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 reimbursement 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 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) in combination with ipilimumab (Yervoy) and two cycles of platinum-based chemotherapy **Submitted Reimbursement** Request: Nivolumab, in combination with ipilimumab and two cycles of platinum-based chemotherapy for the first-line treatment of patients with metastatic or recurrent NSCLC with no EGFR or ALK genomic tumour aberrations	
Submitted By: Bristol-Myers Squibb Canada	**Manufactured By:** Bristol-Myers Squibb Canada
NOC Date: August 6, 2020	**Submission Date:** June 23, 2020
Initial Recommendation: January 8, 2021	**Final Recommendation:** March 4, 2021

Approximate per Patient Drug Costs, per Month (28 Days)	• Nivolumab: $782 and $1,955 for 40 mg and 100 mg vials, respectively; $9,387 per month • Ipilimumab: $5,800 for 50 mg vial; $7,733 per month • Platinum doublet chemotherapy: $5,688 to $6,548 per month • Nivolumab combined with ipilimumab and platinum doublet chemotherapy: $22,864 to $23,668 per month

pERC RECOMMENDATION

☐ **Reimburse**

☒ **Reimburse with clinical criteria and/or conditions***

☐ **Do not reimburse**

*If the condition(s) cannot be met, pERC does not recommend reimbursement of the drug for the submitted reimbursement request.

pERC conditionally recommends the reimbursement of nivolumab plus ipilimumab (nivolumab/ipilimumab) and two cycles of platinum doublet chemotherapy (PDC), for the first-line treatment of adult patients with metastatic or recurrent non-small cell lung cancer (NSCLC) with no known epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumour aberrations, if the following condition is met:

- Cost-effectiveness being improved to an acceptable level.

Eligible patients include those with non-squamous or squamous NSCLC, any PD-L1 expression level including patients with unknown PD-L1 expression, and good performance status. Treatment with nivolumab/ipilimumab should continue until confirmed disease progression or unacceptable toxicity to a maximum of two years, whichever comes first.

pERC made this recommendation because it was satisfied that there is a net overall clinical benefit with nivolumab/ipilimumab plus two cycles of PDC compared to PDC alone based on statistically significant and clinically meaningful improvements in overall survival (OS), progression-free survival (PFS) and objective response rate (ORR), maintenance of quality of life (QoL), and manageable toxicities.

	pERC also concluded that nivolumab/ipilimumab plus PDC aligns with patient values in that it provides a treatment option that limits the duration of chemotherapy, improves OS, delays disease progression, maintains QoL, and has manageable toxicities. pERC concluded that nivolumab/ipilimumab plus PDC was not cost-effective at the submitted price versus PDC alone. The limitations identified with the submitted economic evaluation indicate some uncertainty associated with the results of the economic analysis. pERC acknowledged the lack of a direct or robust indirect comparison to immunotherapy-based regimens and was unable to draw a conclusion on the relative clinical efficacy and safety of nivolumab/ipilimumab plus PDC compared to immunotherapy-based regimens. As such, the cost-effectiveness estimates of nivolumab/ipilimumab plus PDC compared with immunotherapy-based regimens are uncertain. A price reduction would improve the likelihood that nivolumab/ipilimumab plus PDC is a cost-effective treatment regimen and would result in an improved budget impact.
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	**Pricing arrangements to improve cost-effectiveness** Given that pERC was satisfied that there is a net overall clinical benefit of nivolumab/ipilimumab plus PDC, jurisdictions may want to consider pricing arrangements and/or cost structures that would improve the cost-effectiveness of nivolumab/ipilimumab plus PDC. pERC concluded that a reduction in drug price would be required to improve the cost-effectiveness of nivolumab/ipilimumab to an acceptable level and to improve the budget impact. **Please note:** Provincial Advisory Group (PAG) questions are addressed in detail in the Summary of pERC Deliberations and in a summary table in Appendix 1.

SUMMARY OF pERC DELIBERATIONS

Lung cancer represents the second most common cancer among both men and women in Canada and the leading cause of death from cancer. In 2020, there will be approximately 29,800 new cases of lung cancer and 21,200 deaths from lung cancer. Approximately 85% of cases are classified as NSCLC and in approximately 70% of these cases, the histologic subtype is adenocarcinoma. Approximately 50% of NSCLC patients have stage IV metastatic disease at the time of presentation, and the expected five-year survival is only 19%.

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

CLINICAL BENEFIT	**PATIENT-BASED VALUES**
ECONOMIC EVALUATION	**ADOPTION FEASIBILITY**

The majority of patients with locally advanced and metastatic NSCLC have tumours without targetable molecular abnormalities. In these patients, immune checkpoint inhibitor therapy, either alone or in combination with chemotherapy, is considered the current standard of care. Currently, pembrolizumab is the only immune checkpoint inhibitor funded in the first-line NSCLC setting; pembrolizumab monotherapy in patients with high programmed death-ligand 1 (PD-L1) expression (tumour proportion score [TPS] ≥ 50%) or pembrolizumab in combination with four to six cycles of PDC regardless of PD-L1 expression are approved and reimbursed in most jurisdictions. Pembrolizumab-based regimens have increased the median survival of patients from approximately one year to approximately 18 months to 24 months, and approximately one in three patients remain alive at three years. However, despite these survival improvements, metastatic NSCLC remains an incurable disease. pERC agreed with the pCODR Clinical Guidance Panel (CGP) that, in a setting where treatment duration may continue for up to two years, there is a need for treatment that offers improved disease control, reduced toxicities, improved tolerability, and provides patients with options to best meet their individual needs and preferences.

pERC deliberated on the results of one phase III, open-label, international randomized controlled trial (RCT), CheckMate 9LA, that compared nivolumab/ipilimumab and two cycles of PDC compared with PDC alone as first-line treatment in patients with non-squamous or squamous metastatic and recurrent NSCLC regardless of PD-L1 expression who had no EGFR mutations or ALK translocations. pERC noted that the majority of non-squamous patients in the PDC group (66.4%) received pemetrexed maintenance. pERC discussed that the trial demonstrated superior treatment efficacy of nivolumab/ipilimumab plus PDC over PDC alone in terms of OS, the primary end point, and all other secondary efficacy end points assessed, including PFS and ORR per blinded independent central review (BICR). pERC discussed that the OS and PFS improvements are clinically meaningful, independent of PD-L1 expression or histology, and were also sustained at an unplanned, updated analysis conducted after a minimum follow-up of 12.7 months. pERC acknowledged that the duration of follow-up in the trial was short and current OS data are immature; however, pERC considered that median OS was reached in each treatment group, all efficacy outcomes showed a consistent treatment benefit in favour of nivolumab/ipilimumab plus PDC over PDC alone, and these results were observed in the majority of pre-specified patient subgroups.

pERC also discussed the CheckMate 227 trial, which was included in the sponsor's submission as supportive evidence and was used to inform the pharmacoeconomic (PE) model supporting the reimbursement request. The CheckMate 227 trial provides longer-term efficacy data associated with nivolumab/ipilimumab (without PDC) versus PDC alone in a similar population as the CheckMate 9LA trial. After a median follow-up of 29.3 months, the final analysis of OS in patients with PD-L1 expression greater than 1% showed superior OS with nivolumab/ipilimumab compared with PDC alone; however, there was evidence of the survival curves crossing (i.e., non-proportional hazards). Patients treated with nivolumab/ipilimumab compared with PDC alone experienced a slight detriment in OS during the initial months of nivolumab/ipilimumab treatment but, thereafter, the survival curves showed a sustained long-term benefit in OS. The most recent data from the CheckMate 227 trial, based on 43.1 months of follow-up, show sustained benefit from treatment with nivolumab/ipilimumab over PDC in patients regardless of PD-L1 expression. pERC agreed with the CADTH Methods Team's critical appraisal, that although visual comparison of the OS curves from each trial show that the additional short course of PDC added to nivolumab/ipilimumab in the CheckMate 9LA trial addresses the early OS detriment observed in the CheckMate 227 trial, in the absence of a direct comparison of nivolumab/ipilimumab to

nivolumab/ipilimumab plus PDC, equivalent long-term efficacy of these regimens cannot be assumed due to trial differences in treatment regimens evaluated and limitations associated with the CheckMate 227 trial.

