pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pCODR EXPERT REVIEW COMMITTEE (pERC)
FINAL RECOMMENDATION

The CADTH pan-Canadian Oncology Drug Review (pCODR) was established by Canada's provincial and territorial Ministries of Health (with the exception of Quebec) to assess cancer drug therapies and make recommendations to guide drug-funding decisions. The pCODR process brings consistency and clarity to the assessment of cancer drugs by looking at clinical evidence, cost-effectiveness, and patient perspectives.

pERC Final Recommendation
This pCODR Expert Review Committee (pERC) Final Recommendation is based on a reconsideration of the Initial Recommendation and feedback from eligible stakeholders. This pERC Final Recommendation supersedes the pERC Initial Recommendation.

Drug: Nivolumab (Opdivo) **Submitted Funding Request:** For the treatment of patients with advanced or metastatic non-small cell lung cancer who progressed on or after chemotherapy	
Submitted by: Bristol-Myers Squibb Canada	**Manufactured by:** Bristol-Myers Squibb Canada
NOC Date: February 26, 2016	**Submission Date:** October 29, 2015
Initial Recommendation: April 1, 2016	**Final Recommendation:** June 3, 2016

pERC RECOMMENDATION

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 non-small cell lung cancer (NSCLC) with disease progression on or after cytotoxic chemotherapy for advanced disease and have a good performance status. Treatment should continue until confirmed disease progression or unacceptable toxicity.

pERC made this recommendation because it was satisfied that there is a net overall clinical benefit with nivolumab, based on the statistically significant and clinically meaningful improvements in overall survival and objective response rate, a meaningful improvement in the toxicity profile, and at least stable quality of life compared with docetaxel. The Committee was satisfied that nivolumab also aligned with patient values.

pERC concluded that nivolumab compared with docetaxel could not be considered cost-effective in patients with advanced or metastatic NSCLC with disease progression on or after cytotoxic chemotherapy.

POTENTIAL NEXT STEPS FOR STAKEHOLDERS

Pricing Arrangements to Improve Cost-Effectiveness
Given that there is a net clinical benefit of nivolumab, jurisdictions may want to consider pricing arrangements and/or cost structures that would improve the cost-effectiveness of nivolumab to an acceptable level.

Factors Affecting Budget Impact and Adoption Feasibility
pERC noted the unknown duration of treatment with nivolumab, as it continues until confirmed disease progression or unacceptable toxicity, whichever comes first. In considering the high cost of nivolumab, the large new and prevalent population, the potential for drug wastage, and the unknown but potentially long duration of treatment, pERC concluded that a substantial reduction in drug price would be required to improve affordability.

Evidence Generation to Understand Optimal Duration of Therapy
pERC noted that nivolumab is approved at a dose of 3 mg/kg every two weeks until confirmed disease progression or unacceptable toxicity, whichever comes first. pERC acknowledged that there is currently no evidence to identify an optimal set or fixed duration of treatment with nivolumab and agreed that it is important to prospectively collect such data. The Committee also agreed that treatment duration should be reassessed in the event that new evidence emerges on an optimal duration of treatment.

Common Approach to Define Confirmed Disease Progression
pERC noted the unique mechanism of action of immunotherapeutic agents and acknowledged that in a small percentage of patients, standard Response Evaluation Criteria in Solid Tumors (RECIST) defined radiologic disease growth may be due to immune-related inflammation and may not be reflective of true disease progression (i.e., it is pseudoprogression). pERC noted that there is no consistently accepted definition for pseudoprogression in the clinical community. pERC agreed that until such a definition becomes available, it is reasonable to use the definition from within the pivotal trials, which defined true progression as an additional 10% in tumour burden volume and/or development of new lesions since the time of initial disease progression. A confirmatory scan should be done six weeks after initial progression to assess patients for true progression.

Time-Limited Need for Nivolumab
At the time of implementing a funding recommendation for nivolumab, jurisdictions may consider addressing the time-limited need for nivolumab for those patients who are currently receiving treatment with single-agent cytotoxic chemotherapy or who have recently completed treatment with single-agent chemotherapy. pERC noted that this time-limited access should be for patients who have a good Eastern Cooperative Oncology Group Performance Status (ECOG PS) and would otherwise meet the eligibility criteria of the CheckMate 017 and CheckMate 057 studies

Optimal Sequencing of Nivolumab and Other Therapies Unknown
pERC concluded that the optimal sequencing of nivolumab and other treatments now available for the treatment of advanced or metastatic NSCLC is currently unknown. pERC was, therefore, unable to make an evidence-informed recommendation on sequencing. However, pERC recognized that provinces will need to address this issue upon implementation of nivolumab funding and noted that collaboration among provinces to develop a common approach would be of value, as would the development and implementation of an evidence-based clinical practice guideline.

