canada [LCC])
- input from public drug plans and cancer agencies that participate in the CADTH review process
- 2 clinical specialists with expertise diagnosing and treating patients with resectable NSCLC
- input from 2 clinician groups, including Ontario Health–Cancer Care Ontario (OH-CCO) Lung Cancer Drug Advisory Committee and LCC
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

Patient Input

LCC, a member of Global Lung Cancer Coalition and the only national organization in Canada focused exclusively on lung cancer, engages in patient support, education, research, and advocacy. LCC submitted patient group input based on interviews conducted in Canada between September and October 2022 (1 patient with stage I/II, 1 patient with stage III, 2 patients with stage IV NSCLC, and 1 caregiver for a patient with large cell neuroendocrine carcinoma) and 1 interview from the past Environmental Scan (1 patient with

stage IV NSCLC). All participants had experience with nivolumab. The CADTH patient input summary focuses on the 2 patients with stage I to III NSCLC to align with the requested indication.

One patient said they used to be extremely active and was an avid runner for 10 years before lung cancer diagnosis. According to the patient, lung cancer made exercise harder and made her feel more tired than ever, which impacted her independence. She also said that she experienced cough and some mild chest pain before diagnosis of lung cancer. Another patient who had been diagnosed with early-stage NSCLC had two-thirds of his lung removed by surgery leaving him with 50% initial lung capacity. As a result, the patient became unable to do any vigorous exercises or activities because he tires quicker. As for improved outcomes, the input indicated that patients value new treatment options that maintain or improve quality of life (e.g., improve or maintain functionality and mobility), delay onset of symptoms, improve survivorship, and, ultimately, provide a cure. Also, respondents preferred treatment that can be given at a hospital located near home and/or community clinics in case they are in a rural setting to minimize travel time and burden on caregivers. Finally, the input from the patient group emphasized that since CheckMate 816 trial excluded patients with *EGFR* or *ALK* alterations due to a lack of evidence of neoadjuvant immunotherapy in this population, a biomarker screening (a routine practice) will need to be performed before neoadjuvant treatment with nivolumab.

Clinician Input

Input From Clinical Experts Consulted by CADTH

The clinical experts consulted for this review highlighted improved OS (prolonged life) and delay of disease relapse as important treatment goals in NSCLC curative settings. The clinical experts highlighted that neoadjuvant chemotherapy is infrequently used across jurisdictions in Canada because it has not been shown to provide a survival benefit over adjuvant therapy and that, in the process of receiving neoadjuvant chemotherapy, some patients may become ineligible for surgery (due to disease progression or drug-related toxicity that may affect a patient's performance status). The clinical experts highlighted an unmet need for patients with resectable NSCLC tumours because some patients who undergo surgical resection and receive adjuvant chemotherapy may experience disease relapse. The clinical experts added that patients who experience relapse following surgery and/ or adjuvant chemotherapy are generally incurable. Both clinical experts agreed that neoadjuvant nivolumab in combination with chemotherapy will cause a shift in current Canadian treatment paradigm in the curative-intent setting.

The clinical experts indicated that patients with NSCLC with tumours greater than 4 cm and/or node positive, *EGFR* and *ALK* negative, surgically resectable upfront, including patients with locoregional spread of disease to lymph nodes (who remain resectable upfront), would be eligible to receive treatment provided there have no contraindications (severe and uncontrolled autoimmune diseases, frailty, poor baseline organ function). The experts highlighted that neoadjuvant nivolumab in combination with chemotherapy would not be appropriate for patients who are borderline resectable upfront for whom the goal of neoadjuvant therapy is intended to downsize the tumour to become surgery eligible. According to the clinical experts, patients will be identified by a surgical and medical oncologist after appropriate review. The clinical experts added that

knowledge of *EGFR* and *ALK mutations* would be important but may not be routinely performed at all centres for early-stage disease.

The clinical experts added that patient response to treatment in clinical practice is based on preoperative CT scans completed after neoadjuvant systemic chemotherapy, pathologic response, disease recurrence, and OS. The clinical experts highlighted that the schedule of follow-up assessments after completion of curative-intent surgery is not standardized across jurisdictions in Canada because of a lack of definitive literature suggesting the most appropriate timing interval for serial radiography. The clinical experts highlighted that either nivolumab, platinum-doublet chemotherapy, or both could be discontinued upon patient request for treatment discontinuation, in the event of disease progression during the 3 cycles of neoadjuvant therapy, medically dangerous side effects, or intolerable toxicity.

Clinician Group Input

Two clinician groups, OH-CCO Lung Cancer Drug Advisory Committee and LCC, submitted 2 separate inputs. The OH-CCO Drug Advisory Committee provides guidance on drug-related issues in support of CCO's mandate and collected information from 3 clinicians during a Drug Advisory Committee meeting. LCC, a national charity and the only organization in Canada solely focused on lung cancer (education, advocacy, research), gathered information from published clinical data and 12 lung cancer medical oncologists across Canada.

