# 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 patients with advanced or metastatic renal cell cancer who have received prior systemic therapy

**Submitted By:**
Bristol-Myers Squibb Canada

**Manufactured By:**
Bristol-Myers Squibb Canada

**NOC Date:**
April 25, 2016

**Submission Date:**
February 24, 2016

**Initial Recommendation Issued:**
June 30, 2016

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| pERC RECOMMENDATION | pERC recommends reimbursement of nivolumab conditional on the cost-effectiveness being improved to an acceptable level. Reimbursement should be for the treatment of patients with advanced or metastatic renal cell carcinoma (RCC) with disease progression after at least one prior systemic treatment and who have a good performance status. Treatment should continue until disease progression or unacceptable toxicity.<br><br>The Committee made this recommendation because it was satisfied that there is a net clinical benefit with nivolumab compared to everolimus based on statistically significant and clinically meaningful improvements in overall survival and objective response rate and a meaningful improvement in the toxicity profile. pERC also agreed that nivolumab aligned with patient values.<br><br>The Committee concluded that, at the submitted price, nivolumab is not cost-effective in patients with previously treated advanced or metastatic RCC. pERC also noted that there is a potential for a substantial budget impact with nivolumab. |
| POTENTIAL NEXT STEPS FOR STAKEHOLDERS | **Pricing Arrangements to Improve Cost-Effectiveness and Budget Impact**<br>Given that pERC was satisfied that there is a net clinical benefit with nivolumab compared with everolimus in patients with advanced or metastatic RCC who have received at least one prior systemic therapy, jurisdictions may want to consider alternative pricing arrangements and/or cost structures to improve the cost-effectiveness and affordability to an acceptable level. |

**Generalizability of Results Into Patients With Non-Clear Cell Renal Cell Carcinoma**
pERC noted that patients in the CheckMate 025 trial had clear cell RCC and there was no evidence presented on the efficacy and safety of using nivolumab in patients with the non-clear cell histology. However, pERC noted that traditionally, patients with non-clear cell and clear cell RCC receive similar systemic therapies; additionally, pERC noted that non-clear cell RCC is uncommon and heterogeneous; and there are no randomized trials in this difficult-to-study patient population. In this context, pERC concluded that treatment should be extended to include patients with advanced or metastatic RCC who have a non-clear cell histology. pERC also noted that jurisdictions will need to consider the budget impact of including these patients into the reimbursement population.

**Factors Affecting Budget Impact and Adoption Feasibility**
pERC noted the potentially long duration of treatment with nivolumab, as it continues until confirmed disease progression or unacceptable toxicity, whichever comes first. pERC also noted that the market share of nivolumab is likely underestimated in the submitted budget impact analysis and the Committee anticipates that the true budget impact of nivolumab could be substantial. In considering the high cost of nivolumab, the potential for drug wastage, the market share of nivolumab, and the potentially long duration of treatment, pERC concluded that a substantial reduction in drug price would be required to improve affordability.

**Evidence Generation to Understand Optimal Duration of Therapy**
pERC noted that nivolumab is approved at a dose of 3 mg/kg every two weeks until confirmed disease progression or unacceptable toxicity, whichever comes first. pERC acknowledged that there is currently no evidence to identify an optimal set or fixed duration of treatment with nivolumab and agreed that it is important to prospectively collect such data. The Committee also agreed that treatment duration should be reassessed in the event that new evidence emerges on an optimal duration of treatment.

**Common Approach to Define Confirmed Disease Progression**
pERC noted the unique mechanism of action of immunotherapeutic agents and acknowledged that in a small percentage of patients, standard Response Evaluation Criteria in Solid Tumors (RECIST)-defined radiologic disease growth may be due to immune-related inflammation and may not be reflective of true disease progression (i.e., it is pseudoprogression). pERC noted that there is no consistently accepted definition for pseudoprogression in the clinical community. pERC agreed that until such a definition becomes available, it is reasonable to use the definition from within the pivotal trial, which defined true progression as an additional 10% in tumour burden and/or development of new lesions since the time of initial disease progression. A confirmatory scan should be done six weeks after initial progression to assess patients for true progression.