SUMMARY OF pERC DELIBERATIONS

Lung cancer is the leading cause of cancer-related deaths worldwide, with the majority of patients presenting with non-curable disease. In Canada, an estimated 26,600 new cases and 20,900 deaths occurred in 2015 from lung cancer, with a five-year survival rate of < 5%. Non-small cell lung cancer (NSCLC) accounts for 85% of all lung cancers. Non-squamous and squamous cell lung cancer comprise about 70% and 30% of NSCLC, respectively. Treatment decision for advanced or metastatic NSCLC is typically dependent on the presence or absence and type of driver mutation status of patients in the first-line setting. In patients without a driver mutation, treatments in the second-line setting include single-agent chemotherapy with docetaxel or pemetrexed. For patients who have had driver mutation (i.e., ALK or EGFR) targeted therapy upfront, second-line treatment consists of platinum doublet and third-line pemetrexed in those who maintain a good performance status. Given that most patients have advanced age and stage of disease, a greater number have a poor performance status, as well as a higher likelihood of significant comorbidities that affect their ability to tolerate conventional chemotherapy regimens. Therefore, pERC agreed that there is a need for alternative options that reduce toxicity and prolong survival in this patient population.

pERC's *Deliberative Framework* for drug funding recommendations focuses on four main criteria:

CLINICAL BENEFIT	PATIENT-BASED VALUES
ECONOMIC EVALUATION	ADOPTION FEASIBILITY

pERC deliberated upon the results of two open-label randomized controlled trials that compared nivolumab to docetaxel in patients who had non-squamous NSCLC (CheckMate 057, Brahmer et al. 2015) and squamous NSCLC (CheckMate 017, Reckamp et al. 2015) and who had progressed on or after treatment with a cytotoxic chemotherapy. Based on a clinically meaningful and statistically significant improvement in overall survival (OS) and objective response rate (ORR), pERC concluded that there is a net clinical benefit associated with nivolumab in patients with both histological subtypes of NSCLC. While the pattern of responsiveness is different between the two histological types of NSCLC, as demonstrated in the near immediate separation of the Kaplan-Meier OS curves in CheckMate 017 and delayed separation in CheckMate 057, pERC agreed that both populations demonstrated statistically significant and clinically meaningful improvements in OS. pERC discussed the quality of life (QoL) data from the two trials and noted the absence of a clear signal indicating an improvement in QoL; however, neither was there a decline in QoL. pERC therefore agreed that deterioration of QoL was delayed with nivolumab. Finally, pERC discussed the safety data from the two trials and noted meaningful improvements in grade 3 and 4 toxicities with nivolumab compared with docetaxel. pERC discussed the fact that many patients seen in clinical practice generally have a poorer performance status compared with patients included in the two trials, due to advanced age (if with comorbidities) and stage of disease, and that such patients would have a reduced ability to tolerate conventional chemotherapy regimens. pERC therefore considered the generalizability of the trial results to patients with an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of > 1. Based on the toxicity profile of nivolumab observed in the two pivotal trials, pERC agreed it is plausible that patients with an ECOG PS > 1 are likely to tolerate nivolumab well, but the Committee was uncertain of the clinical benefit of nivolumab in this population. While acknowledging the lack of evidence on the efficacy and safety of nivolumab in patients with an ECOG PS > 1, pERC agreed that patients with a good performance status, beyond ECOG PS 1, who can tolerate this treatment may derive benefit, based on opinion of the pCODR Clinical Guidance Panel (CGP) and the mechanism of action of nivolumab. Overall, pERC concluded that there is a net overall clinical benefit with nivolumab, based upon statistically significant and clinically meaningful improvements in OS and the ORR, a meaningful improvement in the toxicity profile, and at least stable QoL compared with docetaxel.

Upon reconsideration of the pERC Initial Recommendation, the Committee noted feedback from the Provincial Advisory Group (PAG) requesting clarity regarding the number of prior lines of therapy patients may have received in order to qualify for nivolumab therapy. PAG also asked about the generalizability of the trial results to patients with brain metastases. In discussing prior lines of therapy, pERC reiterated that patients who have had a cytotoxic chemotherapy for advanced disease, irrespective of prior lines of therapy, should qualify for treatment with nivolumab. pERC also noted that a platinum-based doublet is the standard treatment option for patients prior to qualifying for nivolumab; however, there may be instances where patients cannot tolerate the platinum portion of their treatment. In these instances,

where cytotoxic chemotherapy has been administered, pERC agreed that it would be reasonable to treat patients with nivolumab, provided they meet all other criteria within this Recommendation. pERC also noted that patients with stable brain metastases were entered into both pivotal studies and agreed that treatment with nivolumab should be made available to patients with adequately treated brain metastases (i.e., patients have returned to baseline neurological status, except for any treatment related toxicities, at least 2 weeks prior to enrollment and have been titrated down to a steroid dose equivalent of ≤ 10 mg daily prednisone). The Committee also noted feedback from PAG on whether or not patients with ALK or EGFR mutations would be eligible for treatment with nivolumab. pERC noted that patients with driver mutations were included in both the pivotal studies. While the numbers of patients with activating mutations were low in both trials, pERC agreed that the results in the overall population applied to patients with activating mutations who have also received prior cytotoxic chemotherapy. pERC also reiterated that the results of the trials apply to both squamous and non-squamous populations.