Unmet Needs

According to the OH-CCO group, despite current treatments, a number of patients recur quickly and do not survive. Therefore, neoadjuvant nivolumab would be an additional option for patients with resectable NSCLC. The LCC cited several advantages of neoadjuvant approaches including limiting the risk of systemic dissemination of the cancer; tumour downsizing (decreasing postoperative complications, e.g., pain, infection, decreased performance status, improved surgical outcomes, and recovery times); possibility of easier, safer, and more efficacious surgeries; improving patient capacity to receive postoperative therapies; providing opportunity for smoking cessation, physical therapy, and medical evaluations for surgery; help to manage surgical wait lists; and improving the ability to provide prognosis and risk-stratification after surgery.

Place in Therapy

According to the OH-CCO clinicians, neoadjuvant nivolumab would be an additional option for patients with resectable NSCLC and potentially replace adjuvant chemotherapy in some patients. Similarly, the LCC clinicians said that neoadjuvant nivolumab therapy would eliminate the need of postoperative, prolonged, and more expensive therapies (chemotherapy, radiation, immunotherapy). LCC said it is not clear if all eligible patients would choose neoadjuvant nivolumab therapy; for example, patients with stage II, node-negative disease considered for upfront surgery with optional adjuvant therapies, those at high risk of chemotherapy- or immunotherapy-associated complications, or those preferring upfront surgery.

Patient Population

The OH-CCO clinicians said patients who meet the clinical trial inclusion criteria (i.e., resectable NSCLC stage IIA to IIIB (*AJCC* 8th edition) [sic] and/or those eligible for chemotherapy would be best suited for treatment

with nivolumab. [Of note, CheckMate 816 inclusion criteria were stage IB (≥ 4 cm) to stage IIIA (per *AJCC* 7th edition), which corresponds to stage IB to stage IIIB nonN3; non N2-T4 per *AJCC* 8th edition.] LCC said that neoadjuvant therapy may be favoured for patients with stage IIIA and/or PD-L1-positive NSCLC based on CheckMate 816 study showing favourable results in these populations of patients. However, the LCC group said that a discussion with every eligible patient appears warranted, and treating all eligible patients with a neoadjuvant would be favoured to decrease the treatment burden after surgery (e.g., postoperative chemotherapy and/or atezolizumab). According to the LCC, the patients with NSCLC that would be the least suitable for this treatment would be those with a contraindication to chemotherapy and immunotherapy treatments, such as those with renal failure, heart failure, severe hearing loss, severe neuropathy, an organ transplant, active and symptomatic autoimmune disease (e.g., Crohn disease on immunosuppressive therapy or MS), as well as those with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 2 to 4. LCC added that a history of autoimmune disease or autoimmune disease that is clinically silent (e.g., immune thyroiditis) or well controlled without active immunosuppression is not a major contraindication. Finally, according to LCC's input, the use of neoadjuvant immunotherapy in patients with *EGFR*, *ALK*, *ROS1*, *RET*, and *NTRK* alterations needs further investigation and/or will have to be addressed on a case-by-case setting because these groups have not been specifically addressed in clinical trials.

Assessing Response to Treatment

The OH-CCO clinician group stated that outcomes, such as clinical assessment (to ensure no progression), surgery, and pathological assessment, can be used to determine response to nivolumab. The LCC clinician group said that an additional CT scan assessment after neoadjuvant therapy to evaluative eligibility for surgery will be required. According to LCC, there is currently no clinical, biological, or imaging tool that can be used to identify patients who will have pCR on pathological assessment after neoadjuvant treatment to exclude any patients from surgical treatment. At present, the LCC clinicians said that patients are followed up with standard postoperative care. However, in the future, the LCC clinicians anticipate that risk-adapted follow-up strategies based on, for example, ctDNA postoperative monitoring, in combination with other clinical and pathological features of the cancer will be possible when more experience in neoadjuvant approaches is gained.

Discontinuing Treatment

The OH-CCO clinicians said that intolerable toxicity and clinically obvious disease progression are factors to consider when deciding to discontinue nivolumab treatment. The LCC clinicians stated that clinical and biological evaluations are performed at every cycle of therapy as per standard practice in oncology similarly as patients undergoing chemotherapy immunotherapy in the advanced disease setting.

Prescribing Conditions

The OH-CCO clinicians added that a specialist, ideally as part of a multidisciplinary team, is required in a hospital outpatient clinic to diagnose, treat, and monitor patients receiving nivolumab. The LCC clinicians also stated that, ideally, a multidisciplinary cancer tumour board involving (nonexclusively) respirologists, radiologists, pathologists, thoracic surgeons, medical oncologists, and radiation oncologists should discuss a multimodal treatment approach for patients who are usually referred to oncologic thoracic surgeons

affiliated with major cancer centres. The LCC added that the delivery of care will be planned according to local structures of delivery of care, ideally systemic therapies given to patients as close to home as possible while patients are continuously being monitored by the cancer centre to coordinate neoadjuvant therapies with posttreatment imaging, preoperative evaluations, and the surgical admission itself.

Drug Program Input

The drug programs provide input on each drug being reviewed through CADTH's reimbursement review processes by identifying issues that may impact their ability to implement a recommendation. The clinical experts consulted by CADTH provided advice on the potential implementation issues raised by the drug programs.

