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CADTH Reimbursement Recommendation

# Nivolumab In Combination With Ipilimumab (Opdivo-Yervoy)

**Indication:** Treatment of adult patients with unresectable malignant pleural mesothelioma who have not received prior systemic therapy for malignant pleural mesothelioma

**Sponsor:** Bristol Myers Squibb Canada

**Final Recommendation:** Reimburse with conditions

CADTH

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

# Summary

CADTH

## What Is the CADTH Reimbursement Recommendation for Opdivo Plus Yervoy?

CADTH recommends that Opdivo in combination with Yervoy (nivolumab plus ipilimumab) should be reimbursed by public drug plans for the treatment of malignant pleural mesothelioma (MPM) if certain conditions are met.

### What Are the Conditions for Reimbursement?

Opdivo plus Yervoy should only be reimbursed if prescribed by clinicians with experience in immuno-oncology and treating MPM and if the cost of Opdivo plus Yervoy is reduced.

### Which Patients Are Eligible for Coverage?

Opdivo plus Yervoy should only be covered to treat patients who have not received prior systemic treatment for MPM and who have good performance status at the start of treatment.

### Why Did CADTH Make This Recommendation?

- Evidence from a clinical trial demonstrated that Opdivo plus Yervoy improved overall survival in adults with unresectable MPM with good performance status and who had not received prior MPM treatment.
- Based on public list prices, Opdivo plus Yervoy is not considered cost-effective at a willingness to pay of $50,000 per quality-adjusted life-year (QALY) for the indicated population relative to currently reimbursed alternatives. Economic evidence suggests that a price reduction of at least 72% is needed for both Opdivo and Yervoy to ensure this combination is cost-effective at a $50,000 per QALY threshold.
- Based on public list prices, the 3-year budget impact of Opdivo plus Yervoy is $72 million.

## Additional Information

### What Is MPM?

MPM is a rare cancer of the pleural mesothelium, a layer of cells that surrounds the lungs. Exposure to asbestos, often many years before diagnosis, is implicated in most cases. In Canada, there were 445 cases of mesothelioma in 2016, mostly in men. MPM is an aggressive cancer. The prognosis of patients diagnosed with MPM is poor, with median survival (when half of people with this cancer are still alive) of approximately 1 year.

### Unmet Needs in MPM

Patients often have advanced disease by the time symptoms develop and are not candidates for surgery. Despite chemotherapy, survival is still poor. New treatment options for MPM that can allow patients to live longer with a good quality of life are needed.

### How Much Does Opdivo Plus Yervoy Cost?

Treatment with Opdivo plus Yervoy is expected to cost approximately $16,337 per patient per 28-day cycle.

## Recommendation

The CADTH pCODR Expert Review Committee (pERC) recommends that nivolumab, in combination with ipilimumab, should be reimbursed for the treatment of adult patients with unresectable malignant pleural mesothelioma (MPM) only if the conditions listed in Table 1 are met.

## Rationale for the Recommendation

One phase III, open-label, randomized controlled trial (RCT) (CheckMate 743, N = 605) demonstrated that nivolumab in combination with ipilimumab improved overall survival (OS; median = 18.07 months) compared with standard-of-care chemotherapy (pemetrexed plus cisplatin or carboplatin; median = 14.09 months). The hazard ratio (HR) for OS was 0.74 (95% confidence interval [CI], 0.61 to 0.89; P = 0.002) in favour of nivolumab plus ipilimumab. Patients enrolled in the RCT were adults with unresectable MPM with good performance status and who had not received prior MPM treatment. In their input to CADTH, patients expressed a desire for treatments that would prolong survival.

Using the sponsor-submitted price for nivolumab and ipilimumab, and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for nivolumab in combination with ipilimumab was $300,921 per quality-adjusted life-year (QALY) compared with pemetrexed in combination with platinum-based chemotherapy. At this ICER, nivolumab in combination with ipilimumab is not cost-effective at a $50,000 per QALY willingness to pay (WTP) threshold for the treatment of adult patients with unresectable MPM who have not received prior systemic therapy for MPM. A reduction in price of at least 72% is required for both nivolumab and ipilimumab for this combination to be considered cost-effective at a $50,000 per QALY threshold.