**Time-Limited Need for Nivolumab**
At the time of implementing a funding recommendation for nivolumab, jurisdictions may consider addressing the time-limited need for nivolumab for those patients who are currently receiving treatment with everolimus. pERC noted that this time-limited access should be for patients with clear cell and non-clear cell histology, who have a good performance status, have had at least two prior

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| | treatments, and who would otherwise meet the eligibility criteria of the CheckMate 025 study.<br><br>**Optimal Sequencing of Nivolumab and Other Therapies Unknown**<br>pERC concluded that the optimal sequencing of nivolumab and other treatments now available for the treatment of patients with advanced or metastatic RCC who have had at least one prior treatment is unknown. pERC was therefore unable to make an evidence-informed recommendation on sequencing. However, pERC recognized that provinces would need to address this issue upon implementation of nivolumab reimbursement and noted that collaboration among provinces to develop an evidence-based guideline would be of value. |

# SUMMARY OF pERC DELIBERATIONS

In 2015, the estimated Canadian incidence for kidney cancer was 6,200 new cases, with approximately 1,800 deaths. pERC noted that the majority of kidney cancers (90%) are RCCs. Among these, the majority (80%) are of clear cell histology, whereas 20% are classified as non-clear cell cancers. The most important prognostic factor for outcome is tumour stage. Approximately 25% of patients have metastatic renal cell carcinoma (mRCC) at diagnosis, while 30% to 50% of patients with localized disease will eventually develop metastatic disease. Patients with metastatic disease are rarely cured and have lower survival rates than those with localized tumours. After failure of first-line therapy, the mammalian target of rapamycin (mTOR) inhibitor, everolimus, or the tyrosine kinase inhibitor (TKI), axitinib, are considered standard second-line treatment options. Both of these treatments have demonstrated improvements in progression-free survival (PFS) but no clear overall survival (OS) benefit. The use of both TKIs and mTOR inhibitors is also limited by their toxicity. pERC therefore agreed that there is a need for treatment options with demonstrated improvements in OS and a reduced toxicity profile.

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

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

pERC deliberated upon the results of one phase 3 randomized controlled trial (CheckMate 025) comparing nivolumab to everolimus in adult patients with advanced or metastatic clear cell RCC who have received one or two prior anti-angiogenic therapies. pERC concluded that there is a net clinical benefit of nivolumab over everolimus based on statistically significant and clinically meaningful improvement in OS and objective response rate (ORR). Additionally, pERC acknowledged the limited data available on patient-reported outcomes. While results demonstrated statistically significant improvements from baseline with nivolumab, an improvement from baseline was not demonstrated with everolimus. The Committee however agreed that only limited interpretation could be made on the available data. The Committee discussed the safety profile of nivolumab relative to everolimus and noted the decreased incidence of treatment-related adverse events with nivolumab, and more specifically that the decreased incidence of grade 3 and 4 treatment-related adverse events was meaningful in this patient population. pERC noted supplementary evidence demonstrating similar benefit of nivolumab in patients who have had more than two prior anti-angiogenic therapies and agreed that it would be reasonable to make nivolumab available to this prevalent patient population.

pERC noted that the CheckMate 025 trial included patients with clear cell RCC and there was no evidence presented on the efficacy and safety of using nivolumab in patients with the non-clear cell histology. However, pERC noted that traditionally, with respect to systemic therapy, patients with non-clear cell RCC are treated the same as patients with clear cell RCC. Additionally, pERC noted that non-clear cell RCC represents a smaller proportion of the RCC population (20%) than patients with clear cell RCC and there are no randomized trials in this difficult-to-study patient population. In this context, pERC concluded that treatment should be extended to include patients with advanced or metastatic RCC who have a non-clear cell histology. pERC noted that the CheckMate 025 trial excluded patients with a Karnofsky score of < 70 (approximately Eastern Cooperative Oncology Group [ECOG] Performance Status (PS) 2). The Committee noted that patients with ECOG PS 2 or greater are typically excluded from trials, including those trials used to determine the efficacy of TKIs in this population. Input from the pCODR Clinical Guidance Panel (CGP) also indicated that, in clinical practice, patients with ECOG PS of 2 or greater are, however, treated with TKIs. Given the better toxicity profile of nivolumab compared with everolimus, pERC was satisfied that patients with a poorer performance status are likely to tolerate nivolumab well. pERC also considered whether the exclusion from the CheckMate 025 trial of patients with poorer performance status may have been due to the expected intolerance patients would experience with everolimus. While pERC acknowledged the gap in the evidence for the efficacy and safety of nivolumab in these patients, the Committee was comfortable with generalizing the results of CheckMate 025, as patients may derive a benefit, based on opinion of the CGP and the mechanism of action of nivolumab.