Table 2: Responses to Questions From the Drug Programs

Implementation issues	Response
Relevant comparators	
The comparator is appropriate because if patients were to receive neoadjuvant chemotherapy it would be platinum-doublet chemotherapy. Neoadjuvant platinum-doublet chemotherapy has a similar efficacy as the current Canadian standard of care (adjuvant chemotherapy). Most patients will not receive any treatment in the neoadjuvant setting. In the CheckMate 816 trial, chemotherapy with vinorelbine and cisplatin, gemcitabine and cisplatin, pemetrexed and cisplatin, paclitaxel and carboplatin for up to 3 cycles (9 weeks) was implemented. These regimens are some of chemotherapy options available for neoadjuvant chemotherapy. What chemotherapy regimens are appropriate for neoadjuvant use in combination with nivolumab?	pERC and the clinical experts noted that docetaxel and vinorelbine were only allowed in the chemotherapy arm, 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.
Considerations for initiation of therapy	
In CheckMate 816, participants were excluded if they had known *EGFR* mutations or *ALK* translocation. The funding request does not reference *EGFR* mutation or *ALK* translocation status. Should patients with known *EGFR* mutations or *ALK* translocation be eligible for nivolumab in combination with neoadjuvant chemotherapy for resectable NSCLC? Is PD-L1 status required to be eligible for nivolumab in combination with neoadjuvant chemotherapy for resectable NSCLC?	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 the CheckMate 816 trial regardless of PD-L1 status. Although 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 because the study was not statistically powered to assess PD-L1 subgroups. A clinical benefit was observed in the overall study population.

Implementation issues	Response
	Therefore, PD-L1 status is not required to be eligible for nivolumab in combination with neoadjuvant chemotherapy for resectable NSCLC.
There are no immunotherapy agents currently funded in the neoadjuvant NSCLC setting at this time, and this is the first immunotherapy drug to be reviewed. In other solid tumours, patients are eligible for downstream PD-1 or PD-L1 inhibitors provided that disease recurrence (whether locoregional or distant) occurs 6 months and more from the last dose of the neoadjuvant PD-1 or PD-L1 inhibitor. If nivolumab is funded in this setting, jurisdictions will permit downstream PD-1or PD-L1 inhibitors used in a manner consistent with other tumour sites.	Comment from the drug programs to inform pERC deliberations.
Considerations for discontinuation of therapy	
If a patient cannot tolerate chemotherapy, are they able to continue with nivolumab? Is there a minimum number of chemotherapy cycles that must be given concurrently with nivolumab?	The clinical experts highlighted that patients may likely go straight to surgery if they remain eligible; however, if the adverse event was attributable to chemotherapy only, then patients may receive the remainder of treatment with nivolumab monotherapy. pERC agreed with the clinical experts. The second expert highlighted that treatment discontinuation procedures in practice will likely follow those implemented in the CheckMate 816 trial protocol. The expert highlighted that in the CheckMate 816 trial, if either chemotherapy or nivolumab needed a dose delay, both were delayed until the patient met resumption criteria for both chemotherapy and nivolumab. If an adverse event could be clearly attributed to either the chemotherapy or the nivolumab, and that particular drug had to be discontinued, patients were allowed to continue with the other. In the event that the treating physician or patient chooses to stop both and proceed with surgery before 3 cycles are complete, it was considered appropriate; however, having to stop chemotherapy should not mean the patient cannot continue to a maximum of 3 cycles of nivolumab or vice versa. pERC agreed with the clinical experts.
Considerations for prescribing of therapy	
PAG would like to inform pERC that jurisdictions will implement weight-based dosing up to a cap, similar to other immunotherapy policies (i.e., nivolumab 4.5 mg/kg up to 360 mg every 3 weeks).	Comment from the drug programs to inform pERC deliberations.
Generalizability	
Should patients with an ECOG performance status of 2 or greater be eligible for nivolumab in this indication?	pERC acknowledged that clinicians think it is reasonable to use nivolumab for patients with a good ECOG performance status. Both clinical experts agreed that patients with an ECOG PS of 0 and 1 will benefit from the treatment. One expert noted that patients with an ECOG PS of 2 may be considered, although this patient population will be small. The clinical experts emphasized the need for patients to

Implementation issues	Response
	have a robust performance status to be eligible to receive the treatment given that patients with less clinical reserve will be susceptible to adverse events that may render them ineligible for curative-intent surgery.
There is a time-limited need to allow patients currently on platinum-based doublet chemotherapy to add nivolumab. What time frame is appropriate to add nivolumab for patients actively on treatment (chemotherapy)?	The clinical experts agreed that the time-limited need to allow patients currently on platinum-based doublet chemotherapy to add nivolumab will not be an issue in current practice given the lack of use of neoadjuvant chemotherapy in current clinical practice in Canada. Although it is anticipated to be an unlikely situation given the lack of use of neoadjuvant chemotherapy in current clinical practice in Canada, if this situation would arise, pERC agreed with the clinical experts that it is reasonable to add nivolumab to any of the remaining cycles of neoadjuvant chemotherapy.
Care provision issues	
Nivolumab is already prepared and administered at facilities throughout Canada. Health care professionals have extensive experience with it. Preparation and administration time for nivolumab are reasonable and would not be expected to significantly increase health system resources.	Comment from the drug programs to inform pERC deliberations.
System and economic issues	
Nivolumab use as an additional drug in this patient population would introduce a considerable impact to budget vs. chemotherapy alone.	Comment from the drug programs to inform pERC deliberations.
Nivolumab is used for many other indications at this time; it is anticipated that vial sharing or dose rounding will be possible (especially in larger treatment centres).	Comment from the drug programs to inform pERC deliberations.