Upon reconsideration of the pERC Initial Recommendation, pERC noted that there is no evidence to inform the comparative efficacy of nivolumab with other PD-L1 inhibitors. Additionally, pERC noted that the optimal sequencing of agents in this setting is currently unknown. However, pERC recognized that provinces would need to address this issue upon implementation of nivolumab funding, and noted that collaboration among provinces to develop a common approach would be of value.

pERC deliberated upon input from one patient advocacy group concerning nivolumab and noted that prolonged survival, reduction of toxicities associated with treatment, reduction of disease symptoms, and improvement of QoL were important to patients. The results of both CheckMate 057 and 017 demonstrated statistically significant and clinically meaningful improvements in OS, a meaningful improvement in toxicity profile, and stable QoL compared with docetaxel. The patient advocacy group input included patients who had experience with nivolumab and reported dramatic improvements in symptoms, fewer side effects with nivolumab, better QoL, and ability to get back to work. Therefore, pERC considered nivolumab to align with patient values.

pERC deliberated upon the cost-effectiveness of nivolumab and concluded that, at the submitted price, it is not cost-effective. pERC considered estimates provided by the submitter and reanalysis estimates provided by the pCODR Economic Guidance Panel (EGP) and noted uncertainty regarding the estimates for utilities; extrapolation for OS and progression-free survival (PFS) over a 10-year time horizon; and the duration of treatment. These factors had the largest impact on the incremental cost-effectiveness ratio (ICER) for both the squamous and non-squamous populations. The Committee agreed with the EGP that utilities derived from the trial were high and close to what is observed in the general population. pERC noted that the EGP provided a range for its reanalysis estimates using alternative sources for utilities. Given this, pERC concluded that the true ICER is likely near the upper end of the EGP's reanalysis estimate, which incorporated utility estimates from the literature that pERC considered to be more representative of the clinical population with advanced or metastatic NSCLC. pERC noted that the submitter provided both a partitioned survival and Markov model for the squamous and non-squamous populations. pERC appreciated having both models available for the comparison. While the EGP used the partitioned survival model for its reanalysis estimates, results from both models were similar for each population.

pERC also considered factors affecting the feasibility of implementing a positive funding recommendation for nivolumab for patients with advanced or metastatic NSCLC. pERC noted that the number of prevalent and new cases of advanced or metastatic NSCLC in patients who have progressed on or after a cytotoxic chemotherapy may be large. Therefore, pERC considered that the budget impact of nivolumab could be substantial and that provinces may want to take steps to limit budget impact. pERC noted that the submitter's budget impact analysis is sensitive to the cost of nivolumab, nivolumab's market share, treatment duration, and incidence rates. pERC also noted that jurisdictions will need to consider the uncertainty in these factors during implementation. Furthermore, pERC noted that the potential for drug wastage, given the short stability and weight-based dosing, together with the high cost of nivolumab, would have a substantial impact on the cost-effectiveness and affordability of nivolumab, and that jurisdictions may need to consider alternative pricing arrangements and/or cost structures to improve the cost-effectiveness and affordability to an acceptable level.

Given the considerable uncertainty that exists concerning the role of PD-L1 testing and whether there is a threshold level below which patients should not be treated, pERC agreed that nivolumab should be made available to patients irrespective of PD-L1 levels. Therefore, testing for PD-L1 will not be required. pERC acknowledged that jurisdictions will need to prospectively collect data on optimal duration of treatment

to manage the budget impact of a funding recommendation. pERC re-iterated that that it would be appropriate for jurisdictions to reassess the duration of treatment once evidence is available on the optimal duration of treatment. pERC also recognized that provinces would need to have a common approach to define true disease progression and ensure that patients who experience pseudoprogression may continue treatment with nivolumab until true disease progression occurs. Upon reconsideration of the pERC Initial Recommendation, pERC noted that there is no consistently accepted definition for pseudoprogression in the clinical community. Until such a definition becomes available, pERC agreed that it is reasonable to use the definition from within the pivotal trials. True progression was defined as an additional 10% in tumor burden volume and/or development of new lesions since the time of initial disease progression, demonstrated through a confirmatory scan conducted 6 weeks after initial progression. Lastly, pERC acknowledged a time-limited need for nivolumab for those patients who are receiving treatment with single-agent chemotherapy or who have recently completed treatment with single-agent chemotherapy. This time-limited need would be for patients who would otherwise meet the eligibility criteria of the CheckMate 017 and CheckMate 057 studies.

EVIDENCE IN BRIEF

The CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) deliberated upon:

- A pCODR systematic review
- Other literature in the Clinical Guidance Report that provided clinical context
- An evaluation of the manufacturer's economic model and budget impact analysis
- Guidance from pCODR clinical and economic review panels
- Input from one patient advocacy group (Lung Cancer Canada [LCC])
- Input from pCODR's Provincial Advisory Group (PAG).