pERC noted that patients with brain metastases were excluded from the CheckMate 025 trial. Additionally, given that nivolumab does not cross the blood–brain barrier, pERC was unable to make a conclusion on the clinical benefit of nivolumab in patients with brain metastases without specific evidence demonstrating clinical benefit. Overall, pERC concluded that there is a net overall clinical benefit with nivolumab, based upon statistically significant and clinically meaningful improvements in OS and ORR, and a meaningful improvement in the toxicity profile compared with everolimus.

pERC deliberated upon input from one patient advocacy group concerning nivolumab and noted that patients value long-term stability or reduction of disease, improvement in their physical condition, and improvement in quality of life as important. Whereas patients expressed a willingness to tolerate side effects with new and effective treatment options, they noted the control of pain and problems associated with mobility in the treatment of kidney cancer as being of value. Given that nivolumab demonstrated a statistically significant and clinically meaningful improvement in OS and ORR, and a meaningful improvement in toxicity profile, pERC agreed that nivolumab aligned with patient values. Input from patients indicated that side effects associated with nivolumab were few or were very tolerable, which aligned with the results of the CheckMate 025 trial.

pERC deliberated upon the cost-effectiveness of nivolumab compared with everolimus and concluded that, at the submitted price, nivolumab is not cost-effective. Uncertainty regarding estimates for utilities, mean body weight of patients, and drug wastage were considered in the reanalysis estimates by the pCODR Economic Guidance Panel (EGP). pERC noted that utilities derived from the trial were high and close to what is observed in the general (i.e., healthy) population. The Committee agreed that the lower utility values used by the EGP better reflected those of patients with advanced RCC. The Committee also agreed with the EGP's use of a mean body weight that better reflected the body weight of patients in the clinical setting. These two changes had a substantial impact on the incremental cost-effectiveness ratio (ICER). The incorporation of drug wastage also had an impact on the ICER. Overall, pERC accepted the EGP's reanalysis estimates and concluded that nivolumab is not cost-effective relative to everolimus.

pERC discussed the feasibility of implementing a reimbursement recommendation for nivolumab for patients with advanced or metastatic RCC. The Committee recognized that during implementation, jurisdictions will need to consider costs associated with the additional chemotherapy chair time, given that nivolumab is administered intravenously compared with the standard oral therapy; the need to train health care professionals to administer therapy, particularly in smaller centers; and the need to treat drug-related adverse events. pERC also recognized that provinces would need to address treatment sequencing upon implementation of nivolumab reimbursement and noted that collaboration among provinces to develop a common approach would be of value.

pERC discussed the potential budget impact of nivolumab and disagreed with the submitted estimates for the expected market share of nivolumab. The Committee agreed with the EGP that the submitted budget impact analysis is likely substantially underestimated, as the market share for nivolumab will probably be larger than the submitter estimated. Therefore, pERC considered that there is a potential for a substantial budget impact for nivolumab. Furthermore, pERC noted that the potential for drug wastage, given the short stability and weight-based dosing, together with the high cost of nivolumab and larger market share, would have a substantial impact on the cost-effectiveness and affordability of nivolumab, and that jurisdictions may need to consider alternative pricing arrangements and/or cost structures to improve the cost-effectiveness and affordability to an acceptable level.

