pCODR EXPERT REVIEW COMMITTEE (pERC)
INITIAL 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.

Providing Feedback on This Initial Recommendation
Taking into consideration feedback from eligible stakeholders, the pCODR Expert Review Committee (pERC) will make a Final Recommendation. Feedback must be provided in accordance with *pCODR Procedures*, which are available on the pCODR website. The Final Recommendation will be posted on the pCODR website once available, and will supersede this Initial Recommendation.

Drug: Nivolumab (Opdivo)

Submitted Funding Request:
For the treatment of recurrent or metastatic squamous cell cancer of the head and neck (SCCHN) after platinum-based therapy in adults

Submitted by:
Bristol-Myers Squibb Canada

Manufactured by:
Bristol-Myers Squibb Canada

NOC Date:
May 12, 2017

Submission Date:
January 31, 2017

Initial Recommendation Issued:
June 29, 2017

pERC RECOMMENDATION	The pCODR Expert Review Committee (pERC) recommends the reimbursement of nivolumab conditional on its cost-effectiveness being improved to an acceptable level. Reimbursement should be for the treatment of patients with SCCHN who have a recurrence within six months of potentially curative therapy or after receiving platinum-based therapy in a non-curative setting, and who have a good performance status. Treatment should continue until unacceptable toxicity or disease progression. pERC made this recommendation because it was satisfied that there is a net clinical benefit of nivolumab in patients with recurrent or metastatic SCCHN based on a clinically meaningful improvement in overall survival and an acceptable toxicity profile. pERC also concluded that the therapy aligns with patient values, in that it offers an improvement in overall survival and maintains quality of life (QoL). However, pERC noted that, at the submitted price, nivolumab could not be considered cost-effective compared with standard of care options. pERC also highlighted that the potential budget impact of nivolumab may be underestimated and could be substantial.
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	**Pricing Arrangements to Improve Cost-Effectiveness** Given that pERC was satisfied that there was a net clinical benefit with nivolumab compared with chemotherapy in patients with recurrent or metastatic SCCHN after receiving platinum-based therapy, jurisdictions may want to consider alternate pricing arrangements and/or cost structures to improve the cost-effectiveness and affordability to an acceptable level.

Factors Affecting Budget Impact and Adoption Feasibility
pERC noted that the unknown treatment duration of nivolumab — as it continues until disease progression or unacceptable toxicity, whichever occurs first — affects jurisdictions' abilities to anticipate the budget impact. In considering the high cost of nivolumab, the potential for drug wastage, and the unknown but potentially long duration of treatment, pERC concluded that a substantial reduction in drug price would be required to improve affordability.

Optimal Dosage of Nivolumab
pERC noted that nivolumab was studied and approved at a dose of 3 mg/kg every two weeks until disease progression or unacceptable toxicity, whichever occurs first. pERC acknowledged that a flat dose of nivolumab has also been approved for other indications; however, there is currently no evidence for flat dosing for the current indication.

Time-Limited Need for Nivolumab
When implementing a funding recommendation for nivolumab, jurisdictions may consider addressing the time-limited need for nivolumab in patients currently receiving chemotherapy after experiencing a recurrence after platinum-based regimens. pERC noted that this time-limited access should be for patients with SCCHN who have a recurrence within six months of potentially curative therapy or recurrence after receiving platinum-based therapy in a non-curative setting, and who have a good performance status.

Optimal Sequencing of Nivolumab and Other Therapies Unknown
pERC concluded that the optimal sequencing of nivolumab and other treatments now available to treat patients with recurrent or metastatic SCCHN who have had at least one prior treatment is unknown. Therefore, pERC was unable to make an evidence-informed recommendation on sequencing. However, pERC recognized that the provinces would need to address this issue when implementing nivolumab reimbursement, and noted that collaboration among provinces to develop an evidence-based guideline would be of value.

SUMMARY OF pERC DELIBERATIONS

The burden of illness for patients with recurrent or metastatic SCCHN is high. This is due to significant morbidity associated with SCCHN and the absence of many effective treatment options. The current treatment options that are available for patients with recurrent or metastatic SCCHN who have failed cisplatin-based chemotherapy include docetaxel, capecitabine, or paclitaxel with or without carboplatin. However, pERC agreed with the pCODR Clinical Guidance Panel (CGP) that it is difficult to establish a standard of care due to a lack of clinical evidence. Thus, pERC concluded that there is a need for more effective and tolerable treatments in this patient population.