## Table 1: Reimbursement Conditions and Reasons

| Reimbursement condition | Reason |
|---|---|
| **Initiation** | |
| 1. Patient has not received prior systemic treatment for MPM. | The CheckMate 743 study excluded patients who had received prior MPM treatment. |
| 2. Patient must have good performance status. | CheckMate 743 excluded patients who had an ECOG PS of greater than 1 at baseline. Clinical expert input to pERC noted that patients with ECOG PS of 2 or greater could be considered for treatment with nivolumab plus ipilimumab because ECOG PS may be related to tumour symptoms that may respond to treatment. |
| **Discontinuation** | |
| 1. Reimbursement of treatment should be discontinued for disease progression based on immune-modified RECIST criteria or uncontrollable or serious immunotherapy-associated toxicity. | Criteria used for treatment discontinuation in the CheckMate743 study. |
| 2. The maximum duration of reimbursement is 2 years. | Criteria used in the CheckMate743 study and as per the product monograph. |
| **Prescribing** | |
| 1. The prescribing of nivolumab plus ipilimumab should be restricted to clinicians and centres with experience in immuno-oncology and treating MPM. | To ensure the appropriate patients receive treatment with nivolumab plus ipilimumab and to optimize toxicity management. |
| **Pricing** | |
| 1. A reduction in price. | Nivolumab in combination with ipilimumab is more costly than pemetrexed in combination with platinum-based chemotherapy. The ICER for nivolumab in combination with ipilimumab was $300,921 per QALY. A price reduction of at least 72% for both nivolumab and ipilimumab is necessary for nivolumab in combination with ipilimumab to be considered cost-effective at a $50,000 per QALY threshold. |

ECOG PS = Eastern Cooperative Oncology Group Performance Status; QALY = quality-adjusted life-year; RECIST = Response Evaluation Criteria in Solid Tumors; WTP = willingness to pay.

# Implementation Guidance

1. Prior therapy for MPM, that led to patient exclusion from the CheckMate 743 study was defined in the study protocol as adjuvant or neoadjuvant chemotherapy, radical pleuropneumonectomy (with or without intensity modulated radiotherapy), non-palliative radiotherapy, treatment with an antibody or drug specifically targeting T cell co-stimulation or checkpoint pathways (e.g., anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA-4 antibody), and intraoperative or intracavitary chemotherapy.
2. pERC noted that there is a time-limited need to switch patients who have been previously initiated on first-line systemic treatment and have not experienced disease progression to nivolumab plus ipilimumab. However, there is currently insufficient evidence

supporting nivolumab plus ipilimumab in patients who have received prior systemic treatment for MPM.

3. The CheckMate 743 trial did not have specific guidelines regarding re-treatment with nivolumab plus ipilimumab. pERC agreed with clinical expert input that re-treatment with nivolumab plus ipilimumab would be reasonable if chemotherapy had been discontinued for reasons other than disease progression (e.g., toxicity or completion of the recommended 2-year treatment duration). Re-treatment with nivolumab plus ipilimumab for 1 year should be an option for patients progressing after completion of 2 years of treatment with nivolumab plus ipilimumab and a reasonable off-treatment period. Re-treatment should be with nivolumab plus ipilimumab rather than nivolumab alone. pERC noted that to offer re-treatment after a good response and a reasonable off-treatment period follows oncology treatment principles.
4. pERC agreed with clinical expert input that continuing treatment with nivolumab alone would be clinically appropriate in patients who have been unable to tolerate the nivolumab plus ipilimumab combination, in the absence of disease progression, if the treating clinician determines there would be clinical benefit. This approach was permitted in the CheckMate 743 trial and would align with current treatment practices. Monotherapy with the remaining agent should stop if the patient experiences serious adverse effects, has disease progression, or after completion of 2 years of therapy.
5. For the nivolumab component, jurisdictions will need to choose between administering nivolumab as a weight-based dose of 3 mg/kg every 2 weeks or as flat dose of 360 mg every 3 weeks according to the approved dosing regimen for nivolumab. CheckMate 743 evaluated nivolumab as a weight-based dose of 3 mg/kg every 2 weeks (without a cap). The flat dose of 360 mg every 3 weeks has not been studied in patients with MPM. 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. For weight-based dosing, it would be reasonable for provinces, based on approved dosing schedules in other settings and financial considerations, to provide nivolumab up to a cap (e.g., maximum 360 mg every 3 weeks). Using weight-based dosing with a cap deviates from the existing evidence, but clinical expert input to pERC noted that it may be considered reasonable based on experience in other tumour types.