pERC discussed that the comparator treatment in the CheckMate 9LA trial, PDC alone, is not the current standard of care in most Canadian jurisdictions for patients with metastatic NSCLC and no known EGFR or ALK tumour aberrations. pERC deliberated on the sponsor's submitted indirect treatment comparisons (ITCs) that compared the efficacy of nivolumab/ipilimumab plus PDC to immunotherapy-based treatments currently funded in Canada, which included pembrolizumab plus PDC regimens for non-squamous and squamous NSCLC, and pembrolizumab monotherapy for high PD-L1 expression (TPS ≥ 50%) mixed histology NSCLC. The ITCs were performed to derive comparative efficacy estimates for OS and PFS to inform the PE model; QoL and safety outcomes other than death were not included. Overall, the results showed no statistically significant differences in OS and PFS when nivolumab/ipilimumab plus PDC was compared with pembrolizumab-based treatments, and the results did not substantially change based on sensitivity analyses performed by PD-L1 expression level (TPS ≥ 1%, < 1%) and histology. pERC discussed that the CADTH Methods Team identified several limitations associated with the ITCs that introduces uncertainty in comparative efficacy estimates obtained. Given the heterogeneity of study populations, the differential treatment effects in the common comparator of chemotherapies, varied trial designs, and lengths of follow-up, pERC agreed that the findings of the ITCs should be interpreted with caution. Therefore, pERC agreed that no conclusions could be drawn from the ITCs on the comparative efficacy of nivolumab/ipilimumab plus PDC compared to pembrolizumab-based regimens.

pERC deliberated on the safety profile of nivolumab/ipilimumab plus PDC compared with PDC alone. Patients who received nivolumab/ipilimumab plus PDC experienced more adverse events (AEs) of any grade that are typically attributed to immune checkpoint inhibitors, which included diarrhea, pruritus, rash, and fatigue. Patients who received PDC alone experienced a higher incidence of chemotherapy-related side effects that included nausea, anemia, and neutropenia. Overall, pERC noted that patients in the nivolumab/ipilimumab plus PDC group experienced greater toxicity compared to patients in the PDC group; the incidence of grade 3 or grade 4 AEs, serious adverse events (SAEs), and AEs resulting in treatment discontinuation were all higher in patients treated with nivolumab/ipilimumab plus PDC. Immune-related AEs (irAEs) occurred in more patients in the nivolumab/ipilimumab plus PDC group, but most were low grade and resolved through appropriate monitoring and the use of immune-mediating medications. The incidence of death related to drug toxicity was similar between the two treatment groups. pERC discussed that the CGP and the registered clinicians providing input for this submission indicated the toxicity profile of nivolumab/ipilimumab plus PDC is safe and consistent with other immunotherapy-based treatments used in the first-line treatment setting for patients with locally advanced or metastatic NSCLC. Further, when compared to PDC alone, pERC acknowledged that chemotherapy-specific toxicities were reduced in patients treated with nivolumab/ipilimumab plus PDC, which is an outcome valued by patients. pERC noted that the dosing and schedule of ipilimumab used in the CheckMate 9LA trial was lower and less frequent compared to the dual immunotherapy regimen that is used for several other indications, which may contribute to the tolerability of the combination in patients with NSCLC. Therefore, pERC concluded that the toxicity of nivolumab/ipilimumab plus PDC is considered manageable by clinicians experienced in administering immunotherapy-based regimens.

pERC also discussed the patient-reported QoL data from the CheckMate 9LA trial, which was assessed as an exploratory outcome based on multiple patient-reported outcome (PRO) measures. The PRO data showed that, while on treatment, patients' lung cancer symptoms, overall health status, and QoL improved over time in each treatment group but these improvements did not reach pre-specified thresholds of clinically meaningful change from baseline in either treatment group. pERC noted that a time-to-deterioration (TTD) analysis was conducted for all PRO measures and showed a longer TTD in the nivolumab/ipilimumab plus PDC group compared with the PDC group, and a greater probability of worsening for patients in the PDC group. Based on these data, pERC concluded that QoL was maintained among the patients treated with nivolumab/ipilimumab plus PDC compared to PDC alone in the trial.

pERC deliberated on patient input from two patient advocacy groups. The input received indicated that patients value a new treatment that is durable and longer lasting, limits the duration of chemotherapy and reduces side effects, delays disease progression, improves disease symptoms, and improves QoL. In considering these values, pERC discussed that nivolumab/ipilimumab plus PDC offers an additional effective treatment option for patients with metastatic NSCLC with no known EGFR or ALK tumour aberrations, and may be particularly appealing to subgroups of patients who prefer to limit their exposure to chemotherapy, which may include patients who are elderly and/or have comorbidities and those with

non-squamous NSCLC who want to avoid maintenance therapy with pemetrexed. In addition, pERC concluded that nivolumab/ipilimumab plus PDC also provides a treatment option that improves OS, delays disease progression, maintains QoL, and has manageable toxicities.

pERC concluded there is a net overall clinical benefit of nivolumab/ipilimumab plus two cycles of PDC compared to PDC alone as first-line treatment of patients with metastatic and recurrent NSCLC with no known EGFR or ALK tumour aberrations based on clinically meaningful improvements in OS and PFS, maintenance of QoL, and manageable toxicities.

pERC deliberated on the cost-effectiveness of nivolumab/ipilimumab plus PDC compared with PDC, pembrolizumab monotherapy, pembrolizumab plus chemotherapy, and pembrolizumab plus PDC for patients with previously untreated metastatic or recurrent NSCLC with no known EGFR or ALK genomic tumour aberrations. pERC noted substantial limitations with the indirect comparisons used to inform the economic evaluation, which limited the ability to perform the sequential analysis. As such, pERC concluded that the cost-effectiveness of nivolumab/ipilimumab plus PDC compared with pembrolizumab monotherapy, pembrolizumab plus chemotherapy, and pembrolizumab plus PDC is uncertain. Based on the existing clinical evidence, pERC considered that the comparison based on the extrapolated CheckMate 9LA trial data represented a more appropriate comparison. pERC concluded that nivolumab/ipilimumab plus PDC was associated with more incremental costs and quality-adjusted life years (QALYs) than PDC and that nivolumab/ipilimumab plus PDC was not cost-effective versus PDC at the submitted price given a willingness-to-pay threshold of $50,000 per QALY gained. To be considered cost-effective at a willingness-to-pay threshold of $50,000 per QALY gained, a price reduction of 28% for both nivolumab and ipilimumab would be required. Given the level of uncertainty associated with the economics findings, pERC considered that a greater price reduction may be required to improve the likelihood that nivolumab/ipilimumab plus PDC is a cost-effective treatment. pERC noted the evidence was applicable to the reimbursement request population and Health Canada-approved population.

pERC also discussed the budget impact analysis. pERC considered the estimated budget impact to be associated with substantial uncertainty and noted that the budget impact is highly sensitive to assumptions regarding which treatments would be displaced, drug wastage, treatment regimen dosing, and drug costs.

pERC also deliberated on the input from the PAG regarding factors related to currently funded treatments, the eligible population, implementation factors, and sequencing and priority of treatment. Refer to the summary table in Appendix 1 for more details.

Upon reconsideration of the Initial Recommendation, pERC reviewed the feedback received from all eligible stakeholder groups and focused its deliberation on the feedback received from the PAG, which was the only stakeholder group that did not fully support early conversion of the Initial Recommendation to a Final Recommendation. PAG sought clarity on whether re-treatment with nivolumab/ipilimumab would be limited to nivolumab monotherapy, and requested additional clarifications related to the eligible patient population (i.e., patients with ROS-1 mutations) and the frequency of imaging for pseudoprogression. A summary of pERC's deliberations related to each issue is provided in the summary table in Appendix 1.

EVIDENCE IN BRIEF

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

- a pCODR systematic review
- other literature in the Clinical Guidance Report that provided clinical context
- an evaluation of the sponsor's economic model and budget impact analysis
- guidance from the pCODR clinical and economic review panels
- input from two patient advocacy groups (Lung Cancer Canada [LCC] and Lung Health Foundation [LHF])
- input from two registered clinician groups (Cancer Care Ontario [CCO] Lung Drug Advisory Committee [DAC] and LCC)
- input from CADTH's PAG.

Feedback on the pERC Initial Recommendation was also provided by:

- one patient advocacy group, [LCC]
- two clinician groups, [CCO Lung DAC and LCC]
- PAG
- the sponsor (Bristol-Myers Squibb Canada).

The pERC Initial Recommendation was to conditionally recommend reimbursement of nivolumab/ipilimumab plus PDC for the first-line treatment of adult patients with metastatic or recurrent NSCLC with no known EGFR or ALK genomic tumour aberrations. Feedback on the pERC Initial Recommendation indicated that the patient group, both clinician groups and the sponsor all agreed with the recommendation and supported early conversion to a Final Recommendation. The PAG agreed in part with the recommendation and did not support early conversion.