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 large randomized controlled trial (RCT), CheckMate 141. The trial assessed the efficacy and safety of nivolumab compared with the investigator's choice of chemotherapy (i.e., single-agent therapy with docetaxel, methotrexate, or cetuximab) in patients with recurrent or metastatic SCCHN who had been treated and failed platinum-based chemotherapy. pERC determined that there was a net clinical benefit of nivolumab over chemotherapy due to a clinically meaningful benefit in overall survival in patients with recurrent or metastatic SCCHN. pERC noted that the overall survival curves for nivolumab and chemotherapy crossed each other early in the follow-up period, which increases the uncertainty in the effect estimates, as it suggests the hazard of death is not constant over time. Despite this uncertainty, pERC agreed with the CGP and commented that there did appear to be a clinically meaningful difference between the survival curves. pERC also stated that there were no statistically significant differences between nivolumab and chemotherapy for progression-free survival (PFS) or objective response rate (ORR). However, pERC noted that this lack of difference may be due to nivolumab's mechanism of action as well as the fact that some patients in the trial continued to receive nivolumab after progression because they may have not truly progressed.

pERC discussed the toxicity profile of nivolumab, and noted that there were fewer adverse events in patients treated with nivolumab compared with those treated with standard chemotherapy. pERC also addressed the QoL data reported in the trial. The results of the CheckMate 141 study suggest that QoL is at least maintained for patients treated with nivolumab, including a minimally important decline in painkiller use and an increase in weight gain. There were also minimally important changes for patients treated with standard therapy. However, pERC noted that there was uncertainty in the QoL estimates due to variation in the sample size at the different assessment periods. The limited sample size resulted from later assessment periods and a higher proportion of withdrawals from the chemotherapy arm. Therefore, based on the clinically meaningful and statistically significant improvement in overall survival, maintenance of QoL, and acceptable toxicities compared with chemotherapy, pERC concluded that there was an overall net clinical benefit of nivolumab in patients with metastatic or recurrent SCCHN.

pERC deliberated on the specific eligibility criteria used in the CheckMate 141 trial, which included: histologically confirmed, recurrent, or metastatic SCCHN of the oral cavity, pharynx, or larynx that was not amenable to curative treatment; an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; and tumour progression or recurrence within six months after the last dose of platinum-containing chemotherapy administered as adjuvant therapy or in the context of primary or recurrent disease. Based on these criteria, pERC recommends that the reimbursement of nivolumab is suitable for patients with SCCHN who have recurrence within six months of a potentially curative therapy or who have received and failed platinum-based therapy in the non-curative setting.

pERC also deliberated on the generalizability of the CheckMate 141 trial results, and stated that the following groups of patients may also be eligible for nivolumab: patients with treated and controlled brain metastases; patients with mucosal squamous cell carcinomas arising from any head and neck sub-site, regardless of human papillomavirus (HPV) status (except Epstein-Barr virus-encoded ribonucleic acid [EBER]-positive nasopharyngeal cancer and primary skin cancers); patients with an ECOG performance status of 2; patients who have received multiple lines of prior chemotherapy; and/or patients with HIV and known hepatitis B or hepatitis C infection. First, pERC agreed with the CGP that brain metastases are

a relatively rare occurrence in patients with recurrent or metastatic SCCHN. Second, pERC noted that patients with EBER-negative nasopharyngeal cancers — or with head and neck squamous cell cancers of unknown primary — are similar to those with mucosal SCCHN because they have similar tumour biology and clinical behaviours, and receive identical treatments. Third, pERC agreed that patients with an ECOG performance status of 2, who are still ambulatory to some degree but are poor candidates for chemotherapy, may be eligible for this treatment because of its favourable toxicity profile. Fourth, pERC noted that more than 50% of patients in the CheckMate 141 trial had more than one previous line of therapy. Finally, pERC concluded that patients with HIV and known hepatitis B or hepatitis C infection may qualify if their infection is under control and the treatment decision is at the discretion of the treating physician. pERC also discussed the effect of programmed death-ligand 1(PD-L1) testing in patients with recurrent or metastatic SCCHN. They agreed with the CGP that the results of biomarker analyses in CheckMate 141 were not definitive, and that there is not sufficient evidence to support the use of PD-L1 testing for nivolumab.