# 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 provides clinical context
- An evaluation of the manufacturer's economic model and budget impact analysis
- Guidance from pCODR clinical and economic review panels
- Input from one patient advocacy group, Kidney Cancer Canada (KCC)
- 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 a monotherapy compared with an appropriate comparator, on patient outcomes in the treatment of adult patients with advanced or metastatic renal cell carcinoma (RCC) who have received prior systemic therapy.

### Studies included: One randomized controlled trial

The pCODR systematic review included one double-blind, phase 3, randomized controlled trial, CheckMate 025, comparing nivolumab to everolimus in patients with advanced or metastatic renal cell carcinoma (RCC) who have undergone one or two prior regimens of anti-angiogenic therapy, but no more than three prior regimens of systemic therapy in the metastatic setting.

Key inclusion criteria required that patients have histological confirmation of mRCC with clear cell component and a Karnofsky Performance Score of ≥ 70%. Exclusion criteria were any history of central nervous system (CNS) metastases or prior therapy with a mammalian target of rapamycin (mTOR) inhibitor.

The pCODR review also provided contextual information on two studies: a phase 1 trial (Topalian et al. 2012) assessing the safety, anti-tumour activity and pharmacokinetics of nivolumab in a variety of cancers (34 patients with mRCC), and a randomized, dose-ranging phase 2 trial (Motzer et al. 2015) which assessed the anti-tumour activity, dose-response relationship, and safety of nivolumab in previously treated mRCC patients. The two studies provided results on the efficacy and safety of nivolumab in patients who had received three or more prior systemic regimens. While acknowledging the limitations with the data presented in these two trials, pERC noted that results in patients who have had three or more prior systemic therapies appeared similar to the results observed in the pivotal trial, CheckMate 025.

### Patient populations: Treatment beyond progression, clear cell renal cell carcinoma only, Karnofsky Performance Status Scale 100 to 70 (approximately ECOG PS 0 to 2)

Patients in the CheckMate 025 trial were randomized 1:1 to receive nivolumab at 3 mg/kg every two weeks intravenously or everolimus at 10 mg per day as a tablet. Baseline characteristics were well balanced across the nivolumab and everolimus groups, respectively, including age (median 62 years in both groups), sex (male, 77% and 74%), and favourable (35% and 36%), intermediate (49% in both groups), and poor (16% and 15%) Memorial Sloan–Kettering Cancer Center (MSKCC) risk group status. The majority of patients had a Karnofsky performance status of 100 (31% and 33%), 90 (37% and 32%), 80 (27% and 28%), or 70 (5% and 7%), in the nivolumab and everolimus arms, respectively.

Both arms continued treatment until disease progression, discontinuation due to toxicity, withdrawal of consent, or end of study. Treatment with nivolumab beyond initial progression was allowed for both treatments at the investigator's discretion and as specified within the study protocols. pERC noted the mechanism of action of immunotherapies and the possibility that some patients may experience pseudoprogression — whereby some patients technically meet Response Evaluation Criteria in Solid Tumors (RECIST) criteria for disease progression, but do not have true disease progression — and, therefore, may be treated beyond RECIST-defined disease progression and continue to receive treatment until true disease progression. However, pERC noted that there is no consistently accepted definition for

pseudoprogression in the clinical community. Until such a definition becomes available, pERC agreed that it is reasonable to use the definition from within the pivotal trials, which defined true progression as an additional 10% in tumour burden and/or development of new lesions from the time of initial disease progression, demonstrated through a confirmatory scan conducted six weeks after initial progression. pERC did not support the continuation of treatment with everolimus beyond initial investigator-assessed RECIST 1.1-defined progression, as there is no evidence to support the efficacy and safety of using everolimus beyond RECIST-defined progression.