Feedback on the pERC Initial Recommendation was also provided by:

- Input from PAG
- The submitter (Bristol-Myers Squibb Canada)

The pERC Initial Recommendation was to fund nivolumab (Opdivo) on condition that the cost-effectiveness be improved to an acceptable level. Funding should be for the treatment of adult patients with advanced or metastatic non–small cell lung cancer (NSCLC) who progressed on or after chemotherapy, with a good performance status and until confirmed disease progression or unacceptable toxicity.

Feedback on the pERC Initial Recommendation indicated that the manufacturer agreed with the pERC Initial Recommendation and PAG agreed in part with the Initial Recommendation.

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of the review is to evaluate the safety and efficacy of nivolumab as a monotherapy compared with an appropriate comparator, on patient outcomes in the treatment of adult patients with advanced or metastatic NSCLC with disease progression on or after platinum-based chemotherapy.

Studies included: Squamous and non-squamous non–small cell lung cancer

The pCODR systematic review included two randomized, open-label, phase 3 trials comparing nivolumab with docetaxel in adult patients who had non-squamous (CheckMate 057) or squamous (CheckMate 017) NSCLC and who had progressed during or after platinum-based doublet chemotherapy.

For both studies, the key inclusion criteria required that patients have an Eastern Cooperative Oncology Group Performance Status (ECOG PS) ≤ 1, measurable disease by computed tomography (CT) or magnetic resonance imaging (MRI) per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria, and tumour tissue available for biomarker evaluation. Randomization was stratified by prior maintenance treatment (yes versus no) and line of therapy (second-line versus third-line). CheckMate 057 (non-squamous) allowed enrolment of patients with brain metastases, given that they were treated and stable.

The trial eligibility criteria did not include patients with an ECOG PS > 1 or patients with untreated central nervous system (CNS) metastases.

The pCODR review also provided contextual information on a critical appraisal of a network meta-analysis comparing pemetrexed with nivolumab. pERC noted deficiencies in the systematic approach to trial selection and differences in the trial characteristics that may have impacted the estimates of treatment effect. The statistical heterogeneity among the pairwise comparisons in the network was not explored formally with statistical tests, limiting the interpretation and applicability of these results.

Patient populations: Treatment beyond progression, ECOG PS ≤ 1

Patients in both trials were randomized 1:1 to receive nivolumab at 3 mg/kg of body weight every two weeks or docetaxel at 75 mg/per m^2 of body-surface area every three weeks, administered intravenously over 60 minutes.

CheckMate 057 (non-squamous) enrolled patients with a median age of 62 years and who had an ECOG PS of 0 (31%) or 1 (69%). Patients enrolled in the study also had stage IV disease (92%) and were mostly current or former smokers (79%), with a minority who had never smoked (20%). EGFR mutation positivity was present in 14% of patients, ALK mutation in 4%, and KRAS mutation in 11% of patients. CheckMate 017 (squamous) enrolled patients with a median age of 63 and who had an ECOG PS of 0 (24%) or 1 (76%). Patients enrolled in the study also had stage IV cancer (80%), were current or former smokers (92%), and were mostly white (93%). Driver mutation status was not reported in CheckMate 017. pERC discussed the characteristics of patients included in the two trials and noted that the patients in the trials were likely more fit than patients in a real-world setting, as the patients in the clinical setting would likely have had a poorer performance status, as well as a higher likelihood of significant comorbidities.

Treatment with nivolumab beyond initial progression was allowed in both trials at the investigator's discretion and as specified within the study protocols, whereas treatment with docetaxel beyond disease progression was not permitted. A total of 24% and 21% of patients continued treatment beyond progression in CheckMate 057 and 017, respectively. Crossover was allowed in both trials after the trial, with < 1% and < 5% of patient's crossing over to receive nivolumab from the docetaxel group in CheckMate 057 and 017, respectively. pERC noted the mechanism of action of immunotherapies and the possibility that some patients may experience pseudoprogression — whereby some patients technically meet RECIST criteria for disease progression, but do not have true disease progression — and, therefore, may be treated beyond RECIST-defined disease progression and continue to receive treatment until true disease progression. Upon reconsideration of the pERC Initial Recommendation, pERC noted that there is no consistently accepted definition for pseudoprogression in the clinical community. Until such a definition becomes available, pERC agreed that it is reasonable to use the definition from within the pivotal trials which defined true progression as an additional 10% in tumor burden volume and/or development of new lesions from the time of initial disease progression demonstrated through a confirmatory scan conducted 6 weeks after initial progression.

Key efficacy results: Clinically meaningful improvement in overall survival and objective response rate

The key efficacy outcome deliberated on by pERC included overall survival (OS), the primary outcome in both trials. Both studies were stopped early, having met the pre-specified threshold for superiority by demonstrating superior OS with nivolumab versus docetaxel.

