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

Drug: Nivolumab (Opdivo) **Submitted Reimbursement Request:** For the treatment of adult patients with advanced (not amenable to curative therapy or local therapeutic measures) or metastatic hepatocellular carcinoma who are intolerant to or have progressed on sorafenib therapy	
Submitted by: Bristol-Myers Squibb Canada	**Manufactured by:** Bristol-Myers Squibb Canada
NOC Date: March 23, 2018	**Submission Date:** May 8, 2018
Initial Recommendation: October 4, 2018	**Final Recommendation:** November 29, 2018

Drug Costs	
Approximate per Patient Drug Costs	Nivolumab costs $782.40 per 40 mg vial, or $1,956.00 per 100 mg vial. The cost per administration is $4,474.62, based on a dose of 3 mg/kg on day 1 of each 14-day cycle (intravenous administration over 60 minutes).

pERC RECOMMENDATION

pERC does not recommend reimbursement of nivolumab (Opdivo) for the treatment of adult patients with advanced (not amenable to curative therapy or local therapeutic measures) or metastatic hepatocellular carcinoma who are intolerant to or have progressed on sorafenib therapy.

pERC made this recommendation because, despite a significant unmet need, it was not confident of the net overall clinical benefit of nivolumab because of limitations in the evidence from the available non-comparative non-randomized clinical trial. The Committee was unable to determine how nivolumab compares with other treatments with respect to outcomes important to decision-making, including overall survival (OS), progression-free survival (PFS), and quality of life (QoL).

Although pERC acknowledged that patients value additional treatment options, the Committee was not satisfied that nivolumab addresses the key outcomes that patients have indicated they value including the need for more effective treatment options that have tolerable side effects that lead to better QoL.

pERC noted that, at the submitted price, nivolumab is not cost-effective compared with best supportive care or regorafenib. Additionally, there was a high-level of uncertainty in the cost-effectiveness estimates because of a lack of direct comparative effectiveness data in the submitted

	economic evaluation.
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	**Possibility of Resubmission to Support Reimbursement** pERC considered that randomized controlled trials have been conducted or are currently being conducted in the requested reimbursement patient population. pERC noted that new clinical data comparing nivolumab with currently available treatments in Canada for patients who have progressed on or who are intolerant to sorafenib could form the basis of a resubmission to pCODR if comparative efficacy data important to decision-making, such as PFS, OS or QoL, are available.

SUMMARY OF pERC DELIBERATIONS

In 2017, there were approximately 2,500 new cases of hepatocellular carcinoma (HCC) diagnosed in Canada. The treatment approach to, and prognosis of, patients with HCC depends on the extent of the disease, hepatic functional reserve, and performance status. Child-Pugh class (A, B, or C) is the most commonly used metric to assess hepatic reserve. The prognosis for patients with untreated advanced and unresectable HCC is poor, with a median overall survival (OS) of less than one year. Sorafenib is currently approved and reimbursed across Canada for the first-line systemic treatment of patients with Child-Pugh class A advanced HCC. For patients who experience progression on treatment with sorafenib, the prognosis is poor. Such patients are offered best supportive care (BSC), as there are currently no available treatments outside of clinical trials. Regorafenib was recently recommended for reimbursement for patients who have progressed on sorafenib; however, it is not currently publicly reimbursed in Canada. Additionally, there are no treatment options available for patients who are intolerant to sorafenib. Therefore, pERC concluded that there is a significant unmet need in this setting and that there is a need for more effective and tolerable treatment options.