pERC deliberated on the alignment of nivolumab with patient values. The Committee reviewed input from one patient advocacy group, the Canadian Cancer Survivor Network (CCSN), which highlighted patient and caregiver experiences. The input provided by CCSN gave pERC a broader understanding of patients' experiences with SCCHN and its treatments. pERC noted that patients with SCCHN would like access to treatments that control symptoms, such as trouble swallowing, dry mouth, pain or discomfort, dental problems, and fatigue. Although no patients had received treatment with nivolumab, pERC observed that, compared with their current medications, patients expect nivolumab to reduce side effects, stop disease progression, better control symptoms, and be accessible. Additionally, pERC noted that patients who struggle with disease progression and uncertainty about the future were willing to tolerate fairly major side effects. Thus, pERC concluded that nivolumab aligns with patient values, as it provides a significant improvement in survival (compared with chemotherapy) and in maintaining QoL, and has an acceptable toxicity profile.

pERC deliberated upon the cost-effectiveness of nivolumab and concluded that, at the submitted price, it was not cost-effective compared with chemotherapy. pERC considered estimates provided by the submitter and reanalyses performed by the pCODR Economic Guidance Panel (EGP). pERC noted that the following factors had the largest impact on the incremental cost-effectiveness ratio (ICER): cost of cetuximab as comparator to nivolumab, health utilities, time horizon, duration of treatment, and drug dosage (e.g. average patient weight assumed, flat dosing vs. weight-based dosing). First, pERC noted that including the cost of cetuximab in the economic evaluation underestimated the submitted ICER because of its significant costs and it is not a relevant comparator. Second, pERC agreed with the EGP that the health utilities derived from the trial were high, and were more representative of the general population as opposed to a population of patients with SCCHN. Given this, pERC considered the EGP's reanalysis, where utilities were reduced by 10% to better resemble the clinical population, and stated that the true ICER is likely near the upper end of the EGP's reanalysis estimate. Third, pERC acknowledged that the submitter used a time horizon of 10 years. pERC accepted the EGP's reanalysis, which reduced the time horizon to three years, because it was more representative of patients with recurrent or metastatic SCCHN. Fourth, pERC discussed that patients in the CheckMate 141 trial received nivolumab beyond disease progression as defined by the Response Evaluation Criteria in Solid Tumors (RECIST), and agreed with the EGP's approach to use time-to-treatment discontinuation to better represent the treatment duration of patients who received nivolumab. Finally, pERC acknowledged the reanalysis considering the dosage of nivolumab, in which the EGP performed a reanalysis of weight-based dosing and a flat dose of 240 mg. pERC accepted that the ICER may be higher if a fixed dose of 240 mg of nivolumab is implemented, as this dose coincides with an average patient weight of 80 kg in the treatment population.

pERC considered the feasibility of implementing a funding recommendation for nivolumab. pERC agreed with the EGP that the submitted budget impact analysis was underestimated due to the estimated market shares in the analysis. In the reference budget impact scenario, cetuximab was considered to have the largest market share; but this therapy is not publicly reimbursed in Canada. The reference budget impact also assumed nivolumab would impose nearly half of the market share in a funded scenario. Thus, the EGP performed a reanalysis that omitted the impact of cetuximab in the reference and funded scenarios, which led to a greater budget impact over three years. Furthermore, even with the exclusion of cetuximab, pERC noted that the budget impact analysis still underestimated the market share of nivolumab because it is unlikely that patients would choose a less effective and more toxic treatment over nivolumab. pERC also acknowledged that there may be potential for indication creep; however, early-line use of nivolumab was outside the scope of this review. pERC commented that there may be a potential for drug wastage — due to the small number of patients, unknown length of treatment, and

weight-based dosing — and that this could also have a substantial impact on the cost of nivolumab. Although there was some discussion that a flat dose of nivolumab has also been implemented for other indications, pERC decided that current evidence supports the use of weight-based dosing of nivolumab; and the review did not identify any evidence to use a fixed dose in this patient setting. Thus, pERC concluded that jurisdictions may want to consider alternative pricing arrangements and/or cost structures to improve the cost-effectiveness and affordability to an acceptable level.