In CheckMate 057, median OS was 12.2 months versus 9.4 months with a hazard ratio (HR) of 0.73 (96% confidence interval [CI], 0.59 to 0.89), $P = 0.002$. In CheckMate 017, median OS was 9.2 months versus 6.0 months with an HR of 0.59 (95% CI, 0.44 to 0.79), $P < 0.001$. Longer follow-up conducted after the interim analysis supported the results in both studies. At 12 months, the survival rate was 51% versus 39% in CheckMate 057 and 42% versus 24% in CheckMate 017 for the nivolumab versus docetaxel groups, respectively. Objective response rate (ORR), a secondary outcome in both trials, was higher with nivolumab than docetaxel in CheckMate 057 (19% versus 12%, with an odds ratio [OR] of 1.7 [95% CI, 1.1 to 2.6]; $P = 0.02$) and CheckMate 017 (20% versus 9%, with an OR of 2.6 [95% CI, 1.3 to 5.5], $P = 0.008$).

pERC agreed that the two trials demonstrated a statistically significant and clinically meaningful benefit with nivolumab irrespective of histological subtype. The results were also consistent across most subgroups. Although the number of patients with a driver mutation was low, the Committee agreed that the overall results of both trials are generalizable to this patient population. Upon reconsideration of the

pERC Initial Recommendation, pERC reiterated that the trial results apply to all patients irrespective of driver mutation status and histological subtype. pERC also considered PD-L1 status as a predictor of response and noted that uncertainty exists concerning the role of PD-L1 testing and whether there is a threshold below which patients should not be treated. Given this, the Committee agreed that treatment with nivolumab should be made available to patients irrespective of PD-L1 status. pERC also considered the generalizability of the overall results to patients with an ECOG PS ≥ 1 and noted an absence of evidence to support the effectiveness of nivolumab in this population. Based on nivolumab's toxicity profile, the Committee was confident that it could be tolerated by patients with an ECOG PS > 1. Although uncertainty remained related to its efficacy in this patient population, pERC agreed that the availability of nivolumab should be extended to patients with a good performance status beyond ECOG PS 1.

Upon reconsideration of the pERC Initial Recommendation, the committee noted feedback from PAG requesting clarity around the number of prior lines of therapy patients may have had to qualify for nivolumab therapy. pERC agreed that patients who have had cytotoxic chemotherapy for advanced disease, irrespective of prior lines of therapy, should qualify for nivolumab treatment. pERC noted that a platinum-based doublet is the standard treatment option for patients prior to qualifying for nivolumab; however, there may be instances where patients cannot tolerate the platinum portion of their treatment. In these instances, where cytotoxic chemotherapy has been administered, pERC agreed that it would be reasonable to treat patients with nivolumab provided they meet all other criteria within this recommendation. PAG also requested clarity on the generalizability of the trial results to patients with brain metastases. Given that patients with stable brain metastases were entered into both pivotal studies, pERC agreed that treatment with nivolumab should be made available to patients with adequately treated brain metastases (i.e., patients have returned to baseline neurological status, except for treatment related toxicities, at least 2 weeks prior to enrollment and have been titrated down to a steroid dose equivalent of ≤ 10 mg daily prednisone).

Quality of life: Delay in deterioration of QoL

Patient-reported outcomes were measured using the Lung Cancer Symptom Scale (LCSS) in both studies and the EuroQol 5-Dimensions Quality of Life Questionnaire (EQ-5D) (as an exploratory outcome) in CheckMate 057. For both studies, time to deterioration (TTD) analysis was performed for the LCSS Average Symptom Burden Index (ASBI) and its components (i.e., fatigue, cough, dyspnea, pain, anorexia, and hemoptysis) and for the three-item Index and each of its components (symptom distress, interference with activity level, quality of life [QoL]). The proportion of patients experiencing a clinically meaningful improvement (defined as a change in score of ≥ 10 points) in symptoms by week 12 according to the LCSS ASBI was the objective of the patient-reported outcomes assessment for both studies. This was achieved in 17.8% versus 19.7% in CheckMate 057 and 20.0% versus 21.9% in CheckMate 017 among the nivolumab and docetaxel groups, respectively. For CheckMate 057, following the assessment at week 12, the on-treatment individual symptoms and three-item Index (symptom distress, interference with activities, and global health-related quality of life [HRQoL]) and its components followed the general pattern of the LCSS ASBI. In CheckMate 017, no statistically significant difference in time to first-disease-related deterioration was observed for the LCSS ASBI and its components except for anorexia. For CheckMate 057, HR estimates in TTD for the LCSS ASBI and its individual components were associated with a delay in deterioration in favour of nivolumab. The estimates were, however, not reported. In CheckMate 017, the TTD analysis of the three-item Index and each of its components demonstrated a statistically significant difference in time to first-disease-related deterioration in favour of nivolumab. For CheckMate 057, the estimated HRs for TTD analysis of the 3-item Index and each of its components were consistent with delay in deterioration in patients treated with nivolumab relative to docetaxel. pERC discussed the results of the patient-reported outcomes from both studies and agreed that there was no strong indication that QoL deteriorated or improved with nivolumab compared with docetaxel. pERC concluded that the results of the trials suggested a delay in deterioration of QoL.