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

CLINICAL BENEFIT	PATIENT-BASED VALUES
ECONOMIC EVALUATION	ADOPTION FEASIBILITY

pERC deliberated upon the results of one ongoing, international, multi-centre, non-comparative, open-label phase I/II trial, CheckMate 040. The trial evaluated the efficacy and safety of nivolumab in patients with advanced HCC who were either treatment-naive or previously treated with sorafenib. However, pERC deliberated specifically upon the results of a pooled analysis of second-line patients treated in the dose-expansion phase of the trial, because these results aligned with the requested reimbursement population. pERC noted that the trial was designed to assess the overall response rate (ORR) by blinded independent committee review (BICR). The Committee discussed several limitations of the available evidence, including the non-comparative trial design, pooled analyses of subgroup data, and the potential for selection bias toward more indolent HCC tumours. pERC noted that there may be antitumour activity with nivolumab; however, the Committee noted that the ORR estimated in the dose-expansion pooled analysis subgroup (14.5%; 95% CI, 9.2% to 21.3%) did not reach the clinical significance threshold that was pre-specified in the trial, as the lower confidence limit was less than 10%. Furthermore, the Committee discussed that the ORR was not considered to be sufficient evidence of clinical effectiveness and that there is no evidence demonstrating that the ORR is a surrogate for OS. pERC acknowledged that outcomes, including progression-free survival (PFS) and OS, were collected in the trial; however, the magnitude of effect compared with other therapies was uncertain, given the lack of randomized comparative data. In addition, pERC noted that quality of life (QoL) was an exploratory outcome in the trial. pERC discussed that there were no clinically meaningful changes in QoL during treatment with nivolumab. The Committee also discussed the safety of nivolumab and noted that the most common adverse events were fatigue, pruritus, and rash. pERC noted that, overall, the adverse events (AEs) observed with nivolumab in this patient population were expected and similar to those observed in previous studies of nivolumab in other tumour types. The Committee was not satisfied that the available evidence from the CheckMate 040 trial demonstrated a net overall clinical benefit of nivolumab. Overall, pERC agreed that it was difficult to meaningfully interpret the outcomes important to decision-making, including PFS, OS, and QoL, considering the limitations in the evidence from the available non-comparative non-randomized clinical trial.

Upon reconsideration of the pERC Initial Recommendation, the Committee discussed feedback provided by the submitter that requested pERC to consider reimbursement of nivolumab for patients who are intolerant to or who have discontinued sorafenib due to intolerance and/or toxicity. The submitter highlighted that there are currently no treatment options available for these patients and while regorafenib is an option for patients with HCC following progression on sorafenib, patients who are intolerant to sorafenib cannot tolerate regorafenib.

pERC noted that the majority of patients in the pooled analysis of second-line patients had progressed on treatment with sorafenib and a much smaller proportion of patients were considered sorafenib intolerant

(8.3%, n = 12). pERC acknowledged the significant unmet need for patients who have progressed on or who are intolerant to sorafenib as there are limited treatment options available. However, pERC reiterated that despite a significant unmet need, it was not confident of the net overall clinical benefit of nivolumab because of the limitations in the evidence from the available non-comparative, non-randomized clinical trial. The Committee reiterated that the magnitude of effect of nivolumab compared with other therapies is uncertain.

pERC considered the possibility of resubmission to support reimbursement of nivolumab. pERC discussed that new clinical data comparing nivolumab with currently available treatments in Canada for patients who have progressed on or who are intolerant to sorafenib could form the basis of a resubmission to pCODR if comparative efficacy data important to decision-making, such as PFS, OS or QoL, are available. Additionally, pERC noted that an economic analysis specifically for patients who are intolerant to sorafenib was not submitted. The Committee agreed that a resubmission to pCODR would require new clinical data and also an economic evaluation focused specifically on patients who are intolerant to sorafenib.

The Committee discussed the feasibility of conducting a phase III randomized controlled trial (RCT) in this patient population. pERC considered that RCTs have been conducted in the progressed HCC population, and noted that there are phase III trials investigating other therapies for this patient population, including the RESORCE trial comparing regorafenib with BSC and the ongoing KEYNOTE-240 trial comparing pembrolizumab with BSC. pERC also considered that registered clinicians noted that the decision to reimburse nivolumab for use among patients should be based on phase III RCT evidence. The Committee noted that there is currently no confirmatory phase III RCT comparing nivolumab with other therapies in the second-line HCC setting and noted an ongoing phase III RCT comparing nivolumab with sorafenib in the first-line setting for HCC patients. However, the Committee stated that this ongoing trial was considered out of scope for the requested reimbursement.

In the absence of a direct comparison of nivolumab with other relevant therapies, pERC considered the results of the submitted indirect treatment comparisons (ITCs). pERC noted that the ITCs were conducted to derive comparative efficacy estimates only for PFS and OS, and that ORR, QoL, and safety estimates were not considered and analyzed. The Committee agreed that there were a number of limitations in the evidence that raised considerable uncertainty in the treatment estimates of nivolumab compared with BSC and regorafenib. pERC noted that it was challenging to interpret the submitted data and that limited conclusions could be drawn from the ITC. Overall, pERC stated that it has accepted evidence from non-comparative studies in previous submissions for reasons that are context-specific to the disease and the observed efficacy of the drug. However, in this instance, pERC was not confident of the net overall clinical benefit of nivolumab, given the absence of evidence of a superior advantage over other treatments such as BSC and regorafenib, the feasibility of conducting an RCT in this disease setting, short trial follow-up, and the questionable clinical significance of response rate to treatment in the requested patient population. As a result, the Committee was unable to draw a conclusion concerning the comparative effectiveness of nivolumab for HCC patients who have progressed on, or are intolerant to, sorafenib.