The pERC Chair and pERC members reviewed the feedback, and it was determined that the pERC Initial Recommendation was not eligible for early conversion to a pERC Final Recommendation due to PAG's requests for clarification on re-treatment and the eligible patient population.

OVERALL CLINICAL BENEFIT

pCODR Review Scope

The purpose of the review is to evaluate the safety and efficacy of nivolumab/ipilimumab and two cycles of PDC compared with standard of care for the first-line treatment of adult patients with metastatic or recurrent NSCLC with no known EGFR or ALK genomic tumour aberrations.

Studies Included: One International, Open-Label, Phase III RCT

The pCODR systematic review included one trial, CheckMate 9LA, which is an ongoing, international, multi-centre, open-label, active-controlled, phase III trial evaluating the efficacy and safety of nivolumab/ipilimumab plus PDC compared with PDC alone in patients with metastatic or recurrent NSCLC.

Eligible patients included adults (≥ 18 years) with stage IV or recurrent NSCLC without the presence of known EGFR mutations or ALK alterations, an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1, no prior history of systemic therapy for locally advanced or metastatic disease, and a life expectancy of at least three months. Patients were eligible regardless of their histology (squamous or non-squamous) or PD-L1 expression status. Patients with known EGFR mutations or ALK translocations, untreated CNS metastases, and prior systemic therapy for locally advanced or metastatic disease were excluded.

Patients were randomized 1:1 to receive either nivolumab/ipilimumab plus PDC or PDC alone. Patients in the nivolumab/ipilimumab plus PDC group were administered nivolumab at 360 mg IV every three weeks and ipilimumab at 1 mg/kg IV every six weeks; treatment was permitted until disease progression or unacceptable toxicity for up to 24 months. Two cycles of histology-based PDC were administered every three weeks as follows:

- squamous histology: carboplatin area under the concentration time curve (AUC) 6 IV plus paclitaxel at 200 mg/m^2 IV or 175 mg/m^2 IV as per local institutional practice
- non-squamous histology: carboplatin AUC 5 or 6 IV plus pemetrexed at 500 mg/m^2 IV or cisplatin at 75 mg/m^2 IV plus pemetrexed at 500 mg/m^2 IV.

Patients randomized to the PDC group received four cycles of platinum chemotherapy based on their histology in the same manner as was prescribed to patients in the nivolumab/ipilimumab plus PDC group. In addition, non-squamous patients were provided the option of receiving pemetrexed maintenance after completion of the four cycles of chemotherapy. Treatment crossover was not permitted. Patients in the nivolumab/ipilimumab plus PDC treatment group who experienced disease progression (based on investigator assessment) were permitted to continue receiving nivolumab/ipilimumab (up to month 24) provided they had no rapid disease progression, had stable performance status, and were considered by the investigator to be clinically benefiting from and tolerating the treatment.

The median duration of treatment was 6.1 months (range, 0 to 23.5) for patients in the nivolumab/ipilimumab plus PDC group and 2.4 months (range, 0 to 24.0) in the PDC group. [redacted] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*

Randomization was conducted centrally, and patients were stratified based on histology (squamous, non-squamous), sex (male, female), and PD-L1 status (< 1%, ≥ 1%). Patients for whom PD-L1 status was recorded as "not quantifiable" were eligible to enrol in the trial and were stratified into the PD-L1 less than 1% category.

Patient Populations: Median Age 65 Years; Majority of Patients ECOG PS of 1, Non-Squamous NSCLC, and PD-L1 Expression Less Than 1%

A total of 719 patients were randomized in the CheckMate 9LA trial with 361 randomized to the nivolumab/ipilimumab plus PDC group and 358 to the PDC group. Demographic and disease characteristics at baseline were balanced between the treatment groups except for the percentage of patients with liver metastases, which was lower in the nivolumab/ipilimumab plus PDC group (18.8%) compared to the PDC group (24.0%). The median age of patients in both groups was 65 years. Most patients were white (88.7%), male (70.1%), from Europe (59.1%), had an ECOG PS of 1 (68.4%), were classified as current or former smokers (86.2%), had non-squamous NSCLC (68.8%), and stage IV disease (92.9%). In terms of PD-L1 expression, the percentage of patients with PD-L1 expression less than 1%, 1% to 49%, and 50% or greater were 36.7%, 32.4%, and 24.1%, respectively. The majority of patients (93.5%) had not received any prior systemic therapy for their cancer. Of the patients who had received prior systemic therapy (6.5%), there were no notable differences between the treatment groups in the use or type of systemic therapies used in the adjuvant ([redacted]) or neoadjuvant ([redacted]) setting. Except for two patients in the PDC group, all patients had received prior systemic therapy at least six months before randomization in the CheckMate 9LA trial. *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*

Key Efficacy Results: Superiority of Nivolumab/Ipilimumab Plus PDC Over PDC Alone Across All Efficacy Outcomes

Efficacy results were reported based on a pre-specified interim analysis (DBL: October 3, 2019) that was performed at a minimum follow-up of 8.1 months. An updated analysis (DBL: March 9, 2020) was also performed based on a minimum follow-up of 12.7 months; this analysis was not pre-specified in the trial protocol.

The key efficacy outcome deliberated on by pERC included OS, the primary end point of the trial, and pre-specified secondary end points, including PFS and ORR by BICR, and exploratory end points including health-related QoL (HRQoL) and safety.

At the interim analysis (DBL: October 3, 2019), the trial met its primary end point based on the pre-specified threshold for superiority and the interim analysis is considered the primary analysis of the trial. At the primary analysis, the median OS was 14.1 months (95% CI, 13.24 to 16.16) in the nivolumab/ipilimumab plus PDC group compared with 10.7 months (95% CI, 9.46 to 12.45) in the PDC group, demonstrating a statistically significant prolongation in OS with nivolumab/ipilimumab plus PDC over PDC alone (HR = 0.69; 95% CI, 0.55 to 0.87; P = 0.0006).

At the updated analysis, which provided an additional 4.6 months of follow-up, the assessment of OS showed consistent results and a sustained OS benefit for nivolumab/ipilimumab plus PDC over PDC (hazard ratio [HR] = 0.66; 95% CI, 0.55-0.80).

The OS benefit with nivolumab/ipilimumab plus PDC was observed regardless of histology or PD-L1 expression level. The majority of other pre-specified subgroup analyses of OS also showed an OS benefit of nivolumab/ipilimumab plus PDC over PDC alone at both the primary and updated data analyses, except for patients aged 75 years or older, of other race, who never smoked, or had non-quantifiable PD-L1 status. However, the findings of subgroup analyses should be interpreted with caution due to the exploratory nature of the analyses and the small sample sizes in some groups.

All secondary efficacy end points assessed in the trial demonstrated superior treatment efficacy of nivolumab/ipilimumab plus PDC compared to PDC alone:

- PFS by BICR assessment:
    - At the primary analysis, median PFS was 6.83 months (95% CI, 5.55 to 7.66) in the nivolumab/ipilimumab plus PDC group and 4.96 months (95% CI, 4.27 to 5.55) in the PDC group (HR = 0.70; 95% CI, 0.57 to 0.86; P = 0.0001).
    - At the updated analysis, the clinical benefit with nivolumab/ipilimumab plus PDC was maintained; median PFS was longer in the nivolumab/ipilimumab plus PDC group at 6.74 months (95% CI, 5.55 to 7.75) and 4.96 months (95% CI, 4.27 to 5.55) in the PDC group (HR = 0.68; 95% CI, 0.57 to 0.82).
- ORR by BICR assessment:
    - At the primary analysis, the ORR was 37.7% (95% CI, 32.7% to 42.9%) in the nivolumab/ipilimumab plus PDC group and 25.1% in the PDC group (95% CI, 20.7% to 30.0%; P = 0.0003).
    - At the updated analysis, the ORR remained higher in the nivolumab/ipilimumab plus PDC group at 38.2% (95% CI, 33.2% to 43.5%) compared to 24.9% in the PDC group (95% CI, 20.5% to 29.7%).

Patient-Reported Outcomes: No Clinically Meaningful Differences in QoL Measures in Either Treatment Group Based on Mean Changes From Baseline

HRQoL was assessed in the trial using the Average Burden Symptom Index (ABSI) and three-Item Global Index (3-IGI) scale of the Lung Cancer Symptom Scale (LCSS), as well as the EuroQol 5-Dimensions 3-Levels (EQ-5D-3L) utility index (UI) and visual analogue scale (VAS). Completion rates for the LCSS questionnaire were greater than 90% at baseline and declined over time but remained at a rate of 80% or more at most on-treatment assessments with sufficient data (defined in the trial as ≥ 10% patients). Compliance was lower during the follow-up period, with compliance rates ranging from 60% to 72% in both treatment groups. Similar compliance rates were observed for the EQ-5D-3L (VAS and UI). The results presented are based on the updated analysis and were based on descriptive analyses that did not include an assessment of between-group differences.