### Key efficacy results: Clinically meaningful improvement in overall survival and objective response rate

The key efficacy outcome deliberated on by pERC was overall survival (OS), the primary outcome in the trial. After the minimum follow-up period of 14 months, the median OS was statistically higher in the nivolumab group than in the everolimus group (25.0 versus 19.6 months; hazard ratio [HR] = 0.73; 95% confidence interval [CI], 0.57 to 0.93; *P*=0.002). This OS benefit was consistent across most patient subgroups. pERC noted that an OS benefit has not been demonstrated with other treatments available for patients with advanced or metastatic RCC who have had prior systemic therapy. The Committee therefore agreed that nivolumab provided a statistically significant and clinically meaningful improvement in OS. Objective response rate (ORR) was also statistically higher with nivolumab compared with everolimus (25% versus 5%; odds ratio = 5.98; 95% CI, 3.68 to 9.72; $P < 0.001$). As is seen with other studies evaluating efficacy with immunotherapies, pERC noted that progression-free survival (PFS) was not different between the treatment groups.

pERC considered PD-L1 status as a predictor of response and noted that uncertainty exists concerning the role of PD-L1 testing and whether there is a threshold below which patients should not be treated. Given this uncertainty, the Committee agreed that treatment with nivolumab should be made available to patients irrespective of PD-L1 status. pERC also considered the generalizability of the overall results to patients with a Karnofsky score < 70 (approximately Eastern Cooperative Oncology Group [ECOG] Performance Status [PS] 2) and noted an absence of evidence to support the effectiveness of nivolumab in this population. Based on nivolumab's toxicity profile and current treatment practice, which includes the use of tyrosine kinase inhibitors (TKIs) in previously treated patients, the Committee was confident that nivolumab would be tolerated by patients with a poorer performance status. pERC also discussed the generalizability of the overall trial results in patients who have had three or more prior systemic therapies and considered supplemental evidence provided through phase 1 and phase 2 trial data. The data suggested that nivolumab provides similar benefit in this patient population as was demonstrated in the CheckMate 025 trial. Although uncertainty remained related to nivolumab's efficacy and safety in both these patient populations, pERC was comfortable with generalizing the results of the CheckMate 025 trial into these patient populations. Therefore, pERC agreed that the availability of nivolumab should be extended to patients with a good performance status and to patients who have had more than two prior systemic therapies. pERC acknowledged that nivolumab will likely quickly become the treatment of choice in the second-line setting, and therefore availability in the third line and beyond will be required only for the prevalent population.

pERC further noted that the CheckMate 025 trial included patients with clear cell RCC and there was no evidence presented on the efficacy and safety of using nivolumab in patients with the non–clear cell histology. Given that patients with non–clear cell are typically treated with systemic therapies used in patients with clear cell RCC, pERC discussed the generalizability of the trial results into this patient population. Additionally, pERC noted that non–clear cell RCC represents a smaller proportion of the RCC population (20%) than patients with clear cell RCC and there are no randomized trials in this difficult-to-study patient population. In this context, pERC concluded that treatment should be extended to include patients with advanced or metastatic RCC who have a non–clear cell histology.

### Patient-reported outcomes: Limited interpretation of results

Patient-reported outcomes (PROs) were measured in the CheckMate 025 trial using the Functional Assessment of Cancer Therapy–Kidney System Index (FKSI-DRS) scale, which consists of nine self-reported symptom-specific questions, with summary scores ranging from 0 (worst health status) to 36 (best health status). At the one-year mark, the completion rate was 80% in the nivolumab group and 81% in the everolimus group. The median changes from baseline score (31.0 in both groups) were statistically and consistently better in the nivolumab group at each assessment after baseline for patients in the

nivolumab group, compared with the everolimus group ($P < 0.05$), but the absolute differences in summary scores between groups were small. pERC discussed the results of these data and concluded that limited interpretation could be made at this time.

**Safety: Meaningful improvement in grade 3 and 4 toxicity compared with everolimus**

pERC discussed the toxicity profile of nivolumab as observed in the CheckMate 025 trial. Treatment-related adverse events (AEs) of any grade were reported in 79% and 88% of the nivolumab- and everolimus-treated patients, respectively. Grade 3 and 4 treatment-related AEs were reported in 19% and 37% of the nivolumab- and everolimus-treated patients, respectively. pERC agreed that the reduction in grade 3 and 4 treatment-related AEs with nivolumab compared with everolimus was meaningful in this patient population. This reduction also aligned with values expressed by patients. The most common treatment-related AEs in the nivolumab group were fatigue (33%), nausea (14%), and pruritus (14%), whereas those in the everolimus-treated patients were fatigue (34%), stomatitis (29%), and anemia (24%). Patient also expressed through their input that there is a willingness to tolerate additional toxicities with the introduction of an effective treatment option.