pERC deliberated on input concerning nivolumab from one patient advocacy group. pERC noted that direct input about nivolumab was provided by health professionals, however, indirect patient comments gathered from the group's communication channels were included to provide further insight. pERC noted that none of the patients who provided input had direct experience with nivolumab. pERC discussed that patients value having more options after treatment with sorafenib that are effective, improve QoL by offering fewer and less severe side effects, provide symptom control and provide hope. The Committee considered that, currently, there is a lack of reimbursed treatment options in Canada after progression on sorafenib. Regorafenib was recently recommended for reimbursement; however, it is not yet publicly reimbursed in any jurisdiction in Canada. Overall, although pERC acknowledged that patients value additional treatment options, the Committee was not satisfied that nivolumab addresses the key outcomes that patients have indicated they value including the need for more effective treatment options that have tolerable side effects that lead to better QoL.

The Committee deliberated upon the cost-effectiveness of nivolumab. pERC noted that the pCODR Economic Guidance Panel (EGP) lower-bound estimates that were higher than the submitter's estimates for the comparison of nivolumab with BSC and regorafenib. The Committee noted that the EGP did not provide an upper-bound incremental cost-effectiveness ratio (ICER) estimate for the comparison of

nivolumab with BSC and regorafenib because of the uncertainty in the available indirectly-obtained estimates of effect. The Committee discussed the assumptions upon which the EGP's lower-bound estimates were based. pERC noted the EGP's reanalysis, which included a shortened time horizon from lifetime to three years, to reflect the clinical population of progressed HCC patients, use of utilities that reflect patients seen in clinical practice, and different PFS and OS curves for the BSC comparator to better reflect the BSC patient population. The Committee noted that these changes increased the ICER estimates. pERC discussed the fact that the EGP was unable to estimate an upper bound of the ICER because of the lack of direct comparative estimates of effect and the inability to evaluate the uncertainty in the submitted ITCs. Furthermore, pERC noted that the EGP was unable to evaluate the effect of prolonged treatment with nivolumab — a plausible scenario, considering that treatment was allowed to continue after disease progression in the trial. The Committee agreed with the EGP that there is a high level of uncertainty in the lower-bound ICER and that the estimate of the upper bound is unknown, given the limitations in the submitted model. Overall, pERC noted that the magnitude of long-term benefit associated with nivolumab is unknown, given the limitations in the indirect comparative efficacy data and the lack of long-term data. pERC noted that, at the submitted price, nivolumab compared with BSC and compared with regorafenib is not considered cost-effective in this population. The Committee cautioned that there is a high level of uncertainty in the cost-effectiveness estimates because of a lack of direct comparative effectiveness data in the submitted economic evaluation.

pERC discussed factors that could impact the feasibility of implementing a positive conditional reimbursement recommendation for nivolumab for the treatment of adults who progressed on, or are intolerant to, sorafenib. The Committee discussed that additional chemotherapy chair time and nursing resources would be required to administer nivolumab. Additionally, pERC discussed the Provincial Advisory Group's (PAG's) request for clarity on sequencing for patients who are treated with other therapies, the treatment duration of nivolumab, as well as guidance on whether retreatment with nivolumab would be appropriate for patients following a treatment break. PAG also noted that there is an ongoing phase III trial comparing nivolumab with sorafenib in the first-line setting, and pERC agreed that that a submission would be required to consider reimbursement of nivolumab as a first-line treatment. Finally, pERC also considered the submitted budget impact analysis and noted that the submitter assumed that the market share of second-line nivolumab would decline over time with the assumption that nivolumab would become available in the first-line setting. The Committee discussed that nivolumab is not available in Canada in the first-line setting at this time and that this assumption presupposes the outcome of the ongoing trial of nivolumab compared with sorafenib in the first-line setting. The Committee was uncertain about the assumptions in the submitted budget impact and concluded that the budget impact is likely underestimated.