## Discussion Points

- Patient group and clinician input to CADTH highlighted that MPM is a rare, aggressive cancer with poor prognosis and few treatment options. pERC concluded that nivolumab plus ipilimumab could potentially address unmet patient needs for a durable treatment that alleviates symptoms, has manageable side effects, and prolongs survival, although the impact on quality of life and delays in disease progression is uncertain.
- Final analysis of OS in the CheckMate 743 study was pre-determined for after 473 deaths. The study was stopped early because superiority of nivolumab plus ipilimumab versus chemotherapy for OS had been established; 419 deaths had occurred by the time of database lock at the interim analysis. The longer-term benefit with nivolumab plus ipilimumab on OS is uncertain because of the early stopping. As well, the study design allowed receipt of subsequent cancer treatment following progression and the enrolment of only patients with a baseline Eastern Cooperative Oncology Group Performance Status

(ECOG PS) of 0 or 1, meaning that the OS benefit observed in the trial with nivolumab plus ipilimumab may be overestimated. Thus, the assumptions in the sponsor's economic analysis related to longer-term OS benefit with nivolumab plus ipilimumab versus chemotherapy could not be validated based on the existing clinical data.

- The results of the secondary analysis of progression-free survival (PFS) were difficult to interpret because the proportional hazards assumption for the Cox analysis was not met. Also, the secondary outcomes, including PFS, objective response rate (ORR), and disease control rate (DCR), were not part of the statistical testing hierarchy and therefore no adjustments were made for multiple comparisons of these outcomes. pERC could not draw concrete conclusions about the effects of nivolumab plus ipilimumab versus chemotherapy for these outcomes.
- Nivolumab and ipilimumab were administered in the CheckMate 743 study using weight-based dosing. Scenario analyses in the economic evaluation based on flat dosing of nivolumab (360 mg once every 3 weeks) increased the ICER to $314,901 per QALY compared with pemetrexed plus cisplatin or carboplatin.

# Background

Nivolumab in combination with ipilimumab has a Health Canada indication for the treatment of adult patients with unresectable MPM who have not received prior systemic therapy for MPM. Nivolumab is a PD-1 inhibitor, whereas ipilimumab is a CTLA-4 inhibitor; both are immunotherapies that target the immune checkpoint pathway. Both are administered as IV infusions. The Health Canada–approved dosage of nivolumab is 3 mg/kg every 2 weeks or 360 mg every 3 weeks, and the recommended dose of ipilimumab is 1 mg/kg every 6 weeks. Treatment is continued at the same dose until disease progression, unacceptable toxicity, or up to 2 years. Treatment may also be continued in clinically stable patients with initial evidence of disease progression until disease progression or maximum of 2 years of therapy, whichever occurs first.

# Summary of Evidence

To make their recommendation, pERC considered the following information:

- a review of 1 phase III RCT in adult patients with unresectable MPM
- patient perspectives gathered by 2 patient groups: Lung Cancer Canada and the Canadian Mesothelioma Foundation
- input from 3 clinical specialists with expertise diagnosing and treating patients with MPM
- input from 2 clinician groups: Lung Cancer Canada and Cancer Care Ontario Lung Cancer Drug Advisory Committee
- a review of the pharmacoeconomic model and report submitted by the sponsor.

## Summary of Patient Input

Two patient groups, Lung Cancer Canada and the Canadian Mesothelioma Foundation, collaborated to provide a joint patient input for this submission. Patient perspectives were

obtained from surveys, interviews, and an Environmental Scan. The following is a summary of key input from the perspective of the patient groups:

- More than half of the respondents reported that their experience with mesothelioma has negatively impacted their financial situation, and nearly all reported that their experience with mesothelioma has been stressful. All patients reported that their mesothelioma affected their quality of life, including functionality, activity level, and independence.
- The patient input stated that treatments that allow patients to live longer with a good quality of life are needed because many of these patients do not have the time to wait due to the aggressiveness of the disease and late stage of diagnosis.
- With few available treatment options for this group of patients, there is an unmet need to provide durable treatments that alleviate symptoms, delay disease progression, provide a good quality of life, prolong survival, and have manageable side effects.