**Need: Manageable toxicity and overall survival benefit**

In 2015, the estimated Canadian incidence for kidney cancer was 6,200 new cases, with approximately 1,800 deaths. pERC noted that the majority of kidney cancers (90%) are RCCs. Among these, the majority (80%) are of clear cell histology, whereas 20% are classified as non–clear cell cancers. pERC noted that the most important prognostic factor for outcome is tumour stage. Approximately 25% of patients have metastatic disease at diagnosis, whereas 30% to 50% of patients with localized disease will eventually develop metastatic disease. These patients are rarely cured and have lower survival rates than those with localized tumours. pERC also noted that patients with non–clear cell RCC have a worse prognosis and their disease is difficult to treat.

In patients with advanced metastatic RCC, who have already experienced treatment failure after previous chemotherapy, everolimus (an oral mTOR inhibitor) and axitinib (an oral vascular endothelial growth factor receptor (VEGF-R) TKI) are considered standard treatment options based on a significant PFS benefit. However, the use of these drugs has been limited by their toxicity and demonstrated improvement only in PFS. Neither treatment option has demonstrated a clear survival benefit. pERC therefore agreed that there is a need for treatment options with demonstrated improvements in OS and a reduced toxicity profile.

## PATIENT-BASED VALUES

**Values of patients with advanced or metastatic renal cell carcinoma: Pain and mobility control, impaired ability to work and travel, side effects, and caregiver perceptions**

Patients with RCC ranked pain control and mobility as being of highest importance among aspects of RCC to control. These were followed by fatigue and shortness of breath. Patients noted that kidney cancer's impact on their day-to-day activities has been most significant with regard to their ability to work, followed by their ability to travel, exercise, conduct household chores, fulfill family obligations, and spend time with family and friends. Patients noted fatigue to be the most common side effect with available therapies, followed by diarrhea, loss of appetite, hand-foot syndrome, and skin problems. Patients also expressed having difficulty in accessing treatment, some of which was due to cost of drug, long waiting period to be approved for treatment, or having to travel to the US to access treatment.

Caregivers expressed that symptoms of kidney cancer have the most substantial impact on their ability to travel, followed by their abilities to work and volunteer. Caregivers also faced challenges due to the side effects of the kidney cancer drugs. These included feeling stress when dealing with patient side effects, disruption to daily life including missed work, having to tend to patient medical needs, financial stress, loss of sleep, and management of medications to treat side effects.

**Patient values on treatment: Improved overall survival, slower disease progression, and availability of additional treatment options with new therapy**

When asked to rate the importance of outcomes with a new treatment, patients expressed long-term stability or reduction of disease, improvement to physical condition, and improvement to quality of life as all being important. The majority of patients providing input expressed that it was very important to have

access to new treatments for kidney cancer, as well as the ability to choose treatment based upon known side effects. Patients also expressed a willingness to accept side effects of a new treatment as long as it has proven effectiveness. Based upon statistically significant and clinically meaningful improvements in OS and meaningful reduction in treatment-related grade 3/4 AEs, pERC concluded that nivolumab aligned with patient values. pERC also noted that nivolumab may likely have potential long-term survival benefit in a smaller proportion of patients. pERC agreed that this aligned with the patient value of having access to effective treatments with a long-term stability of disease. pERC was limited with regard to the interpretation it could make on the impact of nivolumab on patient quality of life, given the limited data available.