EVIDENCE IN BRIEF

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

- a pCODR systematic review
- other literature in the Clinical Guidance Report that provided clinical context
- an evaluation of the manufacturer's economic model and budget impact analysis
- guidance from the pCODR clinical and economic review panels
- input from one patient advocacy group, the Canadian Liver Foundation
- input from registered clinicians
- input from pCODR's Provincial Advisory Group (PAG).

Feedback on the pERC Initial Recommendation was also provided by:

- the submitter, Bristol-Myers Squibb Canada
- registered clinicians
- PAG.

The pERC Initial Recommendation was to not recommend reimbursement of nivolumab for the treatment of adult patients with advanced (not amenable to curative therapy or local therapeutic measures) or metastatic hepatocellular carcinoma (HCC) who are intolerant to or have progressed on sorafenib therapy. Feedback on the pERC Initial Recommendation indicated that PAG agreed with the Initial Recommendation. Registered clinicians agreed in part with the Initial Recommendation. The submitter did not agree with the Initial Recommendation. The patient advocacy group, Canadian Liver Foundation, did not provide feedback on the pERC Initial Recommendation.

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of the review is to evaluate the safety and efficacy of nivolumab for the treatment of adult patients with advanced (not amenable to curative therapy or local therapeutic measures) or metastatic hepatocellular carcinoma (HCC) who are intolerant to or have progressed on sorafenib therapy.

Studies included one non-comparative phase I/II trial and pooled analyses of a subgroup of patients from the expansion phase of the trial

The pCODR systematic review included an ongoing, international, non-comparative, open-label, multi-centre phase I/II trial evaluating the efficacy and safety of nivolumab in patients with advanced HCC who were either treatment-naive or previously treated with sorafenib (CheckMate 040). The pCODR submission and pERC deliberations focused on patients treated in the second-line in the dose-expansion phase of the CheckMate 040 trial, because it aligned with the requested reimbursement population. Specifically, pooled analyses were focused on the second-line patients (n = 145) who had progressed on, or were intolerant to, sorafenib, regardless of etiology. The second-line patients comprise 68% of the original trial population. An initial evaluation of efficacy, carried out on March 15, 2016, showed consistent investigator-assessed response rates across the four expansion cohorts. Based on this evaluation, the statistical analysis plan of the trial was amended to conduct pooled efficacy analyses that combined patients from the four cohorts in order to strengthen the estimate of overall response rate (ORR).

Nivolumab was administered intravenously to patients every two weeks at a dose of 3 mg/kg until disease progression, unacceptable toxicity, or treatment discontinuation. The trial permitted treatment beyond disease progression in patients still tolerant to, and benefiting clinically from, nivolumab. Dose modifications were not permitted, but dose delays of up to six weeks (42 days) from the last dose of nivolumab were allowed.

Intolerance to sorafenib was defined in the CheckMate 040 trial as follows: Grade 2 drug-related adverse event (AE) that persisted in spite of comprehensive supportive therapy according to institutional standards *and* persisted or recurred after interruption of sorafenib treatment of at least 7 days and dose reduction by one dose level (to 400 mg once daily). Furthermore, the definition included grade 3 drug-

related AE that persisted in spite of comprehensive supportive therapy according to institutional standards *or* persisted or recurred after interruption of sorafenib treatment of at least 7 days and dose reduction by one dose level (to 400 mg once daily).

The pCODR review also provided contextual information on a critical appraisal of an indirect treatment comparison (ITC) of nivolumab versus other relevant comparators, such as best supportive care (BSC) and regorafenib.

Patient populations: Second-line cohort included patients who progressed on or after treatment with sorafenib, and a small proportion of patients were considered sorafenib intolerant

pERC noted the key eligibility criteria for the CheckMate 040 trial included histologically confirmed advanced HCC that was not amenable to curative surgery or local treatment, with or without hepatitis C virus (HCV) or hepatitis B virus (HBV) infection; HBV infection that required patients be receiving effective antiviral therapy and have a viral load less than 100 IU/mL at trial screening;, previously untreated HCC, or HCC with disease progression while receiving at least one previous line of therapy that included sorafenib; or deemed intolerant to or refused sorafenib treatment, Child-Pugh score of 6 or less (Child-Pugh class A); and Eastern Cooperative Oncology Group (ECOG) performance status of 1 or less.

The second-line cohort comprised of a majority of patients who had progressed on or after treatment with sorafenib (91%, n = 132); a smaller proportion of patients were considered sorafenib intolerant (8.3%, n = 12). Only one patient (< 1%) in this group had refused sorafenib.