At baseline, patients in the nivolumab/ipilimumab plus PDC group had slightly lower (i.e., less symptom burden) mean LCSS ABSI scores compared with patients in the PDC group. At on-treatment assessment timepoints, LCSS ABSI scores decreased in both treatment groups, indicative of improved lung cancer symptoms; however, the minimal clinically important difference (MID) of 10 points was not reached in either treatment group at any time point. Similarly, the 3-IGI, which is a 3-item scale that includes items of symptom distress, interference with activity level, and HRQoL showed trends of improvement in both treatment groups as the mean change from baseline increased over time; however, the MID of 30 was not reached in either treatment group.

Mean EQ-5D UI scores were similar in the treatment groups at baseline. At on-treatment assessment timepoints, EQ-5D UI scores improved in both groups but the mean changes from baseline did not exceed

the MID of 0.08 in either treatment group, [redacted]. At both follow-up visit time points, the mean change in EQ-5D UI scores numerically decreased in both treatment groups indicating worsening of patients' overall health status. *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*

At baseline, the mean EQ-5D VAS scores were slightly higher (i.e., better overall self-rated health) among patients in the nivolumab/ipilimumab plus PDC group compared with patients in the PDC group. At on-treatment assessment timepoints, VAS scores increased in both treatment groups through to week 84 in the nivolumab/ipilimumab plus PDC group and through to week 78 in the PDC group, indicating patients' self-rated health improved in both groups. These improvements from baseline were considered clinically meaningful based on meeting or exceeding the pre-specified MID of 7 points or more at weeks 72 and 84 in the nivolumab/ipilimumab plus PDC group, and at week 72 in the PDC group. At follow-up visit timepoints, the mean change in EQ-5D VAS scores numerically decreased in both treatment groups indicating worsening of patient's self-rated health status.

A TTD analysis was conducted for the ABSI and 3-IGI of the LCSS, and the EQ-5D-3L UI and VAS. The analysis of each scale demonstrated a longer TTD in the nivolumab/ipilimumab plus PDC group compared with the PDC group, and a greater probability of worsening for patients in the PDC group.

Safety: Greater Toxicity Associated With Nivolumab/Ipilimumab Plus PDC, but Toxicity Profile Is Manageable

Safety data were reported for all treated patients (N = 707), including 358 patients in the nivolumab/ipilimumab plus PDC group and 349 patients in the PDC group. Results of safety at the updated analysis were consistent with the primary analysis of safety and no new safety signals were identified for nivolumab/ipilimumab plus PDC at the updated analysis; therefore, results of the updated analysis are presented.

AEs were common in both treatment groups (99.4% in the nivolumab/ipilimumab plus PDC group and 98.0% in the PDC group), with most AEs being of low grade (i.e., grade 1 to grade 2). The most common AEs in the nivolumab/ipilimumab plus PDC group included anemia ([redacted]), nausea ([redacted]), diarrhea ([redacted]), asthenia ([redacted]), and decreased appetite ([redacted]). In the PDC group, the most common AEs were anemia ([redacted]), nausea ([redacted]), asthenia ([redacted]), decreased appetite ([redacted]), and constipation ([redacted]). Nausea and anemia were the most common drug-related AEs in each treatment group, but they occurred in lower frequency in the nivolumab/ipilimumab plus PDC group compared with the PDC group (26.8% versus 35.8% and 23.2% versus 37.8%, respectively). *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*

Overall, more AEs were observed among patients receiving nivolumab/ipilimumab plus PDC compared with PDC alone. The incidences of drug-related AEs (91.6% versus 87.7%), grade 3 or grade 4 AEs (68.4% versus 53.9%), grade 3 or grade 4 drug-related AEs (46.9% versus 37.8%), SAEs (60.1% versus 42.7%), and drug-related SAEs (29.6% versus 17.8%) were all higher in the nivolumab/ipilimumab plus PDC group compared with the PDC group. Neutropenia and anemia were the most common drug-related grade 3 or grade 4 AEs in each treatment group; however, the incidence of neutropenia (6.7% versus 9.2%) and anemia (5.9% versus 14.3%) was lower in the nivolumab/ipilimumab plus PDC group compared with the PDC group. AEs resulting in drug discontinuation occurred in more patients receiving nivolumab/ipilimumab plus PDC compared with patients in the PDC group; 28.2% of patients in the nivolumab/ipilimumab plus PDC group experienced AEs that resulted in drug discontinuation, of which 22.6% were of grade 3 or grade 4. In the PDC group, 17.5% of patients experienced AEs that led to drug discontinuation, of which 12.3% were grade 3 or grade 4.

The trial assessed select AEs, which were defined in the trial as AEs with potential immunologic etiology. Most select AEs were low grade (grade 1 to grade 2) and were deemed drug-related by the investigator. Select AEs as well as drug-related select AEs were more frequent in the nivolumab/ipilimumab plus PDC group compared with the PDC group. In the nivolumab/ipilimumab plus PDC group, the most common grade 3 to grade 4 select AEs were reported as gastrointestinal (5.6%) and skin and hepatic (4.5% each).

Select AEs of any grade in the nivolumab/ipilimumab plus PDC group were resolved in most cases (≥ 68%), except for endocrine events, of which only 39% were resolved.

The assessment of irAEs included events that occurred within 100 days of the last dose of study drug regardless of causality and were reported for all patients requiring immune-modulating medication for treatment of the AE (except for endocrine events which were included in the analysis regardless of treatment because treatment of endocrine events often does not require immunosuppression). Most irAEs were low (grade 1 to grade 2) and were reported in the nivolumab/ipilimumab plus PDC group. Rash ([redacted]), hypothyroidism and/or thyroiditis ([redacted]), hyperthyroidism ([redacted]), pneumonitis ([redacted]), and hepatitis ([redacted]) were the most common any grade irAEs that occurred in the nivolumab/ipilimumab plus PDC group. Hypothyroidism and/or thyroiditis ([redacted]) was the most common irAE in the PDC group. The majority of irAEs in the nivolumab/ipilimumab plus PDC group were managed by instituting established algorithms where resolution of AEs occurred when immune-mediating medications, mostly systemic corticosteroids, were administered. *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*

Deaths related to drug toxicity occurred in seven patients (2.0%) in the nivolumab/ipilimumab plus PDC group and six patients (1.7%) in the PDC group. In the nivolumab/ipilimumab plus PDC group, these deaths were assessed by the investigator to be related to PDC ([redacted]), nivolumab/ipilimumab ([redacted]) and ipilimumab, ipilimumab and PDC, and nivolumab/ipilimumab plus PDC ([redacted]).*(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*

Limitations: Open-Label Design, OS Data Immature, No Comparison to Current Standard of Care

The key limitations and potential sources of bias associated with the CheckMate 9LA trial and supporting evidence included in the submission (i.e., CheckMate 227) are summarized below:

- The open-label study design of the CheckMate 9LA trial allowed for both investigators and patients to be aware of the assigned treatment of patients. OS was the primary end point and is an objective measure that is unlikely to be biased by the open-label study design. For the assessment of key secondary efficacy end points (i.e., PFS, ORR), BICR was implemented to mitigate the potential for bias introduced by this trial design. However, the risk of bias due to lack of blinding is of greater concern for subjective outcomes, including HRQoL and safety, because patient or investigator knowledge of treatment assignment could have influenced the assessment and reporting of these outcomes.
- The testing of some secondary efficacy end points (i.e., PFS and ORR) was adjusted to control for multiplicity and the risk of type I error, although the results of other efficacy end points (i.e., time-to-response, duration of response, efficacy by PD-L1 expression) were not included in the statistical testing hierarchy. There were also many pre-specified subgroup analyses performed for multiple end points. These analyses should be considered exploratory in nature because the trial was not powered to test specific hypotheses in these outcomes and subgroups.
- The OS data from the trial are immature. The updated analysis that was conducted provided an additional 4.6 months of follow-up, and the median duration of follow-up was 12.7 months. This was an unplanned analysis and no statistical considerations were employed to account for multiplicity.
    - Given the short duration of patient follow-up in the CheckMate 9LA trial, data from the CheckMate 227 trial were included in the sponsor's submission as supportive evidence and were used to inform the sponsor's PE model on the long-term efficacy of nivolumab/ipilimumab (without PDC) compared with PDC alone. In this trial, the final analysis of OS in patients with any PD-L1 expression demonstrated superior OS with nivolumab/ipilimumab compared with PDC; however, there was evidence of non-proportional hazards. Patients treated with nivolumab/ipilimumab experienced a slight detriment in OS during the initial months of treatment with nivolumab/ipilimumab but, thereafter, the curves showed a sustained long-term