Among patients providing input, 17 had experience with nivolumab, with seven having received nivolumab monotherapy and 10 combination therapy with nivolumab and another agent. It is notable that 12 to 15 patients responded to questions on side effects associated with nivolumab. A larger proportion of respondents indicated that side effects were not applicable to them, suggesting patients did not experience certain side effects associated with nivolumab. Other patients indicated that the following side effects were very tolerable: diarrhea; headache; shortness of breath; nausea; rash; pain in muscles, bones, and joints; constipation; injection-related side effects at time of infusion; fatigue; decreased appetite; cough; flu-like symptoms; and hand-foot syndrome. One patient indicated that headaches, diarrhea, and pain in muscles, bones, and joints were completely intolerable. pERC noted that input from patients on the side effects associated with nivolumab aligned with the results of the CheckMate 025 trial.

Patients also expressed that they experienced improved tolerability with nivolumab as compared with other treatments for RCC, most notably sunitinib and everolimus. pERC was unable to differentiate between patients who had received monotherapy and combination therapy and was therefore unsure whether reported side effects were due to nivolumab or the combination treatment.

## ECONOMIC EVALUATION

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

The pCODR Economic Guidance Panel (EGP) assessed cost-effectiveness and cost-utility analyses comparing nivolumab with everolimus in patients with advanced or metastatic RCC who had received prior systemic therapy.

### Basis of the economic model: High drug cost, high utilities from trial

Costs included were cost of the drugs, drug administration costs, supportive care costs, and AE management costs. pERC noted that the price of nivolumab had the largest impact on the incremental cost-effectiveness ratio (ICER). Other cost drivers included estimates of mean body weight of patients and drug wastage, both of which were explored in the EGP's reanalysis estimates.

Key clinical effects considered in the analysis were obtained from the CheckMate 025 trial and included OS, time to discontinuation, AE rates, and utility values. pERC considered the extrapolation of OS data over 10 years to be appropriate, as nivolumab appears to have long-term benefit in a proportion of patients that would be captured over the 10-year time horizon. pERC noted concern from the PAG on the potentially long duration of treatment with nivolumab, given that treatment may continue beyond progression in patients experiencing pseudoprogression. pERC noted that the submitted model used time to treatment discontinuation as an input and therefore accounted for this treatment beyond progression. pERC lastly noted that the utility estimates from the trial were high and likely do not reflect the health state utility of patients with advanced or metastatic RCC, as the values were near those observed in the general population.

### Drug costs: High cost of drug

Nivolumab costs $782.22 per 40 mg vial or $1,955.56 per 100 mg vial. At the recommended dose of 3 mg/kg every two weeks, the cost is $293.33 per day and $8,213.35per 28-day course without accounting for wastage, but $307.30 per day and $8,604.44 per 28-day course with wastage accounted for.

Everolimus costs $196.55 per 10 mg tablet. At the recommended dose of 10 mg per day, the cost is $196.55 per day and $5,503.40 per 28-day course.

**Cost-effectiveness estimates: Mean body weight, utility values, and drug wastage**
pERC discussed the submitter's and EGP's best estimate of the ICER of nivolumab compared with everolimus. pERC accepted the EGP's reanalysis estimates and concluded that nivolumab is not cost-effective.

More specifically, pERC noted that the mean body weight used in the submitted model was 70 kg, but that patients in the CheckMate 025 trial had a mean body weight of 82.4 kg. pERC agreed with the EGP's reanalysis using the body weight from the trial, as it better reflected the clinical population. The utility values derived from the trial and used in the economic evaluation were similar to those for the general (i.e., healthy) population and did not reflect the decrements that would be expected with patients who have advanced or metastatic RCC and have previously been treated. pERC agreed with the EGP's use of alternate utilities (derived from an appraisal of axitinib for advanced RCC by the National Institute for Health and Care Excellence [NICE]). Finally, the base case used vial sharing and thus assumed no drug wastage. However, given the potential for wastage in centres where vial sharing is not possible, as indicated in the PAG input, pERC accepted the EGP's reanalysis incorporating drug wastage. The base case for the manufacturer's model was based on a 10-year time horizon. Given the potential for long-term survival benefit in a proportion of patients, as is observed with immunotherapies, pERC agreed with the EGP's decision to leave the time horizon at 10 years, which will capture this long-term benefit.