pERC discussed the CGPs' input that it would be unlikely for patients to switch from first-line chemotherapy to obtain earlier access to nivolumab because these patients would continue their prior therapy until maximum benefit was achieved. However, patients who demonstrated excessive toxicity with first-line chemotherapy may be considered candidates for nivolumab treatment at the time of documented disease progression. Regardless, pERC stated that there is minimal evidence to support the use of nivolumab in the first-line setting. pERC also considered that additional chair time and resources may be required to monitor patients for infusion reactions early in the treatment course. Finally, pERC noted that patients with recurrent metastatic SCCHN who have been previously treated with nivolumab would be suitable candidates for third-line chemotherapy. For these patients, the therapeutic agents that are normally used in the second-line setting could be considered, but the effectiveness of these drugs in this setting is uncertain. Additionally, pERC noted that patients who were not responsive to nivolumab would most likely be unsuitable for subsequent chemotherapy.

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 (Canadian Cancer Survivor Network [CCSN])
- Input from registered clinicians
- Input from pCODR's Provincial Advisory Group (PAG).

OVERALL CLINICAL BENEFIT

pCODR review scope
The purpose of the review is to evaluate the safety and efficacy of nivolumab as monotherapy in patients with recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN) after receiving platinum-based therapy.

Studies included
The pCODR systematic review included one open-label, phase III randomized controlled trial (RCT), CheckMate 141, which compared nivolumab to standard therapy in 361 patients with recurrent SCCHN whose disease had progressed within six months after platinum-based chemotherapy. Adult patients were eligible to enrol in the trial if they had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; histologically confirmed, recurrent, or metastatic SCCHN of the oral cavity, pharynx, or larynx that was not amenable to curative treatment; tumour progression or recurrence within six months after the last dose of platinum-containing chemotherapy administered as adjuvant therapy or in the context of primary or recurrent disease; adequate bone marrow, hepatic, and renal function; and measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. Patients were randomized (2:1) to receive treatment with nivolumab (N = 240) or chemotherapy, which consisted of a single-agent therapy of the investigator's choice (N = 121). In this arm, patients were treated with methotrexate (40 mg/m^2 to 60 mg/m^2 weekly; N = 52), docetaxel (30 mg/m^2 to 40 mg/m^2 weekly; N = 54), or cetuximab (400 mg/m^2 followed by 250 mg/m^2 weekly; N = 15). Randomization was stratified by previous cetuximab therapy. Patients in the nivolumab group could continue to receive nivolumab beyond RECIST-defined disease progression if they continued to demonstrate clinical benefit.

Patient populations
The pCODR Clinical Guidance Panel (CGP) noted that the baseline characteristics of the patient population were well balanced across the treatment groups, except for smoking status. Overall, the median age of patients in the trial was 60 (range: 28 to 83) years of age. The majority of the patients enrolled in the trial were male (83.1%), Caucasian (83.1%), current or former smokers (76.5%), and had an ECOG performance status of 1 (78.4%). Most patients had received prior platinum therapy in the adjuvant, primary, recurrent, or metastatic setting, and 93.9% progressed on or within six months after receiving a prior therapy. In addition, a larger proportion of patients enrolled in CheckMate 141 had received cetuximab as a prior treatment (nivolumab: 62.5%; standard therapy: 59.5%).