ECOG PS = Eastern Cooperative Oncology Group Performance Status; NSCLC = non–small cell lung cancer; PAG = provincial advisory group; PD-1 = programmed cell death protein 1; PD-L1 = programmed cell death ligand 1; pERC = CADTH pan-Canadian Oncology Drug Review Expert Review Committee.

Clinical Evidence

Pivotal Study

Description of Study

CheckMate 816 is an ongoing, open-label, randomized, phase III trial assessing the efficacy and safety of nivolumab (3 mg/kg every 2 weeks up to 3 cycles) in combination with ipilimumab (single 1 mg/kg dose), nivolumab (360 mg flat dose) in combination with platinum-based chemotherapy every 3 weeks for 3 cycles against platinum-chemotherapy alone as neoadjuvant treatment in adult patients, aged 18 years and older, with resectable (stage IB [4 cm or greater], stage II, and resectable stage IIIA) NSCLC. This CADTH review did not include findings from the ipilimumab plus nivolumab arm because the indication under review is for nivolumab monotherapy in combination with platinum-based chemotherapy. Disease staging at screening was based on the American Joint Committee on Cancer/ Union for International Cancer Control (AJCC/ UICC) TNM 7th edition. Following the completion of neoadjuvant treatment, all patients who remained

operative candidates underwent definitive surgery for NSCLC within 6 weeks. Patients were also allowed to receive adjuvant chemotherapy with or without radiation after definitive surgery as per institutional standard at the discretion of the investigator.

Co-primary end points assessed in the trial were pCR by blinded independent pathological review (BIPR) and EFS by blinded independent central review (BICR). Secondary end points included OS, time to death or distant metastases, and major pathological response (MPR). Safety and tolerability and health-related quality of life were exploratory outcomes. Radiologic tumour assessments were sent to and reviewed by a third-party vendor for BICR and BIPR. All investigator-assessed radiographic progressions per Response Evaluation Criteria in Solid Tumours Version 1.1 (RECIST 1.1), to confirm progression or disease recurrence, were confirmed by BICR per RECIST 1.1 guidelines.

CheckMate 816 was initially designed as a 2-arm trial in which patients were randomized in a 1:1 ratio into 2 trial arms: the nivolumab plus ipilimumab arm or the chemotherapy arm. An update to the protocol (protocol revision 2) introduced a third arm, nivolumab plus chemotherapy, allowing patients to be subsequently randomized in a 1:1:1 scheme to any treatment arm. A third update to the protocol (protocol revision 3) withheld further randomization of patients to the nivolumab plus ipilimumab arm. Subsequently, patients enrolled in the study were randomized into the nivolumab plus chemotherapy arm or chemotherapy arm in a 1:1 ratio and stratified according to 3 factors: PD-L1 expression (1% or more; or less than 1%, not evaluable, or indeterminate), disease stage (IB/II versus IIIA), and sex.

The primary data cut-off for the prespecified final pCR analysis was September 16, 2020; and the data cut-off date for EFS interim analysis 1 was October 20, 2021. By the EFS interim analysis 1 data cut-off, [redacted]. Most patients randomized in the nivolumab plus chemotherapy and chemotherapy arm were male (71.5% and 70.9%, respectively) and approximately half were either [redacted]. In total, 48.6% and 53.1% of patients in the nivolumab plus chemotherapy and chemotherapy arms, respectively, had squamous tumour histology; 63.1% and 64.2%, respectively, had stage IIIA disease; and 89.4% and 88.3%, respectively, were current or former smokers.

Efficacy Results

Overall Survival

OS was formally tested at the EFS interim analysis 1 data cut-off date (October 20, 2021) because EFS was significant at the interim analysis 1 cut-off. The median OS was not reached in the nivolumab plus chemotherapy and the chemotherapy arm. The HR for death was 0.57 (99.67% CI, 0.30 to 1.07). The P value for OS (P = 0.008) did not cross the significance boundary (0.0033). A second OS testing is [redacted]

Event-Free Survival

By the October 20, 2021, [redacted]. In total [redacted] had occurred in the nivolumab plus chemotherapy arm and the median EFS was 31.57 months (95% CI, 30.16 to not applicable). In the chemotherapy arm, [redacted] EFS events had occurred, and the median EFS was 20.80 months (95% CI, 14.03 to 26.71 months). The estimated HR between nivolumab plus chemotherapy and

chemotherapy was 0.63 (97.38% CI, 0.43 to 0.91) with a P value of 0.0052 from stratified log-rank test. Sensitivity analyses for EFS were consistent with the primary analysis.

Pathological Complete Response and Major Pathological Response

Both pCR and MPR analyses were conducted at the September 16, 2020, data cut-off. The pCR rate per BIPR in the nivolumab plus chemotherapy arm was 24.0% (43 of 179; 95% CI, 18.0% to 31.0%) compared with 2.2% (4 of 179; 95% CI, 0.6% to 5.6%) in the chemotherapy arm. The stratified OR between the nivolumab plus chemotherapy arm versus the chemotherapy arm was 13.94 (99% CI, 3.49 to 55.75), with a P value of less than 0.0001; the strata-adjusted difference based on Cochran-Mantel-Haenszel method was 21.6% [redacted] pCR sensitivity analyses were consistent with the primary analyses. In total, MPR rate was 36.9% (95% CI, 29.8% to 44.4%) in the nivolumab plus chemotherapy arm and 8.9% (95% CI, 5.2% to 14.1%) in the chemotherapy arm.