## Clinical Trials

The CADTH systematic review included 1 international, multi-centre, open-label, phase III trial that compared nivolumab in combination with ipilimumab to standard-of-care chemotherapy in adult patients with unresectable MPM (CheckMate 743). Enrolled patients were required to have an ECOG PS of 0 or 1, and must not have received prior MPM treatment (i.e., adjuvant/neoadjuvant chemotherapy, radical pleuropneumonectomy, non-palliative radiotherapy). Eligible patients were randomized in a 1:1 ratio to receive nivolumab (3 mg/kg IV every 2 weeks) plus ipilimumab (1 mg/kg IV every 6 weeks) or standard-of-care chemotherapy. Standard of care was the combination of pemetrexed (500 mg/m$^2$ IV) plus either cisplatin (75 mg/m$^2$ IV) or carboplatin (area under the curve 5 IV) given every 3 weeks. Treatment was continued until disease progression, unacceptable toxicity, or completion of maximum of 2 years for nivolumab plus ipilimumab and 6 cycles for chemotherapy. Treatment with nivolumab plus ipilimumab was permitted to continue beyond initial confirmed disease progression if the investigator deemed that the patient met certain criteria demonstrating clinical benefit and tolerance.

The study enrolled 605 patients, with 303 randomized to the nivolumab plus ipilimumab group and 302 patients randomized to the chemotherapy group. Randomization was stratified by histology (epithelioid versus non-epithelioid) and gender. Tumour response was assessed by investigators and a blinded independent central review (BICR) using an adapted version of the modified Response Evaluation Criteria in Solid Tumors (m-RECIST) for pleural mesothelioma and/or RECIST Version 1.1.

Of those who received treatment (300 patients received nivolumab plus ipilimumab and 284 patients received chemotherapy), 98.3% in the nivolumab plus ipilimumab group and all in the chemotherapy group had discontinued treatment by the time of database lock (April 3, 2020). Only 5 patients remained on treatment, all in the nivolumab plus ipilimumab group. The main reason for treatment discontinuation in the nivolumab plus ipilimumab group was disease progression (60.7%) and study drug toxicity (19.7%). The majority of patients in the chemotherapy group (62.0%) discontinued treatment because they had completed the maximum length of treatment or experienced disease progression (15.5%). Notably, the median duration of treatment was 5.55 months in the nivolumab plus ipilimumab group and 3.48 months in the chemotherapy group. At the time of database lock, 459 patients (75.9%) had discontinued from the study (n = 218 in the nivolumab plus ipilimumab group, n = 241 in the chemotherapy group), mainly due to death.

Important limitations of the study were the early stopping based on interim analysis data, only enrolling patients with ECOG PS 0 or 1, and including patients who received subsequent cancer treatment as part of the OS analysis. These points likely lead to an overestimation of treatment effects with nivolumab plus ipilimumab; however, based on the Kaplan–Meier curves and primary outcome of OS, the results and conclusion which showed improved survival with nivolumab plus ipilimumab appear supportive of an overall clinical benefit. Furthermore, the open-label study design is susceptible to reporting, performance, detection, and selection biases as patients and investigators were not blinded to study treatment allocation. In the CheckMate 743 study, the risk for bias related to the design was a concern for some outcomes assessed in the trial, including health-related quality of life (HRQoL).

## Outcomes

Outcomes were defined a priori in CADTH's systematic review protocol. Of these, the committee discussed the following: OS, PFS, ORR, DCR, and HRQoL for efficacy, and total adverse events (AEs), serious adverse events (SAEs), and withdrawals due to adverse events (WDAEs) for the safety evaluation.

The primary efficacy outcome in the CheckMate 743 study was OS, measured after a minimum follow-up of 22.1 months. Secondary end points included BICR-measured PFS, ORR, and DCR, but these end points were not formally tested statistically. HRQoL, an exploratory end point, was measured using the EuroQol 5-Dimensions 3-Levels (EQ-5D-3L) and Lung Cancer Symptom Score with the mesothelioma adaptation (LCSS-Meso) questionnaires.

## Efficacy

Final analysis for OS data was planned for after 473 deaths had occurred. Efficacy results were reported based on a pre-specified interim analysis (approximately 85% of total events or 403 deaths, with minimum survival follow-up of 22.1 months). At the survival data cut-off date (median follow-up of 29.7 months), 419 patients had died, including 200 patients (66.0%) in the nivolumab plus ipilimumab group and 219 patients (72.5%) in the chemotherapy group. The median OS was 18.07 months (95% CI, 16.82 to 21.45) in the nivolumab plus ipilimumab group and 14.09 months (95% CI, 12.45 to 16.23) in the chemotherapy group. The interim OS analysis demonstrated a statistically significant difference between the 2 treatment groups in favour of nivolumab plus ipilimumab (HR = 0.74; 95% CI, 0.61 to 0.89; P = 0.002). Overall survival was identified as the most clinically relevant end point by the patient input and clinical experts consulted for this CADTH review.