After discussing the generalizability of the CheckMate 141 trial results, the CGP stated that given the favourable toxicity profile of nivolumab compared with chemotherapy, nivolumab could be considered for patients with a declining performance status (i.e., Eastern Cooperative Oncology Group Performance Status [ECOG PS] of 2 or more) if the factors that affect performance status are disease-specific and they are considered to be reversible with treatment. The CGP also discussed that cetuximab is not approved or funded for this indication in Canada. However, the CGP recognized that the proportion of patients enrolled in the CheckMate 141 trial who were randomized to receive treatment with cetuximab was small, and that by excluding them, the effect estimates of overall survival (OS) were similar; thus, the results remained generalizable to the Canadian population. The CGP also considered the results of the trial to be generalizable to patients who have squamous cell carcinomas of less common mucosal sites (i.e., nasal cavity and paranasal sinuses) or EBER-negative nasopharyngeal cancer, but not to those with primary skin cancers. In addition, the CGP commented that cancer progression within six months of a

prior treatment in patients with metastatic SCCHN should not be a requirement for nivolumab therapy. The CGP felt that this time frame was not critical and that assessing tumour progression at this time point would impose an excessive restriction to patients who might potentially benefit from nivolumab. Finally, the CGP agreed that patients with recurrent or metastatic SCCHN do not have to be platinum-refractory prior to receiving nivolumab. They stated this because SCCHN is not a sufficiently platinum-sensitive disease; thus, it is reasonable to include patients who may have progressed within six months of starting platinum-based chemotherapy; and most will be heavily platinum-exposed by the time they reach their second-line treatment.

Key efficacy results: Clinically meaningful improvement in overall survival
The key efficacy outcome pERC deliberated on was OS. The CGP and Methods Team agreed that nivolumab was associated with a statistically significant prolongation of OS compared with standard therapy in patients with SCCHN (hazard ratio: 0.70; 97.73% confidence interval [CI], 0.51 to 0.96; *P* = 0.01). Progression-free survival (PFS) and objective response rate (ORR) were not significant. Although the CGP stated that the trial did not provide sufficient evidence to demonstrate an association between PD-L1 levels on disease risk and treatment response to nivolumab, pERC commented that more research is required to explore the effect of this biomarker in patients with SCCHN.

Patient-reported outcomes: Maintenance of quality of life
Patient-reported outcomes were measured using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30 (EORTC QLQ-C30), the Quality of Life Questionnaire Head and Neck module (QLQ-H&N35), and the EuroQol five dimensions questionnaire (EQ-5D-3L) scales. Overall, for patients in the nivolumab treatment group, quality of life (QoL) is at least maintained. There was a minimally important decline in painkiller use reported at weeks 9, 15, and 21, and a minimally important increase in weight reported at weeks 9 and 15 in the EORTC QLQ-H&N35. In contrast, there were a number of minimally important declines and improvements reported in the standard therapy group. However, there was uncertainty in these estimates because of the limited sample sizes at the different assessment periods for the nivolumab and chemotherapy treatment groups.

Safety: Meaningful improvement in grade 3 and grade 4 toxicities
The CGP highlighted that patients treated with nivolumab reported fewer grade 3 to grade 4 treatment-related adverse events (AEs) compared with those treated with standard therapy (13.1% versus 35.1%). Overall, pERC agreed with the CGP that nivolumab demonstrated a meaningful improvement in grade 3 to grade 4 toxicities compared with chemotherapy, and that the AE profiles were better for nivolumab than in the control group.

Need and burden of illness: No standard therapy; more effective therapies required
In 2016, more than 5,700 Canadians were diagnosed with SCCHN; 1,600 died. Patients with SCCHN who have lymph node involvement are at the highest risk of recurrence. PFS at three years for this patient group was estimated to be 38% in carcinogen-associated cancers and 74% in human papilloma virus (HPV)-related cancers when treated with concurrent chemoradiation. Thus, a significant proportion of SCCHN patients will present or develop metastatic disease and require further therapy.

There are not many effective treatments options available for patients with recurrent or metastatic SCCHN whose cancer progresses on or after first-line platinum-based chemotherapy. These types of patients are generally offered best supportive care or participation in a clinical trial. However, evidence from clinical trials has shown that docetaxel has a superior response to methotrexate in patients with SCCHN, while more limited evidence suggests that capecitabine, cetuximab, and paclitaxel (with or without carboplatin) may be effective. Nonetheless, cetuximab has not been used widely because it is not available in most jurisdictions and does not have regulatory approval. Thus, given the lack of data from RCTs, pERC agreed that there is a need for alternative options that prolong survival and improve QoL.