Health-Related Quality of Life

Patients completed the EQ-5D-3L questionnaire at baseline, before on-treatment clinic visits, at post-neoadjuvant visits 1 and 2, and at designated time points during the survival follow-up phase. Completion rates for both study arms were similar at baseline ([redacted]) and did not change significantly at post-neoadjuvant visit 1 ([redacted]). The EQ-5D index (based on the UK time trade-off value set) were collected for both study arms. The mean change from baseline to different time points (weeks 4 and 7, post-neoadjuvant visits 1 and 2) were minimal in the EQ-5D visual analogue score, and EQ-5D utility index score of the questionnaire in the 2 treatment arms.

Time to Death or Distance Metastasis

By the October 20, 2021, data cut-off, [redacted]. The median time to death or distant metastasis was not reached in both study arms (HR = 0.53; 95% CI, 0.36 to 0.77).

Event-Free Survival on Next Line of Therapy

By the October 20, 2021, data cut-off, the median Event-free survival on the next line of therapy (EFS2) per investigator assessment was not reached in both the nivolumab plus chemotherapy and chemotherapy arms. [redacted] The estimated HR was 0.54 (95% CI, 0.37 to 0.80).

Harms Results

Overall, 92.6% (163 of 176) of patients treated in the nivolumab plus chemotherapy arm and 97.2% (171 of 176) in the chemotherapy arm reported at least 1 adverse event (AE) in the CheckMate 816 trial. [redacted]. AEs of grade 3 to 4 were reported in 40.9% (n = 72) and 43.8% (n = 77) of patients in the nivolumab plus chemotherapy and chemotherapy arms, respectively.

Serious AEs of any grade were reported in 30 (17.0%) of patients in the nivolumab plus chemotherapy arm and 24 (13.6%) in the chemotherapy arm. Serious AEs of grades 3 or 4 were reported in in 19 (10.8%) patients in the nivolumab plus chemotherapy arm and 17 (9.7%) patients in the chemotherapy arm.

[redacted]. AEs leading to discontinuation of study treatments were reported in 18 (10.2%) patients in the nivolumab plus chemotherapy arm and 20 (11.4%) in the chemotherapy arms. By the October 20, 2021, data cut-off, [redacted] patients in the chemotherapy arm.

Critical Appraisal

CheckMate 816 is an ongoing, randomized, open-label, phase III trial. Randomization was conducted using an interactive response technology and treatment allocation was concealed. Patients were stratified based on 3 factors: PD-L1 expression, disease stage, and gender or sex. The methods of randomization and the stratification factors were considered appropriate by the clinical experts consulted. Baseline characteristics between the 2 arms of interest were balanced suggesting that randomization was successful. The methods of randomization and treatment allocation were considered appropriate.

Treatment effect for EFS and pCR was estimated during a prespecified interim analysis, adjusted using the Lan-DeMets alpha spending function with O'Brien-Fleming boundaries that accounted for the actual number of events at an overall alpha of 4% or 5%. Overall, the estimate of treatment effect based on the co-primary end points were based on the interim analysis. There is uncertainty in the magnitude of treatment effect given that interim analyses have the tendency to overestimate treatment effect.

OS was statistically nonsignificant at the preplanned interim analysis stopping rule (P = 0.008 against a prespecified level for significance at the interim of 0.0033). Although the results showed a promising trend of significant treatment effect on OS, final analysis may be needed to confirm the findings, particularly the exact estimate of difference in median survival, which were not estimable at the date cut-off. [redacted]

Performance and assessment biases due to the open-label design of the trial was considered unlikely given that radiologic assessments of CT scans for EFS and pathological review of tumour sections were completed by a blinded independent review team based on the prespecified and validated guidelines (RECIST 1.1 guidelines).

Further, the proportion of patients in the nivolumab plus chemotherapy exposed to 3 doses of chemotherapy drugs was slightly higher compared with chemotherapy. There were also slight differences reported in cumulative dose intensity which could bias the findings in favour of nivolumab plus chemotherapy.

More patients received subsequent anticancer therapy and a higher proportion of patients that received adjuvant therapy after surgery in the chemotherapy arm compared with the nivolumab plus chemotherapy arm, which could bias the EFS and OS. However, the potential bias from the use of subsequent anticancer and adjuvant therapy was considered low.

The sponsor's reimbursement request aligns with the Health Canada indication. CheckMate 816 trial enrolled only patients with ECOG PS 0 and 1 were enrolled in the trial. The magnitude of benefit of nivolumab plus chemotherapy in patients with ECOG PS 2 and greater is uncertain.

The clinical experts considered the baseline and demographic characteristics generalizable to Canada. The experts highlighted notable differences in the patient population enrolled in the CheckMate 816 trial compared with the Canadian population (CheckMate 816 had younger patients, more patients with stage IIIA disease, and proportion of patients PD-L1 status enrolled); however, the impact on generalizability of the findings based on these differences was considered low.

The dosing of nivolumab in the reimbursement request aligns with the Health Canada indication. Dose adjustments were allowed for chemotherapy drugs in the trial, but not allowed for nivolumab, which aligns with the Health Canada indication. The experts indicated that a flat dose approach for nivolumab as implemented in the CheckMate 816 trial would be used in practice.