Safety: Meaningful improvement in grade 3 and 4 toxicities

pERC discussed the toxicity profile of nivolumab as observed in CheckMate 057 and 017. Grade 3 to 4 treatment-related adverse events (TRAEs) were less frequent in the nivolumab groups compared with the docetaxel groups in CheckMate 057 (10% versus 54%) and CheckMate 017(8% versus 56%). Overall, pERC agreed that nivolumab demonstrated meaningful improvements in grade 3 and 4 toxicities compared with docetaxel.

Need: Treatment with reduced toxicity, improved quality of life and survival

Lung cancer is the leading cause of cancer-related deaths worldwide, with the majority of patients presenting with non-curable disease. In Canada, an estimated 26,600 new cases and 20,900 deaths occurred in 2015 from lung cancer with a five-year survival rate of < 5%. NSCLC accounts for 85% of all lung cancers. Non-squamous and squamous cell lung cancer comprise about 70% and 30% of NSCLC, respectively. In patients without a driver mutation and who have received cytotoxic chemotherapy in the first-line setting, second-line treatment includes single-agent chemotherapy with docetaxel or pemetrexed. This is based on modest improvements in survival and QoL. For those who received driver mutation–specific therapy in the first line, second-line treatment consists of platinum doublet and third-line pemetrexed for those who maintain a good performance status.

pERC noted that the goals of treatment for patients with advanced-stage NSCLC are primarily palliative; namely, to prolong life while maintaining or improving QoL. Given that most patients have advanced age and advanced stage of disease, pERC noted that a disproportionately greater number of patients at this stage of disease have a poor performance status, as well as a higher likelihood of significant comorbidities that impact their ability to tolerate conventional chemotherapy regimens. Given the toxicity associated with available single-agent chemotherapy in patients who progressed on or after a platinum-based doublet, pERC agreed that there is a need for alternative options that reduce toxicity and prolong survival.

PATIENT-BASED VALUES

Values of patients with advanced or metastatic NSCLC: Control of symptoms and treatment-related toxicity

Patient advocacy group input indicated that lung cancer has a tremendous negative impact on the daily lives of patients and is a devastating illness. Symptoms most frequently experienced by patients include fatigue, loss of appetite, shortness of breath, cough, pain, and blood in sputum. Loss of appetite, cough, pain, and shortness of breath are known to be significant predictors of QoL. Patients living with lung cancer reported that the disease had an impact on many aspects of day-to-day life, including ability to work, travel, socialize, and participate in leisure and physical activities. Patients noted that frequent or constant anxiety or worry is common. Based on patient input, depression rates in advanced lung cancer patients vary from 16% to 50%, and are consistently higher than other cancer sites. pERC noted that treatments that improve survival and QoL would be of value.

In addition, patients' emotional well-being, financial circumstances, and relationships with family members and friends suffer. Furthermore, pERC noted that patients with lung cancer are often burdened with the stigma associated with smoking as the leading cause of their cancer.

Patient values on treatment: Improved efficacy, safety, and QoL with new therapy

Patient advocacy group input indicated that although current chemotherapies can extend life expectancy to a limited extent and are associated with significant toxicities, many patients are not considered fit enough for chemotherapy treatments, for reasons such as performance status, age, or other illnesses. As a result, patients' survival and ability to fight their advanced lung cancer is limited. Severe side effects associated with chemotherapy include nausea, vomiting, hair loss, fatigue, and the risk of fever and infection. According to patients, the burden of chemotherapy was felt during all stages of the treatment. Additionally, patients can experience dehydration, kidney damage, hearing loss, and nerve damage with chemotherapy. Patients felt burdened with the inconvenience of multiple blood tests, intravenous treatment, and multiple visits (with long wait times) to hospital for chemotherapy. Cost of travel is an additional burden, more so in rural communities. Patients indicate that hospital appointments are difficult to obtain and access to chemotherapy suites is limited even in urban areas, and more so in outlying areas.

Patients consider an improvement in efficacy, convenience, or side effect profile over current therapies to be important aspects for consideration. pERC therefore concluded that improvements in survival, symptom control, and QoL were important to patients and noted that an OS benefit and a delay in deterioration of QoL were observed in both CheckMate 057 and 17. Based on this, pERC agreed that nivolumab is aligned with patient values.

pERC also noted the tremendous burden on patients and their caregivers. Caregivers experience stigma unique to lung cancer, which places an additional emotional burden on them. The late diagnosis of lung cancer, often in stage IV, can also be very stressful, particularly when dealing with the declining health of family members or friends. Caregivers reported a significant economic toll on household finances due to lung cancer and difficulty in managing the high symptom burden of lung cancer, both for patients and caregivers.

Among those providing input, six patients and three caregivers had experience with nivolumab. Side effects of nivolumab were reported as more tolerable than chemotherapy; also, the most common side effect was fatigue. Respondents also stated that most of the fatigue appeared to be manageable and did not interfere with daily activity. Patients reported that nivolumab infusions were less stressful, less tiring, caused fewer side effects, and less of a burden, while giving patients more time and more QoL than chemotherapy infusions.