There were 27 patients (18.6%) in the cohort who had prior systemic therapies (two or more) in addition to sorafenib. The majority of patients were from trial sites in Asia (49%) and Europe (40%), with the remaining patients (11%) from the US and Canada. Most patients were male (77%), Asian or white (98%), and under age 65 (56%). The median age of patients in the cohort was 63 years. In terms of etiology, most patients were uninfected (50%); HBV and HCV infection was present in 30% and 21% of patients, respectively. Patients were predominantly Barcelona Clinical Liver Cancer stage C (89%), Child-Pugh score 5 (67%), and ECOG performance status of 0 (64%). Extrahepatic metastases and vascular invasion were present in 71% and 40% of patients, respectively.

pERC noted that, for approximately 20% of patients in the second-line cohort, the time from initial diagnosis to first dose of nivolumab was five years or more, and the median time from initial diagnosis to first dose of nivolumab was 26.5 months. By comparison, in the RESORCE trial (regorafenib), this time span was 21 months. pERC noted that the median five-year survival rate of patients with HCC is in the range of 5% to 6%. Therefore, there appears to have been selection bias in the trial for more indolent (better prognosis) HCC tumours in the CheckMate 040 trial.

The median duration of treatment among the second-line cohort was 5.26 months, and 78 patients (54%) were treated beyond disease progression. At the time of the pooled efficacy analysis, 24 (17%) second-line patients remained on treatment with nivolumab, and 121 (83%) had discontinued treatment. The primary reason for treatment discontinuation was progressive disease (n = 107, 74%).

Key efficacy results: Objective response rate; magnitude of comparative benefit uncertain

The key efficacy outcomes that pERC deliberated upon included the primary end point of ORR by the blinded independent review committee (BICR), with tumour assessment based on RECIST version 1.1, and secondary outcomes, including progression-free survival (PFS) and overall survival (OS).

Among the second-line patient cohort, the ORR by BICR was 14.5% (95% CI, 9.2% to 21.3%). pERC noted that this ORR estimate did not reach the clinical significance threshold pre-specified in the statistical analysis plan, as the lower confidence limit was less than 10%. The ORR by BICR consisted mainly of partial responses (17%; n = 24), and the complete response rate was 1% (n = 2). Responses were observed across the four etiologic cohorts.

The median PFS by BICR among the second-line expansion patients was 2.8 months (95% CI, 2.6 to 4.0 months), which was based on 119 progression events. PFS by investigator assessment was 4.1 months (95% CI, 2.8 to 5.5 months).

A total of 81 deaths occurred among the second-line expansion cohort. The median OS was 15.6 months (95 % CI, 13.24 to 18.89 months). At 12 and 18 months, the estimated OS rates were 60% (95% CI, 54.1% to 67.5%) and 44% (95% CI, 35.3% to 51.9%), respectively. Median OS estimates were similar by etiology, at 16.3 months (95% CI, 11.3 to 19.94 months) in uninfected patients, 14.9 months (95% CI, 9.3 months to not estimable) in HBV-infected patients, and not reached in HCV-infected patients.

Patient-reported outcomes: No clinically meaningful differences in quality of life

pERC noted that patient-reported health-related QoL was an exploratory outcome, measured using the EuroQol 5-Dimensions (EQ-5D) questionnaire. A score difference from baseline to a later time point during treatment of 0.08 was considered the minimal clinically important difference (MCID) for the EQ-5D utility index, and a score difference of 7 was considered the MCID for the EQ-5D visual analogue scale (VAS). EQ-5D index scores were stable while patients were on treatment, with no significant changes from baseline (mean 0.85; 95% CI, 0.82 to 0.89) to week 25 (mean 0.83; 95% CI, 0.77 to 0.87). The mean change from baseline was −0.014 (95% CI, −0·06 to 0·03), which did not meet the MCID of 0.08. EQ-5D-VAS scores were also stable, with no significant changes from baseline (mean 74.5; 95% CI, 69.9 to 79.2) to week 25 (mean 75.8; 95% CI, 69.3 to 82.4). The mean change from baseline was 3.1 (95% CI, −1.0 to 7.6), which did not meet the MCID for VAS of 7. Overall, pERC noted that there were no clinical meaningful differences in QoL from baseline to a later time point during treatment.