Concomitant medications administered in the trial were considered appropriate by the clinical experts; no major discrepancies in concomitant medications administered that could negatively impact the findings were identified.

Indirect Comparisons

Description of Study

The sponsor provided a network meta-analysis (NMA), assessing the efficacy and safety of neoadjuvant nivolumab in combination with chemotherapy relative to other relevant treatments, including neoadjuvant chemotherapy, neoadjuvant chemoradiotherapy, adjuvant chemotherapy, and surgery alone, in patients diagnosed with resectable nonmetastatic NSCLC. The primary efficacy end points used for NMA estimates were EFS and OS. The secondary outcomes included time to locoregional recurrence, time to distant metastases, and pCR. For each outcome, base-case and sensitivity analyses were carried out whenever data were available. The base-case analysis involved patients who were deemed candidates for surgery and underwent third-generation platinum-based doublet chemotherapies. The sensitivity analyses expanded to second-generation platinum-based chemotherapies, the resected patient populations, data stratified by PD-L1 status (i.e., PD-L1 ≥ 1% and < 1%), and data from the intention-to-treat population of the CheckMate 816 trial instead the subpopulations of CheckMate 816 (i.e., stage IB-II, stage IIIA, and stage IIIA N2) used in the base-case stage-specific networks. Furthermore, for each outcome, in addition to the stage-agnostic network that included studies regardless of the staging of the patient population, the network was also stratified by tumour staging (i.e., stage IB-II, stage IIIA, and stage IIIA N2). Eight randomized controlled trials (RCTs) were eventually included in the base-case analyses, 5 additional RCTs in the sensitivity analyses involving second-generation chemotherapies, and 4 additional RCTs in the sensitivity analyses expanding to resected patients.

Efficacy Results

Although both EFS and OS were selected as primary end points in the sponsor-submitted NMA, OS data from the CheckMate 816 trial were based on an immature data cut. According to the base analysis on EFS, patients with stage IIIA NSCLC undergoing neoadjuvant nivolumab in combination with chemotherapy had a significantly lower risk of experiencing an event (i.e., EFS HR < 1 and the credible interval excluding 1) than those undergoing neoadjuvant chemotherapy or surgery alone. For patients with stage IIIA N2 NSCLC, the risk of having an event in patients receiving neoadjuvant nivolumab in combination with chemotherapy was

also significantly lower than those receiving neoadjuvant chemoradiotherapy or neoadjuvant chemotherapy. However, in patients with stage IB to stage II NSCLC, the difference in EFS improvement was not significant between neoadjuvant nivolumab in combination with chemotherapy and neoadjuvant chemotherapy, adjuvant chemotherapy, or surgery alone. For patients with stage-agnostic NSCLC (i.e., stage IB to stage IIIA), although the EFS results suggested that neoadjuvant nivolumab in combination with chemotherapy led to a significantly lower risk of experiencing an event than neoadjuvant chemotherapy, adjuvant chemotherapy, or surgery alone, the results were considered significantly biased due to large heterogeneity in tumour staging, supported by significant differential treatment effects observed between patients with stage IB to stage II NSCLC versus patients with stage IIIA or stage IIIA N2.

Harms Results

The sponsor-submitted NMA was not able to quantitively synthesize evidence on safety outcomes due to sparseness of the data and the differences in treatment regimens across the base-case studies. As a result, the sponsor provided a narrative description only.

Critical Appraisal

The systematic literature review conducted by the sponsor to identify potentially eligible studies for the NMA was methodologically sound. The sponsor used a comprehensive literature search strategy, performing study selection and data extraction in duplicate, assessing risk of bias appropriately, as well as describing the characteristics of the included studies and narratively summarizing the results in adequate details. However, it was unclear whether the risk of bias assessment was carried out by a single assessor or multiple assessors. The reporting of the sponsor-submitted NMA generally followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist.

According to the clinical experts consulted by CADTH, the heterogeneity in tumour staging for the patients with stage-agnostic NSCLC in the sponsor-submitted NMA was significant. Indeed, the efficacy results of neoadjuvant nivolumab in combination with chemotherapy on EFS by stage, for example, were inconsistent between patients with stage IB to stage II and patients with stage IIIA or stage IIIA N2 NSCLC (i.e., statistically significant versus nonsignificant) when comparing to neoadjuvant chemotherapy in the base-case analysis. Due to the significant differential treatment effects between the 2 stage categories (stage IB to stage II versus stage IIIA or stage IIIA N2), the pooled ITC results from the patients with stage-agnostic cancer would be deemed significantly biased and the pooling is inappropriate, methodologically, although neoadjuvant nivolumab in combination with chemotherapy markedly improved EFS than neoadjuvant chemotherapy, adjuvant chemotherapy, and surgery alone in patients with stage-agnostic NSCLC.

For each outcome examined in the NMA, both random-effects and fixed-effects models were run. The random-effects model was considered by the sponsor as the default model. However, the fixed-effects model was selected by the sponsor for all analyses in the NMA due to the sparseness of network not being able to estimate the between-study standard deviation with enough precision. Although it was considered appropriate to use the fixed-effects model instead of the random-effects model when the network is sparce, it is important to note that the fixed-effects model is not capable of capturing heterogeneity.

