pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pCODR EXPERT REVIEW COMMITTEE (pERC)
INITIAL RECOMMENDATION

The 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 cancer drug assessment process by looking at clinical evidence, cost-effectiveness and patient perspectives.

Providing Feedback on this Initial Recommendation
Taking into consideration feedback from eligible stakeholders, the pERC will make a Final Recommendation. Feedback must be provided in accordance with *pCODR Procedures*, which are available on the pCODR website. The Final Recommendation will be posted on the pCODR website once available, and will supersede this 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 Issued:
April 1, 2016

pERC RECOMMENDATION	The pCODR Expert Review Committee, 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) who progressed on or after chemotherapy, with a good performance status and 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 who progressed on or after 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.

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 RECIST criteria radiologic disease growth may be due to immune related inflammation and may not be reflective of true disease progression (i.e. it is pseudoprogression). As such, and in clinical practice some patients may be treated beyond initial RECIST-defined disease progression to either confirm subsequent response or true disease progression. pERC recognized that provinces would need to address this issue upon implementation of a funding recommendation for nivolumab and noted that collaboration among provinces to develop a common approach to defining confirmed disease progression would be of value.

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 have previously progressed on or after treatment with a platinum based doublet and are currently receiving treatment with single agent chemotherapy or who have recently completed treatment with single agent chemotherapy. pERC noted that this time-limited access should be for patients who would otherwise meet the eligibility criteria of the CheckMate 017 and CheckMate 057 studies.

SUMMARY OF pERC DELIBERATIONS

pERC's *Deliberative Framework* for drug funding recommendations focuses on four main criteria:	
CLINICAL BENEFIT	PATIENT-BASED VALUES
ECONOMIC EVALUATION	ADOPTION FEASIBILITY

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 would occur 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 of 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. Due to advanced age and stage of disease, greater number of patients have a poor performance status, as well as a higher likelihood of significant co-morbidities that impact 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 deliberated upon the results of two open label randomized controlled trials which compared nivolumab to docetaxel in patients with 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 platinum based doublet. 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 among the two histological types of NSCLC, as demonstrated in the near immediate separation of the Kaplan-Meir overall survival 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 data (QoL) 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 to docetaxel. pERC discussed the fact that many patients seen in clinical practice generally have a poorer performance status compared to 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 Co-operative 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 on 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 who can tolerate this treatment may derive benefit, based on opinion of the 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 overall survival and the objective response rate, a meaningful improvement in the toxicity profile, and at least stable quality of life compared with docetaxel.

pERC deliberated upon input from patient advocacy group concerning nivolumab and noted that prolonged survival, reduction of toxicities associated with treatment, reduction of disease symptoms, and improvement of quality of life were important to patients. The results of both CheckMate 057 and 017, demonstrated statistically significant and clinically meaningful improvements in overall survival, a meaningful improvement in toxicity profile, and stable quality of life 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 quality of life and ability to get back to work. Therefore, pERC considered that nivolumab aligns 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: 1) the estimates for utilities; 2) extrapolation for OS and progression-free survival (PFS) over a 10 year time horizon; and 3) the duration of treatment. These factors had the largest impact on the incremental cost effectiveness ratio for both the squamous and non-squamous populations. pERC noted that the EGP provided a range for its re-analysis estimates using alternative sources for utilities. The Committee agreed with the EGP that utilities derived from the trial were high and close to what is observed in the general population. Given this, pERC concluded that the true ICER is likely near the upper end of the EGP's re-analysis 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 their re-analysis 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 platinum based therapy 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 discussed that jurisdictions will need to consider the uncertainty in these factors during implementation. Furthermore, pERC also 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 cut off 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 also recognized that provinces would need to have a common approach to define true disease progression and ensure that patients experience pseudoprogression may continue treatment with nivolumab until true disease progression occurs. Lastly, pERC acknowledged a time-limited need for nivolumab for those patients 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

pERC deliberated upon a pCODR systematic review, other literature in the Clinical Guidance Report providing 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), and input from pCODR's Provincial Advisory Group.

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of the review is to evaluate the safety and efficacy of nivolumab as a monotherapy compared to an appropriate comparator, on patient outcomes in the treatment of adult patients with advanced or metastatic non-small cell lung cancer (NSCLC) who progressed on or after chemotherapy.

Studies included: Squamous and non-squamous NSCLC

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

For both studies, the key inclusion criteria required that patients have an ECOG PS ≤1, measurable disease by CT or MRI per RECIST 1.1 criteria, and tumor 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 enrollment 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 CNS metastases.

The pCODR review also provided contextual information on a critical appraisal of a network meta-analysis comparing pemetrexed to 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 2 weeks or docetaxel at 75 mg/per m^2 of body-surface area every 3 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 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 patients in the clinical setting would likely have a poorer performance status, as well as a higher likelihood of significant co-morbidities.