Safety: Limited evidence suggests tolerable and manageable toxicity

pERC noted that the most frequently reported all-cause AEs were fatigue (35.9%), pruritus (28.3%), diarrhea (26.9%), abdominal pain (24.1%), cough (22.1%), and decreased appetite (21.4%). All-cause grade 3 to 4 AEs occurred in 49% of patients and were mainly attributable to abdominal pain (3.4%) and fatigue (2.8%). Treatment discontinuations due to any AE occurred in 11% of patients. Drug-related serious AEs occurred in 9% of patients, and drug-related treatment discontinuations occurred in 2% of patients and included discontinuation due to stomatitis, polyarthritis, and pneumonitis. As of the November 29, 2016, database lock, a total of 65 (45%) deaths had occurred in the second-line patient cohort; 91% of deaths were due to disease progression. Eight (5.5%) and 29 (20%) patients died within 30 and 100 days of the last nivolumab dose, respectively.

Limitations: No direct comparative data to best supportive care and regorafenib

pERC noted that the submitter provided ITCs in order to provide estimates of comparative efficacy between nivolumab and relevant comparators as second-line treatment for advanced HCC in patients who progressed on, or were intolerant to, sorafenib. The ITCs included covariate-adjusted and match-adjusted indirect comparison (MAIC) analyses to derive comparative estimates for the outcomes of OS and PFS. pERC noted that these analyses were funded by the manufacturer and have not been fully published or peer-reviewed. The methods and results of the ITCs were critically appraised by the pCODR Methods Team according to the recommendations of the ISPOR Task Force on Indirect Treatment Comparisons and best practice principles for MAIC. The critical appraisal focused on the ITCs performed that pCODR considered to be appropriate comparators in the Canadian context, which included nivolumab compared with BSC and regorafenib. The pCODR Methods Team noted a number of limitations, including differences in important baseline characteristics of patients in the included trials, selection bias toward more indolent HCC tumours, methodological issues in covariate-adjustment and matching, and the use of mixed-quality digitized Kaplan Meier data in the analyses. For OS, the results of the covariate-adjusted analysis and MAICs were consistent, and showed a statistically significant treatment benefit for nivolumab when compared with BSC/placebo and regorafenib. For PFS, a treatment benefit was shown for nivolumab that was marginally better than BSC/placebo. However, no difference in PFS was observed when nivolumab was compared with regorafenib. pERC noted that the pCODR Methods Team concluded that the ITC results should be interpreted with caution, considering the number of limitations associated with the analyses. These limitations raise considerable uncertainty in the treatment estimates obtained.

Need and burden of illness: Currently no funded treatment options after progression on sorafenib

In 2017, there were approximately 2,500 new cases of HCC diagnosed in Canada. The treatment approach to, and prognosis of, patients with HCC depends on the extent of the disease, hepatic functional reserve, and performance status. Child-Pugh class (A, B, or C) is the most commonly used metric to assess hepatic reserve. The prognosis for patients with untreated advanced and unresectable HCC is poor, with a median OS of less than one year. Sorafenib is currently approved and reimbursed across Canada for the first-line systemic treatment of Child-Pugh class A patients with advanced HCC. For patients who experience

progression on treatment with sorafenib, prognosis is poor. These patients are offered BSC, as there are currently no available publicly reimbursed treatments outside of clinical trials. Recently, regorafenib was recommended for reimbursement for patients who have progressed on sorafenib, conditional on its cost-effectiveness being improved. However, it is currently not reimbursed in Canada. Additionally, there are no treatment options available for patients who are intolerant to sorafenib. Therefore, pERC concluded that there is a significant unmet need in this setting.

Registered clinician input: Unmet need for patients who have progressed on, or are intolerant to, sorafenib
Clinicians providing input noted that there is currently an unmet need, as the current treatment options for patients with HCC are limited, and that nivolumab would be useful to patients if made available. The clinicians providing input noted that it is not clear whether the reimbursement request for nivolumab should be based on a phase I/II trial, as a phase II trial may not be sufficient to influence a drug reimbursement recommendation. The opinion of the clinicians emphasized that the decision to approve nivolumab for use among patients should be based on data from a phase III randomized controlled trial.