ECONOMIC EVALUATION

Economic model submitted: Cost-effectiveness and cost-utility analysis

The pCODR Economic Guidance Panel (EGP) assessed cost-effectiveness and cost-utility analyses comparing nivolumab with docetaxel in patients with non-squamous or squamous NSCLC who progressed on or after a platinum-based chemotherapy.

Basis of the economic model: Treatment beyond progression, high utilities from trial

Costs included were cost of treatment, adverse event management costs, and resource costs for disease follow-up. pERC noted that the cost estimates for nivolumab were based on progression-free survival (PFS) data from the two trials. pERC considered the appropriateness of PFS to inform this input, as a significant proportion of patients in both studies continued to receive nivolumab after disease progression based on the investigator's assessment of whether a patient would derive clinical benefit from continuing treatment. pERC accepted the EGP's approach to use time-to-treatment discontinuation as an alternative data source that would more accurately reflect the treatment duration of patients who received nivolumab.

Key clinical effects considered in the analysis included OS, PFS, and utilities. pERC noted that OS data were extrapolated over 10 years in the base-case analysis and agreed with the truncation of the time horizon to five years, to better reflect survival of patients at this advanced stage of disease. pERC also noted that the utility estimates from the trial, particularly in the progressive disease state, were high and likely do not reflect the health state utility of patients with advanced lung cancer. pERC noted that the utilities from the trial may have been high for patient population of interest, as the values were near those observed in the general population.

Drug costs: High cost of drug

Nivolumab costs $1,955.56 per 100 mg vial or $782.22 per 40 mg vial; at the recommended dose of 3 mg/kg once every 14 days, the average cost per day in a 28-day course of nivolumab is $293.33 and the average cost per 28-day course is $8,213.31.

Generic and brand-name docetaxel costs $11.42 per mg. At the recommended dose of 75 mg/per m^2 every three weeks, docetaxel costs $69.36 per day and $1,942.00 per 28-day cycle.

Cost-effectiveness estimates: Utilities, overall survival, and treatment beyond progression

pERC discussed the submitter's and EGP's best estimate of the incremental cost-effectiveness ratio (ICER) in patients with non-squamous and squamous NSCLC. In both settings, pERC accepted the EGP's reanalysis estimates and concluded that nivolumab is not cost-effective.

pERC noted that uncertainty regarding the estimates for utilities, extrapolation for OS and PFS over a 10-year time horizon, and duration of treatment had the greatest impact on the ICER for both the squamous and non-squamous populations. To explore uncertainty with the health state utilities, the EGP provided a range of reanalysis estimate using utility values derived from the trials or literature. The Committee noted the utilities derived from the trials were high and close to what is typically observed in the general population. Given this, pERC concluded that the true ICER is likely near the upper end of the EGP's reanalysis estimate, which incorporated utility estimates for this patient population from the literature,

and which pERC considered to be more representative of the clinical population with advanced or metastatic NSCLC. pERC also agreed with the truncation of the time horizon from 10 years to five years, which was considered to better reflect survival in patients in this advanced stage of NSCLC. The EGP also explored the use of time-to-treatment discontinuation to estimate drug costs as opposed to PFS, given that nearly 20% of patients from both trials continued to receive nivolumab after disease progression. pERC agreed that treatment beyond progression is possible, given the nature of immunotherapies and the possibility of pseudoprogression; that is, where patients have the appearance of progression as measured by RECIST criteria, but may continue to benefit from treatment beyond progression until confirmed disease progression.

pERC noted that the submitter provided both a partitioned survival and Markov model each for the squamous and non-squamous populations. While the EGP used the partitioned survival model for its reanalysis estimates, results from both analyses were similar between the two models for each population modelled. pERC members were impressed with these data and commended the submitter for validating concerns regarding structural uncertainty through the provision of these models.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: High drug cost, high incidence of disease, and uncertain duration of treatment

pERC considered the feasibility of implementing a funding recommendation for nivolumab. pERC noted PAG's concern about the long duration of therapy and more frequent treatment cycles with nivolumab as compared to other immunotherapies. pERC noted that the mechanism of action of immunotherapies suggests that it is reasonable to investigate whether a shorter treatment course could provide an optimal disease response while minimizing patients' risk for potential side effects. pERC acknowledged that there is currently no evidence to suggest an optimal duration of treatment with nivolumab but agreed that it is important for jurisdictions to prospectively collect this data to manage the budget impact of a funding recommendation.

pERC acknowledged that drug wastage is an important concern for PAG. pERC noted that the EGP included wastage in the model and it is reflected in the ICER in both of the modelled populations. Overall, due to the large new and prevalent population of patients with advanced or metastatic NSCLC, the high cost of nivolumab, and the unknown but potentially long duration of treatment, pERC concluded that a substantial reduction in drug price would be required to improve cost-effectiveness and affordability to an acceptable level. pERC noted that the submitted budget impact analysis was sensitive to the cost of nivolumab, duration of treatment, the number of patients eligible for nivolumab, and the estimated market share for nivolumab. pERC noted that jurisdictions will need to consider the uncertainty in these factors during implementation.