## ADOPTION FEASIBILITY

**Considerations for implementation and budget impact: High drug cost, potentially substantial budget impact, uncertain duration of treatment**
pERC discussed factors affecting the feasibility of implementing a reimbursement recommendation for nivolumab for patients with advanced or metastatic RCC who have previously been treated. pERC noted the PAG's concern about the long duration of therapy and acknowledged that the mechanism of action of immunotherapies suggests that it is reasonable to investigate whether a shorter treatment course could provide an optimal disease response while minimizing patients' risk for potential side effects. pERC acknowledged that there is currently no evidence to suggest an optimal duration of treatment with nivolumab, but agreed that it is important for jurisdictions to prospectively collect these data to manage the budget impact of a reimbursement recommendation.

pERC acknowledged that drug wastage is an important concern for the PAG and noted that the EGP included wastage in its reanalysis estimates. pERC also noted that the estimates for the market share of nivolumab in submitted budget impact analysis were underestimated, as the Committee expects nivolumab will take a larger market share once available in this setting. pERC therefore agreed that the budget impact of nivolumab may be substantial. Overall, due to the high cost of nivolumab, the potential for drug wastage, the larger marker share, and the potentially long duration of treatment, pERC concluded that a substantial reduction in drug price would be required to improve cost-effectiveness and affordability to an acceptable level. pERC noted that jurisdictions will need to consider the uncertainty in these factors during implementation.

pERC acknowledged a time-limited need for nivolumab for those patients who are receiving treatment with everolimus in the second-line setting. pERC noted that there is no evidence for the use of nivolumab in the first-line setting, as this was out of the scope of this review. There are, however, ongoing phase 3 trials evaluating the efficacy and safety of nivolumab in the first-line setting, which can help inform a reimbursement decision. Similarly, the input recognized that there are many treatments available for mRCC in the second-line setting and beyond; thus, a national guideline for the sequencing of these treatments may be helpful.

pERC recognized that provinces would need to have a common approach to define true disease progression and ensure that patients who experience pseudoprogression — whereby some patients technically meet RECIST criteria for disease progression but do not have true disease progression — may continue treatment with nivolumab until true disease progression occurs. Until a widely accepted definition for pseudoprogression becomes available, in the context of nivolumab and other immune checkpoint inhibitors, pERC agreed that it is reasonable to use the definition from within the pivotal trial, which defined true progression as an additional 10% in tumour burden and/or development of new lesions

since the time of initial disease progression. pERC agreed that this would need to be demonstrated through a confirmatory scan conducted six weeks after initial progression.

# DRUG AND CONDITION INFORMATION

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| **Drug Information** | • Nivolumab is a PD-1 immune checkpoint inhibitor.<br>• Nivolumab is available at $782.22 per 40 mg vial or $1,955.56 per 100 mg vial.<br>• The recommended dose is 3 mg per kg of body weight every two weeks. |
| **Cancer Treated** | • Previously treated advanced or metastatic RCC |
| **Burden of Illness** | • 6,200 new cases of kidney cancer in Canada in 2015<br>• Approximately 1,800 deaths from kidney cancer in Canada in 2015<br>• 90% of kidney cancers are RCC, with 25% of those being metastatic (mRCC) |
| **Current Standard Treatment** | • Everolimus is the standard of care treatment for previously treated patients with advanced or metastatic RCC.<br>• Axitinib is the standard of care treatment for previously treated patients with advanced or metastatic RCC who cannot tolerate everolimus. |
| **Limitations of Current Therapy** | • Unmanageable toxicities<br>• No confirmed overall survival benefit |

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

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

- Valerie McDonald, who did not vote due to her role as a patient member alternate
- Paul Hoskins and Kelvin Chan, who were not present.

### Avoidance of conflicts of interest

All members of 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 advanced or

metastatic renal cell carcinoma, through their declarations, six members had a real, potential, or perceived conflict, and based on application of the *pCODR Conflict of Interest Guidelines*, none of these members was 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.

### Disclaimer

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