PATIENT-BASED VALUES

Patient values on treatment: Need for more effective treatment options after sorafenib
pERC noted patient input from one patient advocacy group concerning nivolumab. pERC noted that direct input about nivolumab was provided by health professionals, however, indirect patient comments gathered from the group's communication channels were included to provide further insight. pERC noted that none of the patients who provided input had direct experience with nivolumab. The Committee noted that the key symptoms HCC patients experience include fatigue, abdominal pain, and nausea. Patient input noted that current first-line treatment has many side effects, with short duration of benefit. pERC discussed that patients value more effective treatment options after treatment with sorafenib that have fewer side effects for better QoL. The Committee considered there is a lack of currently publicly reimbursed options in Canada after progression on sorafenib. Regorafenib was recently recommended for reimbursement; however, it is not yet available in any jurisdictions. Overall, although pERC acknowledged that patients value additional treatment options, the Committee was not satisfied that nivolumab addresses the key outcomes that patients have indicated they value including the need for more effective treatment options that have tolerable side effects that lead to better QoL.

ECONOMIC EVALUATION

Economic model submitted: Cost-effectiveness and cost-utility analysis
The pCODR Economic Guidance Panel (EGP) assessed the cost-effectiveness and cost-utility analyses comparing nivolumab with BSC, as well as a scenario analysis comparing nivolumab with regorafenib.

Basis of the economic model: Clinical and cost inputs
The modelled patient population was the second-line expansion cohort of the CheckMate 040 trial and consisted of adult patients with advanced (not amenable to curative therapy or local therapeutic measures) or metastatic HCC, with documented progression during or after sorafenib therapy or intolerance to sorafenib therapy.

Costs included were drug acquisition, drug administration and monitoring, management of disease progression, end-of-life care, and management of AEs.

Key effectiveness estimates considered in the analysis included OS, PFS, time to treatment discontinuation (to define the time on treatment for nivolumab and regorafenib), utilities, and disutilities. The comparison of nivolumab with BSC and regorafenib was informed by the manufacturer-sponsored ITC. The key efficacy data underlying the ITC were obtained from CheckMate 040 for nivolumab, BRISK-PS for BSC, and RESORCE for regorafenib.

Drug costs: High drug cost

Nivolumab costs $782.40 per 40 mg vial, or $1,956.00 per 100 mg vial. The cost per administration is $4,474.62, based on a dose of 3 mg/kg on day 1 of each 14-day cycle, intravenous administration over 60 minutes.

Zero drug costs were assigned to BSC.

Regorafenib costs $6,115.51 per pack of 40 mg 84 tablets. The total cost per administration is $2,038.50.

Cost-effectiveness estimates: Not cost-effective at the submitted price

The Committee deliberated upon the cost-effectiveness of nivolumab compared with BSC. pERC noted that the EGP estimate of the lower-bound incremental cost-effectiveness ratio (ICER) ($193,458 per quality-adjusted life-year [QALY]) was higher than the submitter's estimate ($161,944 per QALY). pERC noted that an upper-bound ICER could not be estimated due to the uncertainty in the comparative efficacy estimates obtained from the submitted ITC.

The Committee also deliberated upon the cost-effectiveness of nivolumab compared with regorafenib based on a scenario analysis. pERC noted that the EGP estimate of the lower bound ($159,708 per QALY) was higher than the submitter's estimate ($135,584 per QALY).

The Committee noted the assumptions upon which the EGP estimates for the comparison of nivolumab with BSC and regorafenib were based. pERC agreed with the EGP's reanalysis, which included:

- shortening the time horizon to a three-year time horizon from a lifetime time horizon, with input from the Clinical Guidance Panel
- using utilities from a previous pCODR review of regorafenib as second-line treatment for patients with HCC following treatment with sorafenib; these utilities were considered more appropriate considering the progressed patient population
- using the RESORCE trial (instead of the BRISK trial) as the data source for PFS and OS curves, to appropriately reflect the BSC patient population.

The Committee noted that these changes to the estimates of the incremental effect and costs increased the lower-bound ICER estimates. pERC noted that the EGP was unable to estimate an upper bound of the ICER because of the lack of direct comparative effectiveness estimates and the inability to evaluate the uncertainty in the submitted ITCs. Furthermore, pERC noted that the EGP was unable to evaluate the effect of prolonged treatment of nivolumab — a plausible scenario, considering that treatment post-progression was allowed in the trial. The Committee noted that the pCODR EGP requested an updated model to evaluate the effect of prolonged treatment with nivolumab; however, the submitter did not provide an updated model. The Committee agreed with the EGP that there is a high level of uncertainty in the lower-bound ICER and that the estimate of the upper bound is unknown, given the limitations in the submitted economic model. Overall, pERC noted that the magnitude of long-term benefit associated with nivolumab is unknown, given the limitations in the comparative efficacy data and the lack of long-term data. pERC noted that, at the submitted price, nivolumab compared with BSC and regorafenib is not considered cost-effective in this population. The Committee cautioned there is a high level of uncertainty in the cost-effectiveness estimates because of a lack of direct comparative effectiveness data in the submitted economic evaluation.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: Additional chemotherapy and nursing resources, uncertain assumptions in the budget impact analysis