Sensitivity analyses also showed consistent results with the primary analysis. Subgroup analyses for the primary end points of OS were also generally consistent with the intention-to treat population, with most HRs favouring treatment with nivolumab plus ipilimumab. However, results should be considered exploratory because these subgroup analyses did not account for multiplicity. Secondary end points, such as PFS, ORR, and DCR, did not demonstrate that nivolumab plus ipilimumab was favourable to chemotherapy, but these end points were reported descriptively without performing formal statistical testing. As CheckMate 743 was not designed to test multiple outcomes and did not have a statistical testing framework for secondary outcomes, firm conclusions cannot be made based on the assessments of PFS, ORR, and DCR.

Measures of HRQoL, which was identified as an outcome of particular importance by patients, showed a numerical improvement for patients in the nivolumab plus ipilimumab group, and no clear change or decline in scores in the chemotherapy group. A published, validated, minimally important difference has not been established for the LCSS-Meso questionnaire in patients with MPM. Consequently, it is unclear whether the threshold used in the trial (i.e., minimally important difference of 10 points) is appropriate and reflective of a clinically meaningful change in outcome in patients with MPM. The disease-related symptom deterioration rate at week 12 was numerically higher in the nivolumab plus ipilimumab group compared with the chemotherapy group. As HRQoL outcomes were exploratory, the true impact of the study treatments on HRQoL is unknown, and no firm conclusions can be made based on these results.

## Harms (Safety)

Overall, AEs reported in the CheckMate 743 study were consistent with the known AE profile of each drug included in the study. A similar proportion of patients in each treatment group experienced an AE. A higher proportion of patients treated with nivolumab plus ipilimumab experienced all-cause grade 3 to 4 AEs (53.0% versus 42.6%) and all-cause SAEs (54.7% versus 25.4%). Malignant neoplasm progression, pleural effusion, colitis, pneumonitis, infusion-related reactions, pyrexia, and pneumonia accounted for most of the differences in reported SAEs. The frequency of hypersensitivity or infusion reaction in the nivolumab plus ipilimumab group (12.0% versus 2.5% chemotherapy) was higher than previously reported in other cancers; however, most reactions were grade 1 or 2 in severity and resolved within a day. Duration of treatment was different between the groups; therefore, the study reported incidence rates adjusted for the different lengths of exposure. The exposure-adjusted incidence per 100 person-years were consistently higher in the chemotherapy group for all-cause AEs, grade 3 to 4 AEs, and SAEs.

A greater proportion of patients who received the immunotherapy combination discontinued study treatment due to an AE from any cause (29.3% versus 20.4% for chemotherapy group). In patients treated with nivolumab plus ipilimumab, the most common WDAEs were colitis, diarrhea, infusion-related reaction, and pneumonitis. The most common WDAEs in patients treated with chemotherapy were anemia, asthenia, nausea, fatigue, neutropenia, and thrombocytopenia.

Most deaths that occurred in the study were due to disease progression. Toxicity from the study drug led to 3 deaths (1.0%) in the immunotherapy group and 1 death (0.4%) in the chemotherapy group.

## Indirect Evidence

The sponsor provided an indirect treatment comparison (ITC) evaluating the efficacy of nivolumab plus ipilimumab to pemetrexed plus cisplatin or carboplatin, raltitrexed plus cisplatin, bevacizumab plus pemetrexed and cisplatin, gemcitabine plus cisplatin, or cisplatin monotherapy. However, the most relevant comparator was identified to be pemetrexed plus cisplatin or carboplatin. The ITC provided little additional evidence to inform the assessment of the clinical benefits associated with nivolumab plus ipilimumab. The results were consistent with those from the CheckMate 743 study, indicating favourable OS with nivolumab plus ipilimumab compared with pemetrexed plus cisplatin or carboplatin; nivolumab plus ipilimumab was also favoured over cisplatin monotherapy. However, comparisons between nivolumab plus ipilimumab and bevacizumab plus pemetrexed plus