benefit in OS in favour of nivolumab/ipilimumab over PDC. Similar findings were shown for PFS. Under the assumption of non-proportional hazards, the treatment effect estimates from the trial were interpreted as overall estimates of the average treatment effect. In a positive trial, such estimates may be biased toward overestimating the magnitude of clinical benefit and, in this case, the clinical benefit associated with nivolumab/ipilimumab. The most recent data from the trial, based on 43.1 months of follow-up, show a sustained benefit from treatment with nivolumab/ipilimumab over PDC in patients with PD-L1 of 1% or greater and PD-L1 less than 1%. The trials used similar eligibility criteria and therefore the distributions of most baseline characteristics were similar. Aside from the addition of two cycles of PDC to the combination of nivolumab/ipilimumab, there were notable differences in the treatment regimens evaluated that included the timing and dosing of nivolumab (i.e., a flat dose of 360 mg IV every three weeks in the CheckMate 9LA trial versus a weight-based dose of 3 mg/kg IV every two weeks in the CheckMate 227 trial) and the type of PDC administered to patients with squamous NSCLC. The better survival of the PDC control group in the CheckMate 227 trial, based on one-year survival estimates, suggested differential treatment effects of the PDC regimens used in each trial. Overall, a visual comparison of the KM curves of OS and PFS from each trial showed that the additional short course of PDC added to nivolumab/ipilimumab in the CheckMate 9LA trial addresses the early OS detriment observed in the CheckMate 227 trial. However, in the absence of a direct trial comparison of nivolumab/ipilimumab to nivolumab/ipilimumab plus PDC, equivalent long-term efficacy of the nivolumab/ipilimumab-based regimens cannot be assumed due to differences between the trials and limitations associated with the CheckMate 227 trial.

- Censoring in the analysis of OS, the primary end point, did not take into consideration the use of subsequent therapies that patients received after completion of assigned study treatment. The types of subsequent therapies differed between the groups with the most common subsequent systemic therapy being chemotherapy in the nivolumab/ipilimumab plus PDC group and immunotherapy in the PDC group. It is expected that patients in the PDC group who received subsequent immunotherapy would experience additional clinical benefit, which confounds the analysis of OS and likely underestimates the treatment effect associated with nivolumab/ipilimumab plus PDC compared to PDC alone.
- Patient compliance rates for PRO questionnaires dropped to a low of approximately 72% to 60% over the course of the trial in each treatment group. The number of patients left in the trial who completed assessments at later timepoints are likely not representative (i.e., have better HRQoL) of all patients randomized in each treatment group. In this scenario, data are not missing at random because patients who left the trial are likely sicker or have died; therefore, the results at later timepoints are likely biased. In addition, there is currently no established MID to guide the analysis and interpretation of data using the LCSS ABSI in patients with metastatic NSCLC. It is unclear if the threshold used in the trial (i.e., MID of 10 points) is appropriate and reflective of a clinically meaningful change in outcome in the trial population.
- The CheckMate 9LA trial compared nivolumab/ipilimumab plus PDC with PDC alone. Pembrolizumab, with or without PDC, is currently considered the standard of care in Canada for the treatment of patients with metastatic or recurrent NSCLC with no EGFR or ALK genomic tumour aberrations; therefore, PDC is not the most relevant treatment comparator.

Comparator Information: ITC of Nivolumab/Ipilimumab Plus PDC Compared With Pembrolizumab-Based Regimens

In the absence of direct trial evidence, the sponsor submitted an ITC that compared the efficacy of nivolumab/ipilimumab plus PDC to standard-of-care immunotherapy-based treatments currently funded in Canada. The ITC provided the comparative efficacy inputs for the sponsor's PE model in order to evaluate the cost-effectiveness and budget impact of nivolumab/ipilimumab plus PDC compared with other currently funded treatments in Canada. Individual ITCs performed were based on the pivotal CheckMate 9LA trial of nivolumab/ipilimumab plus PDC and four comparator trials contributing to three comparisons: pembrolizumab plus PDC in patients with non-squamous NSCLC (KEYNOTE 189), pembrolizumab plus PDC in squamous NSCLC patients (KEYNOTE 407), and pembrolizumab monotherapy in high PD-L1 expression (≥ 50%) and mixed histology NSCLC patients (KEYNOTE 024 and KEYNOTE 042). The data from the full intention-to-treat population from the CheckMate 9LA trial were used in the ITCs despite patient population differences compared with the comparator trials with respect to PD-L1 expression level and histology; this was based on the assumption that histology and PD-L1 expression levels do not modify

treatment effect. The primary ITC results showed comparable, statistically non-significant differences in OS, PFS, and ORR when nivolumab/ipilimumab plus PDC was compared with immunotherapy-based treatment for each comparison. In sensitivity analyses, the results did not change significantly when data from the CheckMate 9LA trial based on PD-L1 expression (≥ 1%, < 1%) and histology were used (non-squamous and squamous). Given the identified limitations of the ITC, which include heterogeneity of study populations, differential treatment effects in the common comparator of chemotherapies, varied trial designs, and lengths of follow-up, the findings of the ITC should be interpreted with caution.

Need and Burden of Illness: Incurable Disease; Need for Additional Treatment Options That Offer Patient Choice

Lung cancer represents the second most common cause of cancer among both men and women in Canada but the largest cause of death from cancer. In 2020, it is estimated there will be approximately 29,800 new cases of lung cancer and 21,200 deaths from the disease. Approximately 85% of these cases are classified as NSCLC and in approximately 70% of these cases, the histologic subtype is adenocarcinoma. Approximately 50% of NSCLC patients have stage IV disease at the time of presentation, with another 20% to 25% presenting with locally advanced stage III disease. Only 20% to 25% of patients present with early stage disease amenable to surgical resection. The incidence of NSCLC rises with age, and the median age at diagnosis is 70 years. Given the high proportion of patients presenting with advanced stage of disease, the expected five-year survival is only 19%.

Recent advances in molecular profiling of NSCLC have demonstrated the presence of underlying molecular (oncogenic) drivers. The most frequent molecular abnormalities include mutations of the EGFR gene and translocations of the ALK gene. These two abnormalities are distinct subgroups of lung adenocarcinomas, with a combined frequency of approximately 20%. Oral TKIs targeting the underlying molecular abnormality represent the most effective initial treatment for these subgroups of NSCLC. However, most patients with metastatic NSCLC have tumours without targetable molecular abnormalities, thus treatment for these patients is dependent on tumour histology and expression of PD-L1. Multiple randomized trials have established immune checkpoint inhibitor therapy, either alone or in combination with chemotherapy, as the standard of care for the initial management of locally advanced or metastatic NSCLC. Pembrolizumab trial data have demonstrated the extension of median survival from approximately one year up to approximately 18 months or 24 months, and approximately one in three patients remain alive at three years. Despite these improvements in survival, locally advanced or metastatic NSCLC is still considered an incurable illness, and better therapies are needed that not only offer more effective and/or less toxic treatment options but provide patients with options to best meet their individual needs and preferences.

Registered Clinician Input: Nivolumab/Ipilimumab Plus PDC Is an Additional Treatment Choice Offering Limited Exposure to Chemotherapy

Two registered clinician inputs were provided to inform CADTH's appraisal of nivolumab/ipilimumab plus PDC: two clinicians provided input on behalf of CCO Lung Drug Advisory Committee (DAC) and 15 clinicians provided input on behalf of LCC. Registered clinicians reported that the standard of care in the first-line treatment setting for NSCLC with no EGFR or ALK genomic tumour aberrations varies based on PD-L1 level and histology. For tumours with unknown or any PD-L1 expression level, four to six cycles of PDC plus pembrolizumab is typically administered. For squamous histologies, the PDC administered is carboplatin and paclitaxel followed by pembrolizumab maintenance. For non-squamous histologies, the PDC administered is cisplatin or carboplatin plus pemetrexed followed by pembrolizumab and pemetrexed maintenance. For tumours with a PD-L1 expression level of 50% or greater, pembrolizumab monotherapy is another funded treatment option. Both clinician groups indicated that nivolumab/ipilimumab plus PDC serves as an alternative first-line treatment option for patients with newly diagnosed metastatic NSCLC without a driver mutation or for patients without contraindications to immunotherapy. The LCC clinicians indicated they would be most interested in offering nivolumab/ipilimumab plus PDC to the PD-L1 negative patient population; whereas the CCO clinicians indicated a preference for use in patients pre-treated with durvalumab. Both clinician groups highlighted the favourability of nivolumab/ipilimumab plus PDC for patients seeking to minimize the duration and associated toxicity of chemotherapy due to the reduced number of chemotherapy cycles. Regarding the preferential use of nivolumab/ipilimumab plus PDC among currently available treatment options, the CCO clinicians specified that patient choice and desire to avoid an additional two cycles of chemotherapy are justifying factors for preferential administration. The LCC clinicians stated that most clinicians would administer pembrolizumab monotherapy to patients with tumours that have high PD-L1 expression of 50% or greater. However, an exception to this practice may include patients with a heavy disease burden in which achieving an objective response early in the

treatment course is highly desirable (where both pembrolizumab and pembrolizumab plus chemotherapy are available in the PD-L1 highly expressing patient population). Patients with tumours that have PD-L1 expression less than 50% would be administered chemotherapy plus immunotherapy for the benefits of the latter.