Misclassification of tumour stage using different versions of tumour classification criteria could have also affected the ITC estimation. In the sponsor-submitted NMA, of the 8 RCTs in the base-case analysis, the CheckMate 816 trial was the only study using the TNM 7th edition classification, whereas 2 other trials adopted TNM 5th edition, 3 used TNM 6th edition, and 2 used International Staging System (ISS) 1997. Different staging criteria could lead to different classifications of patients with NSCLC and would consequently result in differences in prognosis estimation and treatment selection.

Safety outcomes were only narratively described in the NMA. Without a quantitative synthesis, a balanced judgment of comparative benefits relative to comparative harms could not be made. In addition, outcomes that are important to patients, such as health-related quality of life, were not reported in the NMA. Furthermore, analyses comparing neoadjuvant nivolumab in combination with chemotherapy with adjuvant atezolizumab was determined by the sponsor to be not feasible and inappropriate due to significant methodological challenges. Nonetheless, feedback from the clinical experts consulted by CADTH emphasized that adjuvant atezolizumab was an appropriate treatment option for patients with resected stage IB to stage IIIA NSCLC (7th edition lung cancer TNM classification) with PD-L1 of 50% or more. Therefore, the lack of relevant analyses may have introduced uncertainty into the sponsor's submitted analysis.

Other Relevant Evidence

Description of Study

As part of the submission for nivolumab, the sponsor submitted a systematic review and a meta-analysis describing clinical evidence in nonmetastatic resectable NSCLC. The sponsor-conducted meta-analysis assessed the potential of pathological response (pCR and MPR) as a surrogate end point for long-term outcomes (EFS, OS) in resectable NSCLC. The systematic review conducted was informed by patient-level data from 32 studies that presented evidence of an association between OS or EFS and pCR or MPR measured as HRs or had a reported KM curves for OS or EFS by pCR or MPR status allowing for the reconstruction of HRs.

Efficacy Results

OS by pCR status (pCR versus no pCR) [redacted]

Critical Appraisal

The sponsor-submitted meta-analysis was informed by studies selected from an adequately conducted systematic review with clearly prespecified PICOs (population, intervention, comparison, and outcomes) and conducted using the PRISMA guidelines. The study selection and data extraction methods were considered appropriate. The study selection and data extraction methods were considered appropriate. In the absence of detailed information of the baseline and study characteristics of patients enrolled in the studies included in the meta-analysis, the degree of heterogeneity between the included studies could not be assessed. Studies included were considerably variable in terms of study design (observational versus RCTs) and sample sizes. Heterogeneity was not reported for the Bayesian analysis and owing to the lack of baseline

data on the trials included an assessment of the level of heterogeneity could not be made. The meta-analysis suggests that achieving pCR was associated with improved OS based on the Bayesian and frequentist methods implemented in the analyses.

Description of Study

The sponsor submitted 1 real-world study conducted with data from electronic health record supplemented with chart review. The purpose of this retrospective, observational study was to generate real-world evidence characterizing the relationship between pathological responses and survival and to describe the patient profiles and neoadjuvant treatment patterns in patients with surgically resectable NSCLC (stage IB [tumours 4 cm or greater] to IIIA) treated in the US community oncology setting. Neoadjuvant treatment regimens were characterized as chemotherapy or chemoradiotherapy in the study.

Efficacy Results

[redacted]

Critical Appraisal

Several limitations were identified with the study. Neoadjuvant treatment only consisting of chemotherapy and chemoradiotherapy, incomplete or missing data for several variables for analyses, and reduced sample size (and reduced power) to assess relationship between pCR or MPR and survival end points. Thus, it is difficult to conclude that this retrospective, observational study (i.e., real-world evidence characterizing the relationship between pathologic responses and survival), as well as the patient profiles and neoadjuvant treatment patterns in patients with surgically resectable NSCLC (stage IB [tumours 4 cm or greater] to stage IIIA) treated in the US community oncology setting] provide all the information required to address gap in the evidence in support of validity of end points in the pivotal trial.

Economic Evidence

Table 3: Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population	Adult patients newly diagnosed with histologically confirmed stage IB (≥ 4 cm), stage II, and stage IIIA NSCLC, based on the 7th edition of the AJCC TNM criteria, who are considered resectable.
Treatment	Nivolumab, in combination with PDC, followed by surgery PDC includes cisplatin + (pemetrexed, gemcitabine, vinorelbine, or docetaxel), and carboplatin + (paclitaxel, pemetrexed, gemcitabine, vinorelbine, or docetaxel)