pERC recognized that provinces would need to have a common approach to define true disease progression and ensure that patients who experience pseudoprogression — whereby some patients technically meet RECIST criteria for disease progression but do not have true disease progression — may continue treatment with nivolumab until true disease progression occurs. Upon reconsideration of the pERC Initial Recommendation, pERC noted that there is no consistently accepted definition for pseudoprogression in the clinical community. Based on the Clinical Guidance Panel's input, pERC noted that pseudoprogression may be characterized by an increase of lesion size related to treatment that simulates progressive disease. In the context of Nivolumab and other immune checkpoint inhibitors, 'pseudoprogression' may be due to peritumoral lymphocyte infiltration or delayed immune activity. Until a widely accepted definition becomes available for pseudoprogression, pERC agreed that it is reasonable to use the definition from within the pivotal trials which defined true progression as an additional 10% in tumor burden volume and/or development of new lesions since the time of initial disease progression demonstrated through a confirmatory scan conducted 6 weeks after initial progression.

pERC also acknowledged a time-limited need for nivolumab for those patients who are receiving treatment with single-agent cytotoxic chemotherapy and who would otherwise meet the eligibility criteria of the CheckMate 017 and CheckMate 057 studies.

DRUG AND CONDITION INFORMATION

Drug Information	• Immunomodulatory agent • 40 mg and 100 mg vials submitted for review • Recommended dose of 3 mg/kg every 2 weeks
Cancer Treated	• Advanced or metastatic non-small Cell Lung Cancer
Burden of Illness	• Five-year survival rate of < 5% • Large prevalent and new population • Patients generally have advanced age, advanced stage of disease, poor performance status, and a higher likelihood of significant comorbidities
Current Standard Treatment	• Docetaxel • Pemetrexed
Limitations of Current Therapy	• Modest improvements in survival and quality of life with current therapies • Poor performance status of patients makes it difficult for many patients to tolerate toxicities of chemotherapy

ABOUT THIS RECOMMENDATION

The pCODR Expert Review Committee

Recommendations are made by the CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) following the pERC Deliberative Framework. pERC members and their roles are as follows:

Dr. Anthony Fields, Oncologist (Chair)
Dr. Maureen Trudeau, Oncologist (Vice-Chair)
Dr. Scott Berry, Oncologist
Bryson Brown, Patient Member
Dr. Kelvin Chan, Oncologist
Dr. Matthew Cheung, Oncologist
Dr. Craig Earle, Oncologist
Dr. Allan Grill, Family Physician
Dr. Paul Hoskins, Oncologist
Don Husereau, Health Economist
Dr. Anil Abraham Joy, Oncologist
Carole McMahon, Patient Member
Dr. Catherine Moltzan, Oncologist
Valerie McDonald, Patient Member Alternate
Jo Nanson, Patient Member
Karen MacCurdy-Thompson, Pharmacist
Danica Wasney, Pharmacist

All members participated in deliberations and voting on the Initial Recommendation, except:

- Maureen Trudeau, Kelvin Chan, and Scott Berry, who were not present for the meeting
- Anil Abraham Joy, who was excluded from deliberations and voting due to a conflict of interest
- Carol McMahon, who did not vote due to her role as a patient member alternate
- Valerie MacDonald, who did not vote due to her role as a patient member-in-training.

All members participated in deliberations and voting on the Final Recommendation, except:

- Matthew Cheung, Jo Nanson, and Allan Grill, who were not present for the meeting
- Anil Abraham Joy, who was excluded from deliberations and voting due to a conflict of interest.

Avoidance of conflicts of interest

All members of pERC must comply with the *pCODR Conflict of Interest Guidelines*; individual conflict of interest statements for each member are posted on the pCODR website, and pERC members have an obligation to disclose conflicts on an ongoing basis. For the review of nivolumab (Opdivo) for non–small cell lung cancer, through their declarations, five members had a real, potential, or perceived conflict and, based on application of the *pCODR Conflict of Interest Guidelines*, one of these members was excluded from voting.

Information sources used

pERC is provided with a *pCODR Clinical Guidance Report* and a *pCODR Economic Guidance Report*, which include a summary of patient advocacy group and Provincial Advisory Group input, as well as original patient advocacy group input submissions, to inform its deliberations. pCODR guidance reports are developed following the pCODR review process and are posted on the pCODR website. Please refer to the pCODR guidance reports for more detail on their content.

Consulting publicly disclosed information

pCODR considers it essential that pERC recommendations be based on information that may be publicly disclosed. All information provided to pERC for its deliberations was handled in accordance with the *pCODR Disclosure of Information Guidelines*. There was no non-disclosable information in this Recommendation document.

Use of this Recommendation

This Recommendation from pERC is not intended as a substitute for professional advice, but rather to help Canadian health systems leaders and policy-makers make well-informed decisions and improve the quality of health care services. While patients and others may use this Recommendation, it is for informational and educational purposes only, and should not be used as a substitute for the application of clinical judgment respecting the care of a particular patient, for professional judgment in any decision-making process, or for professional medical advice.

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