PATIENT-BASED VALUES

Values of Patients With Metastatic NSCLC: Disease Symptoms Affect QoL; Preference for Durable Treatment Options That Limit Chemotherapy

Two patient groups, LCC and the LHF, provided input to inform CADTH's appraisal of nivolumab/ipilimumab plus PDC. LCC submitted information from two previous pCODR reviews of chemotherapy and immunotherapy, as well as input from two female patients located in Canada who were diagnosed with stage IV NSCLC. The LHF provided input based on one phone interview with a female patient from Ontario. Both patient groups were unable to contact patients with treatment experience with nivolumab/ipilimumab plus PDC; however, LCC reported on the experience of two patients treated with nivolumab/ipilimumab without PDC. Patients highlighted several important symptoms of the disease that affect QoL including fatigue, weight loss, severe cough, difficulty breathing, and pleural effusion. Chemotherapy, immunotherapy, or a combination of both are often the standard of care in advanced NSCLC without EGFR mutations or ALK translocations. According to patients, chemotherapy treats the cancer but has well-known side effects such as nausea, vomiting, and fatigue, which vary in severity depending on the dose. Durability of treatment is a concern among patients as many patients respond to chemotherapy but subsequently progress and require additional treatment. Further, the hematologic toxicity associated with chemotherapy lowers patients' immunity and limits their social activities. Patients indicated a desire to not undergo chemotherapy longer than necessary; LCC specified durability of treatment as an unmet need for NSCLC patients who are not treated with targeted therapies. Immunotherapy was reported by patients to be associated with fewer side effects compared with chemotherapy. Most patients providing input reported immunotherapy-related side effects to be mild, tolerable, and easily managed with little interference with daily life, and chemotherapy and immunotherapy combination treatment with a pembrolizumab-based regimen was noted to improve disease symptoms (e.g., pleural effusion) and control the disease with manageable side effects.

Patient Values on Treatment: Reduce Symptoms and Side Effects, Delay Disease Progression, and Improve QoL

Overall, patients expressed a desire for new treatments that reduce or eliminate symptoms (e.g., pain, fatigue, nausea, and shortness of breath); stop, slow, or delay disease progression; and improve appetite and QoL to a state that enables patients to function independently. Among the two patients who had experience with nivolumab/ipilimumab (not in combination with PDC), one patient received nivolumab/ipilimumab for one year but discontinued due to health issues related to their pancreas but has remained stable and has not received treatment for their lung cancer since nivolumab/ipilimumab was discontinued. The other patient completed a two-year trial of nivolumab/ipilimumab and has only received radiation therapy for metastasis to the brain since then but is considered stable following discontinuation of the combination. Both patients developed occasional fatigue while receiving nivolumab/ipilimumab that did not affect their daily activities, and both indicated they were able to be independent, functional, and physically active.

ECONOMIC EVALUATION

The sponsor's assumed dosing regimen for nivolumab is 4.5 mg/kg, up to a maximum of 360 mg, which should be administered as an IV infusion every three weeks. Ipilimumab should be administered at a dose of 1 mg/kg as an IV infusion every six weeks. Two cycles of PDC should be administered three weeks apart. After the completion of PDC, treatment with nivolumab/ipilimumab should continue until disease progression, unacceptable toxicity, or for a maximum of 24 months in patients without disease progression. At the sponsor's submitted prices for nivolumab ($782 per 40 mg vial and $1,955 per 100 mg vial) and ipilimumab ($5,800 per 50 mg vial), with two cycles of PDC ($646 each), the total cost per treatment cycle is $16,178.

The sponsor submitted a cost-utility analysis comparing nivolumab/ipilimumab plus PDC versus four treatment comparators (PDC alone, pembrolizumab monotherapy, pembrolizumab plus PDC, and

pembrolizumab plus chemotherapy) for adults with untreated metastatic or recurrent NSCLC with no known EGFR or ALK genomic tumour aberrations. The sponsor's partitioned survival model comprised three health states characterized by PFS, progressed disease, and death. Time spent in each state was based on direct modelling of OS and PFS curves, which the sponsor extrapolated over the time horizon of the analysis using parametric methods. In the model, the patient may also discontinue treatment, at which point the cost of treatment is no longer incurred. Duration on treatment (DoT) was assumed equal to PFS. The CheckMate 9LA trial and CheckMate 227 trial were used to inform treatment efficacy for nivolumab/ipilimumab plus PDC and PDC alone. An ITC was used to inform the comparison to all pembrolizumab-based regimens.

CADTH identified the following key limitations with the sponsor's submitted economic analysis:

- The CADTH Clinical Review identified several limitations with the sponsor-submitted ITC and concluded that applicability of the ITC results must be interpreted with caution.
- Trial-observed DoT for each comparator and feedback from clinical experts consulted by CADTH indicated that PFS overestimates DoT.
- The CADTH Clinical Review identified concerns regarding the generalizability of data from the CheckMate 227 trial to represent long-term treatment outcomes for patients in the CheckMate 9LA trial.
- The modelled dosage assumption did not align with the nivolumab product monograph and with the vial sharing assumptions, leading to an underestimation of the cost per dose of nivolumab plus ipilimumab.
- The sponsor's assumptions regarding drug wastage for ipilimumab was felt to be substantially underestimated for ipilimumab based on clinical expert and CADTH-participating drug plan feedback.
- The sponsor's model had limited flexibility to allow CADTH to test the sensitivity of treatment outcomes.

CADTH undertook a reanalysis that excluded indirect comparisons, used product monograph dosing for nivolumab, included no vial sharing for nivolumab or ipilimumab, used a revised approach for modelling DoT, and based OS extrapolations exclusively from the CheckMate 9LA trial data.

According to CADTH's reanalyses, the incremental cost-effectiveness ratio (ICER) for nivolumab/ipilimumab plus PDC compared with PDC alone was $146,827 per additional QALY gained ($73,063 incremental costs, 0.50 incremental QALYs). CADTH undertook a scenario analysis to estimate the cost-effectiveness of nivolumab/ipilimumab plus PDC compared with PDC, pembrolizumab monotherapy, pembrolizumab plus chemotherapy, and pembrolizumab plus PDC. Based on the sequential analyses, nivolumab/ipilimumab plus PDC was more costly and produced more QALYs than PDC, pembrolizumab monotherapy, and pembrolizumab plus chemotherapy. In this scenario, nivolumab/ipilimumab plus PDC was not cost-effective as it was extendedly dominated through pembrolizumab monotherapy and pembrolizumab plus PDC (i.e., treatment has a higher ICER compared with the previous cost-effective treatment and the next more effective treatment). At a willingness-to-pay threshold of $50,000 per QALY gained, a price reduction of 28% for both nivolumab and ipilimumab is required for nivolumab/ipilimumab plus PDC to be considered cost-effective.

Due to structural or data limitations, CADTH was unable to address the uncertainty associated with the sponsor's ITC, methodological limitations in the derivation of survival outcomes for select comparators and the omission of relevant treatment comparators. Therefore, results of the CADTH analysis should be interpreted with caution.

ADOPTION FEASIBILITY

Considerations for Implementation and Budget Impact: Budget Impact Is Highly Uncertain
pERC also discussed the budget impact analysis and noted that the factors with the greatest influence on the estimated budget impact were the estimated treatment duration, treatment costs, and assumptions regarding treatment displacement. pERC noted that the CADTH reanalyses ranged from a cost savings of $83,230,349 to an incremental cost of $20,508,252 over a three-year period.