Component	Description
Submitted price	Nivolumab, 10 mg per mL, solution: $19.55 per mg ($782.22 per 40 mg vial; $1,955.56 per 100 mg vial)
Treatment cost	The 21-day cycle cost of nivolumab is $7,431, and the total cost $22,293 (3 cycles). In combination with PDC, the 21-day cycle cost of the nivolumab neoadjuvant therapy would range between $8,516 (nivolumab + CISPVINO [cisplatin + vinorelbine]) and $12,277 (nivolumab + CRBPPEME [carboplatin + pemetrexed]). The total cost across all 3 cycles would range between $25,548 (nivolumab + CISPVINO) and $36,831 (nivolumab + CRBPPEME).
Comparators	Surgery, followed by adjuvant PDC Neoadjuvant PDC, followed by surgery Surgery only
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (35 years)
Key data source	CheckMate-816 trial; ITC
Key limitations	• The model did not account for differential progression and overall survival between patients with stage IB to stage II and stage IIIA. Data shows that progression and overall survival is different for those with stage IB to stage II than stage III disease. Subgroup analysis from the CheckMate-816 trial also shows a high degree of uncertainty regarding the efficacy of nivolumab in those who are stage IB to stage II. Since stage IIIA was overrepresented in the modelled cohort, relative to the real-world Canadian patient population, pooled survival curves may overestimate the benefit of nivolumab + PDC in the full Health Canada indication. • The sponsor used a fixed "one-off" approach for patients entering the DM state, whereby lump sum costs, LYs, and QALYs were applied. These were calculated using the results from an external model developed by the sponsor. This model was not included as part of the submission so could not be reviewed or validated by CADTH. Therefore, costs and outcomes as they pertain to DM are uncertain within the analysis. • The sponsor assumed a continued and increasing effect of treatment on delaying LR and DM long after treatment curtailment. This was uncertain and not supported by trial data. • Patients who are "cured" were assumed to experience the same long-term survival as the general age- and sex-matched Canadian population. The clinical expert consulted by CADTH for the review indicated mortality for patients who had NSCLC but are cured is unlikely to follow that of the general population. This was also supported by external data provided by the sponsor. The sponsor therefore overestimates the survival benefit attributed to a cure. • Progression from LR to DM was assumed to be constant over time. However, patients with LR may achieve cure if they remain progression-free beyond 5 years and are therefore no longer considered at risk of progression. The sponsor therefore overestimates long-term mortality risk associated with LR. • The CADTH Clinical Review identified several limitations with the sponsor-submitted ITC and concluded that the ITC results must be interpreted with caution. Cost-effectiveness relative to adjuvant therapies and surgery alone is therefore uncertain. • Assumptions regarding the fixed dose regimen of nivolumab does not reflect its likely use in practice. • In the model, 56% of patients received carboplatin-based adjuvant regimens. However, clinical expert feedback highlighted that these are not commonly prescribed in the adjuvant setting.
CADTH reanalysis results	• CADTH undertook reanalyses to address several key limitations identified in the sponsor's model by applying alternative parametric extrapolations for time to progression, removing the assumption of general population mortality for patients considered cured, assuming that 7.7% of patients with NSCLC in LR would transition to DM annually, assuming cure for patients with LR from year 7 onward, assuming that the efficacy of adjuvant PDC and surgery alone would equal that of neoadjuvant, applying weight--

Component	Description
	based dosing for nivolumab, and revising the adjuvant PDC composition to reflect Canadian clinical practice. Due to inflexible modelling, CADTH could not resolve all outstanding uncertainty in the analysis and relied on scenario analyses to explore the impact of these limitations. • CADTH's reanalysis demonstrates that nivolumab + PDC was more costly ($19,571) and produced more QALYs (0.60) than surgery alone, resulting in an ICER of $32,846 per QALY. Neoadjuvant PDC and adjuvant PDC were dominated by surgery alone due to the assumption of equivalent treatment effects. • CADTH notes, due to limitations with the sponsor's modelling approach, this result may not reflect cost-effectiveness in the full Health Canada–approved indication because cost-effectiveness in patients who have stage IB to stage II NSCLC is highly uncertain.

AJCC = American Joint Committee on Cancer; DM = disease metastasis; ICER = incremental cost-effectiveness ratio; ITC = indirect treatment comparison; LR = locoregional recurrence; LY = life-year; NSCLC = non–small cell lung cancer; PDC = platinum-doublet chemotherapy; QALY = quality-adjusted life-year; TNM = tumour, node, and metastasis .

Budget Impact

CADTH identified the following limitations in the sponsor's base case: the use of a fixed dose for nivolumab despite the fact that weight-based dosing is applied consistently across nivolumab indications in Canadian clinical practice and the use of a simulation approach for disease progression that effectively relied upon highly uncertain OS estimates originated from the sponsor-submitted pharmacoeconomic model.

CADTH performed reanalyses, in line with clinician expert opinion, by assuming weight-based dosing for nivolumab and excluding the treatment costs that could be accrued in the simulated postprogression health state.

Based on the CADTH reanalyses, the budget impact from the introduction of nivolumab plus PDC is expected to be $8,149,659 in year 1, $8,833,668 in year 2, and $10,113,125 in year 3, with a 3-year total of $27,096,452. Cost savings may result from preventing distant metastasis in this period although the degree to which this would occur is highly uncertain.

pERC Information

Members of the Committee

Dr. Maureen Trudeau (Chair), Mr. Daryl Bell, Dr. Jennifer Bell, Dr. Matthew Cheung; Dr. Winson Cheung, Dr. Michael Crump, Dr. Leela John, Dr. Christian Kollmannsberger, Mr. Cameron Lane, Dr. Christopher Longo, Dr. Catherine Moltzan, Ms. Amy Peasgood, Dr. Anca Prica, Dr. Adam Raymakers, Dr. Patricia Tang, Dr. Marianne Taylor, and Dr. W. Dominika Wranik.

Meeting date: February 8, 2023

Regrets: 1 expert committee member did not attend

Conflicts of interest: None