cisplatin, gemcitabine plus cisplatin, or raltitrexed plus cisplatin identified no treatment that was favoured for OS. Likewise, the results for PFS and ORR did not clearly demonstrate that 1 regimen was favourable over the others. Although certain treatment regimens appeared to be favoured based on reported 95% credible intervals (CrIs), no definitive conclusions can be made due to inherent limitations, such as concerns with violations of the proportional hazards assumption for PFS and high degree of heterogeneity across trials for ORR analysis. The sponsor's ITC included analyses of only efficacy (i.e., OS, PFS, ORR) between nivolumab plus ipilimumab and other comparators; therefore, the sponsor's ITC cannot be used to inform conclusions regarding relative safety or HRQoL between treatment regimens. The main limitations of the efficacy comparisons pertained to trial differences in baseline and clinical characteristics, use of subsequent therapies that could bias results toward comparator groups, and trial length.

## Cost and Cost-Effectiveness

At the sponsor's submitted prices for nivolumab ($782.22 per 40 mg vial and $1,955.56 per 100 mg vial) and ipilimumab ($5,800.00 per 50 mg vial), the average drug acquisition cost per 21-day treatment cycle is $12,253 per patient, assuming a patient weight of 70 kg and drug wastage. The average annual cost of treatment with nivolumab and ipilimumab would be $107,413 per patient.

The sponsor submitted a cost-utility analysis comparing nivolumab plus ipilimumab to pemetrexed with cisplatin or carboplatin, and raltitrexed with cisplatin or carboplatin, for the first-line treatment of adult patients with unresectable MPM. The sponsor's partitioned survival model comprised 3 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 survival analysis. The CheckMate 743 trial was used to inform treatment efficacy for nivolumab plus ipilimumab and pemetrexed with cisplatin or carboplatin. Results from the sponsor-submitted ITC were used to inform the comparison with raltitrexed in combination with cisplatin or carboplatin.

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

- There is some uncertainty of the magnitude of benefit observed with nivolumab and ipilimumab with regards to OS, and there is limited evidence on the long-term comparative efficacy of nivolumab plus ipilimumab to pemetrexed with platinum-based chemotherapy.
- The relevance of raltitrexed with platinum-based chemotherapy as a comparator is questionable given its lack of use in Canadian clinical practice. Additionally, uncertainty exists with its comparative efficacy to nivolumab plus ipilimumab due to differing patient populations and trial conditions identified in the sponsor's network meta-analysis.
- The sponsor assumed vial sharing for nivolumab and ipilimumab (no drug wastage) in their base case. This was not aligned with their product monographs which indicated they are single-use vials.
- The prices of pemetrexed, carboplatin, and cisplatin used by the sponsor did not align with estimates obtained from public sources (such as IQVIA Delta PA), leading to an underestimate of the drug acquisition costs for the comparator regimens.

CADTH undertook a reanalysis that included excluding raltitrexed as a comparator, omitting vial sharing for all treatment options, and updating treatment costs. In the CADTH base case,

nivolumab plus ipilimumab compared to pemetrexed with platinum-based chemotherapy was associated with an ICER of $300,921 per QALY gained ($126,305 incremental costs, 0.42 incremental QALYs). Based on a WTP threshold of $50,000 per QALY, there is a 0% probability that nivolumab plus ipilimumab would be considered cost-effective, and a price reduction of 72% for both nivolumab and ipilimumab is required for nivolumab plus ipilimumab to be considered cost-effective. Due to the uncertainty around the comparative long-term treatment efficacy, the results of the CADTH analysis should be interpreted with caution.

## Budget Impact

The sponsor estimated the incremental budget impact of reimbursing nivolumab in combination with ipilimumab to be $63,982,324 over 3 years. CADTH identified limitations with the submitted budget impact analysis and undertook a reanalysis which estimated the incremental budget impact of reimbursing nivolumab in combination with ipilimumab was $72,959,111 over 3 years.

## Members of the pCODR Expert Review Committee

Dr. Maureen Trudeau (Chair), Dr. Catherine Moltzan (Vice-Chair), Mr. Daryl Bell, Dr. Jennifer Bell, Dr. Kelvin Chan, Dr. Matthew Cheung, Dr. Winson Cheung, Dr. Michael Crump, Dr. Avram Denburg, Dr. Leela John, Dr. Christine Kennedy, Dr. Christian Kollmannsberger, Mr. Cameron Lane, Dr. Christopher Longo, Ms. Valerie McDonald, Dr. Marianne Taylor, and Dr. Dominika Wranik.

**Meeting Date**: April 15, 2021

**Regrets**: None

**Conflicts of Interest**: None