pERC noted factors that could impact the feasibility of implementing a positive conditional reimbursement recommendation for nivolumab for the treatment of adults who have progressed on, or are intolerant to, sorafenib. The Committee discussed that additional chemotherapy chair time and nursing resources would be required to administer nivolumab the Provincial Advisory Group (PAG) also noted that there is an ongoing phase III trial comparing nivolumab with sorafenib as first-line treatment and indicated that a submission would be required for reimbursement consideration of nivolumab as first-line treatment. pERC also noted that the PAG had requested a comparison of nivolumab with BSC and regorafenib. Additionally, pERC discussed PAG's request for clarity on sequencing of treatments for

patients who are treated with other therapies, and the treatment duration of nivolumab, as well as guidance on whether retreatment with nivolumab would be appropriate for patients following a treatment break. Finally, pERC also considered the submitted budget impact analysis and noted that the submitter assumed that the market share of second-line nivolumab would decline over time with the assumption that nivolumab would become available in the first-line setting. The Committee discussed that, at this time, nivolumab in the first-line setting is not available in Canada and that this assumption presupposes the outcome of the ongoing trial of nivolumab in the first-line setting. The Committee was uncertain about the assumptions in the submitted budget impact analysis and concluded that the budget impact is likely underestimated.

DRUG AND CONDITION INFORMATION

Drug Information	• Immunotherapy (monoclonal antibody) • Solution for injection at a concentration of 10 mg/mL in either 40 mg or 100 mg single-use vial • Nivolumab is administered intravenously at a dose of 3 mg/kg over 60 minutes every two weeks until disease progression or unacceptable drug toxicity.
Cancer Treated	• Unresectable or metastatic hepatocellular carcinoma (HCC)
Burden of Illness	• Approximately 2,500 new cases of HCC were diagnosed in Canada in 2017. • Patients with this condition face a poor survival prognosis, with limited options after progression on sorafenib.
Current Standard Treatment	• Best supportive care
Limitations of Current Therapy	• Select fit population that can be treated due to adverse effects

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:

pERC Membership During Deliberation of the Initial Recommendation

Dr. Maureen Trudeau, Oncologist (Chair)
Dr. Catherine Moltzan, Oncologist (Vice-Chair)
Dr. Kelvin Chan, Oncologist
Lauren Flay Charbonneau, Pharmacist
Dr. Matthew Cheung, Oncologist
Dr. Winson Cheung, Oncologist
Dr. Avram Denburg, Pediatric Oncologist
Leela John, Pharmacist
Dr. Anil Abraham Joy, Oncologist
Dr. Christine Kennedy, Family Physician
Cameron Lane, Patient Member Alternate
Christopher Longo, Economist
Valerie McDonald, Patient Member
Carole McMahon, Patient Member
Dr. Marianne Taylor, Oncologist

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

- Cameron Lane, who did not vote due to his role as a patient member alternate.

pERC Membership During Deliberation of the Final Recommendation

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

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

- Daryl Bell, Dr. Winson Cheung, Dr. Avram Denburg, Dr. Kelvin Chan, and Dr. Christine Kennedy who were not present for the meeting.

Avoidance of conflicts of interest

All members of the pCODR pERC must comply with the *pCODR Conflict of Interest Guidelines*; individual conflict of interest statements for each member are posted on the pCODR website, and pERC members have an obligation to disclose conflicts on an ongoing basis. For the review of nivolumab (Opdivo) for HCC, through their declarations, three members had a real, potential, or perceived conflict, and, based on application of the *pCODR Conflict of Interest Guidelines*, no members were excluded from voting. For the Final Recommendation, four members had a real, potential, or perceived conflict, and based on application of the *pCODR Conflict of Interest Guidelines*, no members were excluded from voting.

Information sources used

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

Consulting publicly disclosed information

pCODR considers it essential that pERC recommendations be based on information that may be publicly disclosed. All information provided to pERC for its deliberations was handled in accordance with the *pCODR Disclosure of Information Guidelines*.

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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