PATIENT-BASED VALUES

Values of patients with squamous cell carcinoma of the head and neck: Symptom management, quality of life, and overall survival
Patient advocacy input from CCSN indicated that head and neck cancer has both negative physical and psychological impacts on patients living with advanced cancer. The symptoms most frequently experienced by patients include pain or discomfort, fatigue, trouble swallowing, sleep deprivation,

depression, and anxiety. Patients with SCCHN indicated that they would like to control the following symptoms: trouble swallowing, dry mouth, pain or discomfort, dental problems, and fatigue. pERC noted that these problems and issues affect patients' QoL and ability to enjoy life.

Patient values on treatment: More effective treatment options, improved overall survival, disease control, and quality of life
Input from CCSN indicated that current therapies — such as cisplatin, radiotherapy plus cetuximab, paclitaxel, carboplatin, carboplatin plus paclitaxel, cisplatin plus 5 FU (fluorouracil), and cetuximab — can extend life expectancy, but are associated with significant toxicities. Common side effects include fatigue, loss of appetite, hair loss, and constipation. Patients have also experienced nausea, hypothyroidism, peripheral neuropathy, low blood count, trismus, and infections with these treatment options. There is also a high burden of this disease for patients and their caregivers. Caregivers experience difficulties with food and meal preparation, understanding tongue discomfort, helping their loved ones deal with depression, post-traumatic stress disorder, and anxiety, and must spend time dealing with insurance companies.

None of the patients who provided input had experience with nivolumab. However, input from CCSN indicated that patients would like nivolumab to reduce their side effects from their current treatments, stop disease progression, control their symptoms, and be accessible. pERC acknowledged that patients who struggle with disease progression and uncertainly about the future are willing to tolerate significant side effects.

ECONOMIC EVALUATION

Economic model submitted: Cost-utility and cost-effectiveness analysis
The pCODR Economic Guidance Panel (EGP) assessed a cost-effectiveness and cost-utility analysis comparing nivolumab with single-agent chemotherapy in patients with SCCHN who had disease progression on or after platinum therapy.

Basis of the economic model: Clinical and cost inputs
Costs considered in the analysis were those associated with disease management, end of life or terminal care, drug acquisition, administration, AEs, monitoring, and subsequent therapies.

Data on clinical effect estimates (i.e., OS and PFS) and utilities in the progression-free and post-progression states were obtained from the CheckMate 141 trial. In contrast, information on disutilities was taken from the literature or identified from a review of previous Health Technology Assessment submissions to the National Institute for Health and Care Excellence (NICE) for advanced or metastatic SCCHN.

Drug costs: Nivolumab more expensive than all comparators
At the recommended dose of 3 mg per kg every two weeks, the cost of nivolumab is $293.33 per day (no wastage); $307.30 per day (with wastage); $8,213.35 per 28-day course (no wastage), and/or $8,604.44 per 28-day course (with wastage).

At the list generic price, docetaxel costs $12.13 per mg, $117.81 per day, and $3,298.68 per 28-day course. Methotrexate costs $8.00 per 25 mg, $4.66 per day, and $130.56 per 28-day course. Finally, the list generic price of cetuximab is $7.58 per 2 mg, $229.96 per day, and $6,498.75 per 28-day cycle.

Cost-effectiveness estimates: Not cost-effective compared with chemotherapy
pERC discussed the submitter's and the EGP's reanalysis estimates of the incremental cost-effectiveness ratio (ICER) in patients with recurrent or metastatic SCCHN with disease progression on or after platinum therapy. In both settings, pERC accepted the EGP's reanalysis estimates and concluded that nivolumab was not cost-effective.

In the submitted cost-effectiveness model, use of cetuximab as a comparator, health utilities, time horizon, duration of treatment, and nivolumab dosing (e.g. average patient weight assumed, flat dosing vs. weight-based dosing) had the greatest impact on the ICER. First, including the cost of cetuximab in the economic evaluation may have underestimated the submitted ICER because of its significant cost and it is not a relevant comparator. Next, although the treatment-specific utilities were derived from