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. Maureen Trudeau, Oncologist (Chair)
Dr. Catherine Moltzan, Oncologist (Vice-Chair)
Daryl Bell, Patient Member
Dr. Jennifer Bell, Bioethicist
Dr. Kelvin Chan, Oncologist
Dr. Michael Crump, Oncologist
Dr. Matthew Cheung, Oncologist
Dr. Winson Cheung, Oncologist
Dr. Avram Denburg, Pediatric Oncologist
Dr. Leela John, Pharmacist
Dr. Anil Abraham Joy, Oncologist*
Dr. Christine Kennedy, Family Physician
Dr. Christian Kollmannsberger, Oncologist
Dr. Christopher Longo, Health Economist
Cameron Lane, Patient Member
Valerie McDonald, Patient Member
Dr. Marianne Taylor, Oncologist
Dr. W. Dominika Wranik, Health Economist

*No longer a member of the CADTH pERC.

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

- Dr. Kelvin Chan and Dr. Matt Cheung, who were not present for the discussion of nivolumab/ipilimumab plus PDC during the meeting
- Dr. Anil Abraham Joy, who was excluded from voting due to a conflict of interest
- Dr. Maureen Trudeau, who did not vote due to her role as the pERC Chair.

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

- Dr. Maureen Trudeau, who did not vote due to her role as the pERC Chair.

Avoidance of conflicts of interest

All members of the CADTH 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 CADTH website and pERC members have an obligation to disclose conflicts on an ongoing basis. For the review of nivolumab/ipilimumab plus PDC, through their declarations, one member had a real, potential, or perceived conflict and based on application of the *pCODR Conflict of Interest Guidelines*, this member was excluded from voting on the Initial Recommendation.

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 PAG 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 CADTH 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*. Bristol-Myers Squibb as the primary data owner, did not agree to the disclosure of some data from the CheckMate 9LA trial; therefore, this information has been redacted in this recommendation and publicly available guidance reports.

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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Redactions: Confidential information in this document has been redacted at the request of the sponsor in accordance with the *pCODR Disclosure of Information Guidelines*.

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.

APPENDIX 1: CADTH pCODR RESPONSES TO PAG IMPLEMENTATION QUESTIONS

PAG implementation questions	pERC recommendation
Eligible patient population	
• Clarity on whether the following patients would be eligible for treatment with nivolumab/ipilimumab plus PDC:	
○ Patients with PS ≥ 2	○ Clinicians routinely extrapolate trial evidence to patients with an ECOG PS of 2, and previous lung cancer CADTH submissions have generalized recommendations to an ECOG PS of 2. However, pERC agreed with the CGP that nivolumab/ipilimumab plus PDC should not be offered to patients with an ECOG PS of 3 or 4.
○ Patients with no PD-L1 results	○ In the CheckMate 9LA trial, the clinical benefit of nivolumab/ipilimumab plus PDC was observed in patients with all levels of PD-L1 expression. Therefore, pERC agreed that patients with no PD-L1 results would also be eligible for nivolumab/ipilimumab plus PDC.
○ Patients with untreated CNS metastases	○ The CheckMate 9LA trial excluded patients with untreated brain metastases. However, the CGP noted, patients with asymptomatic brain metastases have been included in other trials of immunotherapy in NSCLC. Therefore, pERC agreed with the CGP that patients with asymptomatic brain metastases should be eligible for nivolumab/ipilimumab plus PDC.
○ Patients with stage IIIB NSCLC	○ The CheckMate 9LA trial included patients with stage IIIB NSCLC who were not candidates for radical treatment; therefore, these patients would be eligible for nivolumab/ipilimumab plus PDC.
○ Patients with non-metastatic or non-recurrent disease that is not amenable to resection	○ pERC agreed with the CGP that patients with non-metastatic or non-recurrent disease that is not amenable to resection or radical radiation should be eligible for nivolumab/ipilimumab plus PDC.
○ Patients who have experienced disease progression on anti-PD-L1 therapy (e.g., durvalumab) for stage III NSCLC, or who have experienced disease progression on chemotherapy for stage III NSCLC within 6 months of completion, or for stage III NSCLC who have experienced disease progression after 6 months of completion	○ pERC agreed with the CGP that patients with stage III NSCLC progressing on consolidation durvalumab, or within 6 months of completion of durvalumab would not be eligible for nivolumab/ipilimumab plus PDC. However, patients who have experienced disease progression after 6 months from the completion of durvalumab should be eligible for nivolumab/ipilimumab plus PDC to be consistent with other funded immunotherapy regimens (i.e., pembrolizumab).
○ Patients who progressed on maintenance pemetrexed in the non-squamous setting	○ pERC agreed with the CGP that patients who progressed on maintenance pemetrexed would not be eligible for nivolumab/ipilimumab plus PDC as they would already have received initial PDC for locally advanced and/or metastatic disease.

○ Patients with rare subtypes of lung cancer (e.g., typical or atypical carcinoid).	○ pERC agreed with the CGP that patients with typical or atypical carcinoid tumours should not be eligible for nivolumab/ipilimumab plus PDC as these subtypes of lung cancer are treated differently than NSCLC. However, patients with large cell neuroendocrine tumours or other uncommon subtypes of NSCLC should be eligible if they are being treated with a NSCLC treatment regimen.
• Guidance on whether specific subgroups of patients defined by PD-L1 expression (≥ 50%, any, unknown, or other) or histology (squamous vs. non-squamous) should be treated differently.	• Patients with PD-L1 expression ≥ 50% are most commonly treated with pembrolizumab monotherapy. However, these patients are eligible for pembrolizumab in combination with platinum-based chemotherapy. Therefore, pERC agreed with the CGP that they should also be eligible for nivolumab/ipilimumab plus PDC.
• Confirmation that other driver mutations (e.g., ROS-1, NTRK) should also be excluded when results are available.	• The CheckMate 9LA trial excluded patients with EGFR mutations and ALK translocations; therefore, pERC agreed with the CGP that these patients should not be eligible for nivolumab/ipilimumab plus PDC. However, the trial did not exclude patients with other rare molecular abnormalities (e.g., ROS-1, NTRK), and therefore pERC agreed with the CGP that these patients should be eligible for nivolumab/ipilimumab plus PDC. ○ In response to PAG's feedback on the Initial pERC Recommendation requesting clarity on the eligibility of patients with ROS-1 mutations, and whether their inclusion is consistent with pERC's recommendations on pembrolizumab in this setting: During reconsideration of the Initial Recommendation, pERC acknowledged the inconsistency in the recommendations with respect to the inclusion of ROS-1 patients. However, pERC noted that based on the eligibility criteria of all the trials informing these recommendations, only patients with EGFR mutations and ALK rearrangements were excluded. pERC also noted that most provincial jurisdictions have only restricted funding for pembrolizumab for patients with EGFR and ALK molecular abnormalities. Therefore, pERC agreed with the CGP that the only patients who should be considered ineligible for nivolumab/ipilimumab plus PDC are those who were specifically excluded from the CheckMate 9LA trial (i.e., patients with EGFR mutations and ALK rearrangements), and patients with ROS-1 mutations should be eligible for nivolumab/ipilimumab plus PDC.
Implementation factors	
• After 2 cycles of induction treatment, nivolumab/ipilimumab treatment (nivolumab 360 mg IV every 3 weeks and ipilimumab 1 mg/kg IV every 6 weeks) will continue until disease progression, unacceptable toxicity, or other reasons. PAG would like clarification of "disease progression" and "other reasons" for discontinuation.	• pERC agreed with the CGP that criteria for disease progression and treatment discontinuation should follow standard RECIST and iRECIST criteria.
• Patients in the CheckMate 9LA trial were treated with	• At the outset of nivolumab/ipilimumab therapy, a patient should be a candidate for two cycles of PDC to be eligible for