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 patients 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.

Key efficacy results: Clinically meaningful improvement in OS and ORR

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%CI, 0.59 to 0.89), P=0.002. In CheckMate 017 median OS was 9.2 months versus 6.0 months with a 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 compared to docetaxel in CheckMate 057 [19% versus 12%, with an odds ratio of 1.7 (95%CI, 1.1 to 2.6); P =0.02] and CheckMate 017 [20% versus 9%, with an odds ratio of 2.6(95% CI: 1.3-5.5), *P*=0.008].

pERC agreed that the two trials demonstrated 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 panel agreed that the overall results of both trials are generalizable to this patient population. pERC also considered PD-L1 status as a predictor of response and noted uncertainty exists concerning the role of PD-L1 testing and whether there is a cut off level below which patients should not be treated. Given this, the panel 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 would be tolerated by patients with an ECOG PS ≥1 but uncertainty remained related to its efficacy in this patient population. Therefore, pERC agreed that nivolumab should be made available to patients with a good performance status.

Quality of life: Delay in deterioration of QoL

Patient-reported outcomes were measured using the lung cancer symptom scale (LCSS) in both studies and EQ-5D (as an exploratory outcome) in CheckMate 057. For both studies, time to deterioration (TTD) analysis was performed for the LCSS ASBI and its components (i.e., fatigue, cough, dyspnea, pain, anorexia and hemoptysis) and for the 3-item Index and each of its components (symptom distress, interference with activity level, 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 average symptom burden index (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% vs 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 3-item index (symptom distress, interference with activities and global 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, hazard rate 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 3-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 hazard ratios 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 3-4 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 QoL 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 would occur 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. In patients without a driver mutation and who have received a platinum based doublet 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 quality of life. 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 quality of life. Given the 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 co-morbidities that impact their ability to tolerate conventional chemotherapy regimens. Given the toxicity associated with available single agent chemotherapy in patients that 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 Symptom 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 quality of life. 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 16-50%, and are consistently higher than other cancer sites. pERC noted that treatments that improve survival and quality of life would be of value.

In addition, patients' emotional well-being, financial circumstances and relationships with family members and friends also 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, patient's 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 also 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 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 quality of life were important to patients and noted that an OS benefit and a delay in deterioration of quality of life were observed in both CheckMate 057 and 17. Based on this pERC agreed that nivolumab aligned with patient values.

pERC also noted the tremendous burden on patients and their caregivers. Caregivers experience stigma unique to lung cancer which places 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, have fewer side effects, and less of a burden, while giving patients more time, and more quality of life than chemotherapy infusions.

ECONOMIC EVALUATION

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

The pCODR Economic Guidance Panel 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 events management costs, and resource costs for disease follow-up. pERC noted that the cost estimates for nivolumab were based on progression-free survival 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 was extrapolated over 10 years in the base case analysis and agreed with the truncation of the time horizon to 5 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 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 m2 every 3 weeks docetaxel costs $69.36 per day and $1,942.00 per 28-day cycle.

Cost-effectiveness estimates: Utilities, OS, and Treatment beyond Progression

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

pERC noted uncertainty around 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 incremental cost effectiveness ratio (ICER) both for the squamous and non-squamous populations. To explore uncertainty with the health state utilities, the EGP provided a range of re-analysis estimate using utility values derived from the trial or literature. The Committee noted the utilities derived from the trial 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 re-analysis estimate which incorporated utility estimates for this patient population from the literature, 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 5 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 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 their re-analysis 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 of structural uncertainty through the provision of these models.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: High drug cost, high incidence of disease and 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 with nivolumab as compared to other immunotherapies with shorter treatment cycles. pERC noted that the mechanism of action of immunotherapies suggests that it is reasonable to investigate whether a shorter treatment exposure period could provide an optimal response to patients while minimizing exposure to 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 modeled 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 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 discussed 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. pERC also acknowledged a time-limited need for nivolumab for those patients receiving treatment with single agent chemotherapy or who have recently completed treatment with single agent 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 • 40mg and 100mg vials submitted for review • Recommended dose of 3mg/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 co-morbidities
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 make it difficult for many patients to tolerate toxicities of chemotherapy

ABOUT THIS RECOMMENDATION

The pCODR Expert Review Committee (pERC)

Recommendations are made by the pCODR Expert Review Committee 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 Alternate
Dr. Catherine Moltzan, Oncologist
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

Avoidance of conflicts of interest

All members of the pCODR Expert Review Committee 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

The pCODR Expert Review Committee 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 their 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 the pCODR Expert Review Committee for its deliberations was handled in accordance with the *pCODR Disclosure of Information Guidelines.*

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