CheckMate 141, the EGP felt that the included utilities were high for the patient population. Given this uncertainty, the EGP conducted a reanalysis, where they reduced the utilities by 10% to be more representative of the clinical population. In addition, the EGP truncated the time horizon from 10 years to 3 years, which was considered to provide a more accurate reflection of survival in patients with SCCHN in this setting. In addition, the EGP explored the use of time-to-treatment discontinuation to estimate drug costs as opposed to the assumption that treatment duration is equal to time to progression. Finally, the EGP's analysis investigating the dosing of nivolumab demonstrated that flat dosing will have a larger impact on the cost of nivolumab, which would subsequently increase the ICER and the budget impact.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: High drug cost, potentially substantial budget impact, and uncertain duration of treatment

pERC discussed the feasibility of implementing a funding recommendation for nivolumab in patients with SCCHN. pERC acknowledged that there is currently no evidence to suggest an optimal duration of treatment with nivolumab, but agreed that it is important for jurisdictions to manage the budget impact of this reimbursement recommendation.

pERC noted PAG's concern of drug wastage based on the small number of patients and weight-based dosing. To address this concern, pERC discussed the reanalysis by EGP, where the impact of different patient weight averages and the potential use of flat dosing in patients with SCCHN were assessed. In this model, the EGP used a range of weights for patients with SCCHN and also applied a flat dose of 240 mg. pERC noted that if flat dosing was implemented, then costs would most likely increase. pERC also agreed with the EGP that the submitted budget impact analysis was underestimated because nivolumab will likely take a larger market share in this funded scenario. The substantial budget impact of nivolumab resulted from the high cost of nivolumab, the potential for flat dosing/drug wastage, a large market share, and an unknown/potentially long duration of treatment. Thus, a substantial reduction in the price of nivolumab will be required to improve cost-effectiveness and bring affordability to an acceptable level. pERC stated that jurisdictions will need to consider the uncertainty in these factors during implementation.

pERC discussed PAG's concern that nivolumab may have the potential for indication creep into earlier lines of therapy because of the limited number of treatment options available for patients with recurrent or metastatic SCCHN. However, pERC also recognized that the use of nivolumab in the first-line setting was beyond the scope of this review. Furthermore, the CGP was unaware of any clinical trials that supported the use of nivolumab in the first-line setting.

pERC stated that the provinces would need to have a common approach to define true disease progression for PD-L1 inhibitors. This will ensure that patients who experience pseudo-progression — whereby some patients technically meet RECIST criteria for disease progression, but do not have true disease progression — may continue treatment with nivolumab until true disease progression occurs. pERC also acknowledged a time-limited need for nivolumab for those patients receiving treatment with single agent chemotherapy or who have recently completed treatment with single agent chemotherapy and who would otherwise meet the eligibility criteria of the CheckMate 141.

DRUG AND CONDITION INFORMATION

Drug Information	• Nivolumab is a PD-L1 immune checkpoint inhibitor. • Nivolumab 3 mg/kg administered as an intravenous infusion over 60 minutes every 2 weeks. • 40 mg vial, 100 mg vial
Cancer Treated	• For the treatment of recurrent or metastatic squamous cell carcinoma of the head and neck after platinum-based therapy in adults as long as clinical benefit is observed or until treatment is no longer tolerated by the patient.
Burden of Illness	• In 2016, more than 5,700 patients in Canada were diagnosed with SCCHN and 1,600 died from it. • 32% of SCCHN patients were diagnosed with localized disease, 44% with regionally advanced disease, and 18% with distant metastases.
Current Standard Treatment	• Docetaxel • Paclitaxel • Methotrexate • Gemcitabine • Vinorelbine • Etoposide
Limitations of Current Therapy	• Current therapies offer only modest improvements in survival and quality of life. • Poor performance status of patients makes it difficult for many patients to tolerate the toxicities of chemotherapy.

ABOUT THIS RECOMMENDATION

The pCODR Expert Review Committee

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

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

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

- Jo Nanson, who was not present for the meeting

Avoidance of conflicts of interest
All members of the pCODR Expert Review Committee must comply with the *pCODR Conflict of Interest*

Guidelines; individual conflict of interest statements for each member are posted on the pCODR website and pERC members have an obligation to disclose conflicts on an ongoing basis. For the review of nivolumab (Opdivo), through their declarations, no members had a real, potential, or perceived conflict. Based on application of the *pCODR Conflict of Interest Guidelines*, none of these members was excluded from voting.

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

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

Use of this Recommendation
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