nivolumab/ipilimumab for a maximum of 2 years. PAG is looking for confirmation that the patient must be a suitable candidate for 2 cycles of PDC before being considered for nivolumab/ipilimumab therapy.	this regimen. pERC agreed with the CGP that in cases where a patient experiences a major toxicity from the initial cycle of PDC, particularly if that results in hospitalization, then there should be a process to proceed with nivolumab/ipilimumab without the need to administer a second cycle of PDC.
• Guidance on the adequacy of alternate weight-based dosing for nivolumab (4.5 mg/kg) with or without a cap of 360 mg. PAG noted that q.3.w dosing and the 360 mg fixed dose both differ from approved nivolumab monotherapy regimens (flat 240 mg every 2 weeks or 480 mg every 4 weeks) and may cause confusion.	• The trial evaluated nivolumab in a fixed dose of 360 mg every 3 weeks. The CGP noted that this is not one of the approved dosing schedules but represents the same average dose intensity. pERC noted that there is no direct evidence to suggest that flat dosing is superior to weight-based dosing. However, for many patients, flat dosing results in a larger dose and greater cost. Jurisdictions will need to choose between administering nivolumab as a flat dose of 360 mg every 3 weeks as per the CheckMate 9LA trial, or according to the approved dosing regimens for nivolumab monotherapy.
• Information on the use of nivolumab/ipilimumab in combination with other chemotherapy regimens (e.g., non-platinum-based regimens).	• There is no evidence for the use of nivolumab/ipilimumab in combination with other non-platinum regimens. Accordingly, pERC agreed with the CGP that nivolumab/ipilimumab should not be used in combination with non-platinum doublets or single-agent chemotherapy. However, the CGP noted that platinum and gemcitabine have been combined with durvalumab plus tremelimumab in the CCTG IND 226 and BR342 trials. Given there were no safety concerns identified in those trials, pERC agreed with the CGP that jurisdictions may wish to consider allowing the use of platinum and gemcitabine with nivolumab/ipilimumab.
• Greater monitoring would be required because significant toxicities are likely in the presence of both immunotherapy drugs. PAG is seeking guidance on dose adjustment and/or discontinuation of one of the drugs in the event of such toxicity.	• Clinicians are familiar with the AEs from immune checkpoint inhibitors. pERC agreed with the CGP that these may occur with increased frequency with dual immunotherapy, but the types of AEs are the same. pERC agreed with the CGP that if there is a significant AE, then as per the CheckMate 9LA trial, ipilimumab should be omitted and continuing treatment with nivolumab monotherapy can be considered.
• Guidance on whether there are any special considerations for older patients with comorbidities.	• pERC agreed with the CGP that older patients or those with comorbidities are at an increased risk of treatment-related AEs, but beyond this there are no additional or unique concerns to consider.
• Clarity on whether pseudoprogression is recognized or likely with this treatment. If so, PAG noted that prompt access to more frequent imaging may be required to re-assess.	• The CGP noted that pseudoprogression may occur and is always a concern; however, the frequency is lower in lung cancer compared with other malignancies. Therefore, pERC agreed that clinicians should be given the flexibility to continue treatment if pseudoprogression is suspected. If pseudoprogression is suspected, then as recommended by the CGP, imaging should be repeated within 2 months to confirm disease status. ○ In response to PAG's feedback on the Initial pERC Recommendation requesting clarity on the frequency of imaging for pseudoprogression and whether it is consistent with other immunotherapy recommendations in this setting (i.e., pembrolizumab): During reconsideration of the Initial Recommendation, pERC confirmed that the recommendations on pembrolizumab do not address imaging for pseudoprogression. pERC noted that the practice and science of imaging for

	pseudoprogression in patients treated with immunotherapy is an area that is evolving over time based on experience.
• For patients having initiated platinum chemotherapy, PAG would like confirmation that they should discontinue chemotherapy after 2 additional cycles in combination with nivolumab/ipilimumab.	• In the scenario where an immunotherapy-eligible patient has only received 1 to 2 cycles of PDC, pERC agreed with the CGP that it is reasonable to offer two additional cycles of PDC when initiating treatment with nivolumab/ipilimumab.
Sequencing and priority of treatments	
• PAG is seeking to confirm the place in therapy and sequencing with nivolumab/ipilimumab plus PDC, including the scenarios below:	
○ factors justifying the preferential use of nivolumab/ipilimumab plus PDC, pembrolizumab monotherapy, or pembrolizumab plus PDC	○ pERC agreed that the majority of patients with PD-L1-positive NSCLC (TPS ≥ 50%) will be treated with pembrolizumab monotherapy. As noted by the CGP, there may be some patients with high tumour burden for whom pembrolizumab plus PDC or nivolumab/ipilimumab plus PDC might be preferred. For patients with PD-L1 expression < 50%, there are no clinical factors that predict improved efficacy for nivolumab/ipilimumab plus PDC or pembrolizumab plus PDC. However, there may be patient- or physician choice factors (i.e., desire to limit chemotherapy) that influence the decision between nivolumab/ipilimumab plus PDC or pembrolizumab plus PDC.
○ confirmation that subsequent anti-PD1/PD-L1 cannot be given upon progression while on nivolumab/ipilimumab plus PDC	○ pERC agreed with the CGP that patients progressing on nivolumab/ipilimumab would not be eligible for subsequent immunotherapy.
○ suitability of re-treatment with nivolumab/ipilimumab plus PDC or treatment with pembrolizumab (and timing thereof) upon relapse after the 2-year treatment	○ The CheckMate 9LA trial did not allow re-treatment with nivolumab/ipilimumab after 2 years. However, in Canada, patients receiving pembrolizumab who complete 2 years of therapy and then progress are eligible for re-treatment. pERC agreed with the CGP that there should be consistency across immunotherapy treatment options and that re-treatment with nivolumab/ipilimumab for 1 year be an option for patients progressing after completion of 2 years of nivolumab/ipilimumab. ▪ In response to PAG's feedback on the Initial Recommendation requesting clarity on whether re-treatment would be limited to nivolumab monotherapy: During reconsideration of the Initial Recommendation, pERC agreed with the CGP's assessment that re-treatment should be an option to ensure consistency between funded first-line treatment options for immunotherapy. The trials of pembrolizumab and nivolumab/ipilimumab arbitrarily stopped treatment at two years, and pERC agreed with the CGP that patients who remain in response after two years and stop treatment should have the same access to re-treatment should they progress. pERC noted that to offer re-treatment after a good response and a reasonable off treatment period follows oncologic principles. pERC reiterated that re-treatment should be with nivolumab/ipilimumab, and not nivolumab monotherapy based on the evidence

	from the CheckMate 026 trial, which compared nivolumab alone to platinum-based chemotherapy and failed to demonstrate a survival benefit with nivolumab as monotherapy. pERC discussed that the CheckMate 9LA trial protocol did not allow for re-treatment so there are no data on re-treatment from the trial; and therefore, pERC could not comment on its advisability. However, pERC noted that at the time of issuing the recommendations for pembrolizumab, although the trial protocols allowed for re-treatment, there also were no data to inform on re-treatment.
○ addition of nivolumab/ipilimumab to any ongoing first-line chemotherapy regimen and termination of the latter after 2 additional cycles (i.e., induction)	○ As noted above, there is no evidence for platinum and gemcitabine combined with nivolumab/ipilimumab. However, as also pointed out, platinum and gemcitabine have been combined with durvalumab plus tremelimumab in the CCTG IND 226 and BR34 trials. Given there were no safety concerns identified in those trials, jurisdictions may wish to consider allowing the use of platinum and gemcitabine with nivolumab/ipilimumab.
○ optimal choice of next-line chemotherapy upon disease progression ○ in the next-line setting, appropriateness of full platinum chemotherapy despite the 2 cycles of PDC given in the nivolumab/ipilimumab plus PDC induction phase ○ appropriateness of re-treatment with agents used in PDC during the nivolumab/ipilimumab plus PDC induction phase (e.g., pemetrexed, paclitaxel, cisplatin, carboplatin).	○ pERC agreed that patients progressing on nivolumab/ipilimumab plus 2 cycles of PDC would be most appropriately treated with chemotherapy as the next treatment option. For patients progressing more than 6 months from completion of PDC, re-treatment with a histology-appropriate platinum doublet would be recommended. Patients progressing within 6 months would likely be treated with docetaxel. The CGP noted that re-treatment with pemetrexed may pose funding issues in some jurisdictions and this gap should be addressed during implementation. pERC agreed with the CGP that patients with non-squamous NSCLC who have only received 2 cycles of pemetrexed, should have access to the most effective PDC (i.e., platinum plus pemetrexed).
Companion diagnostic testing	
• PAG would like confirmation that PD-L1 testing is not required.	• In the CheckMate 9LA trial, the benefit of nivolumab/ipilimumab plus PDC over PDC was seen irrespective of PD-L1 expression. Therefore, pERC agreed with the CGP that PD-L1 expression will not be used to provide guidance on which patients are eligible for nivolumab/ipilimumab plus PDC. However, as stated above, patients with PD-L1 ≥ 50% are likely to be treated with pembrolizumab monotherapy and so PD-L1 testing will still be required in the standard pathology workup of a patient with NSCLC.

AE = adverse event; ALK = anaplastic lymphoma kinase; CGP = Clinical Guidance Panel; EGFR = epidermal growth factor receptor; ECOG PS = Eastern Cooperative Oncology Group Performance Status; NSCLC = non-small cell carcinoma; PAG = Provincial Advisory Group; PDC = platinum doublet chemotherapy; PD-L1 = programmed death-ligand 1; pERC = CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee; q.3.w. = every three weeks; RECIST = Response Evaluation Criteria in Solid Tumors.