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
Upon consideration of feedback from eligible stakeholders, pERC members considered that criteria for early conversion of an Initial Recommendation to a Final Recommendation were met and reconsideration by pERC was not required.

Drug: Nivolumab (Opdivo) plus Ipilimumab (Yervoy) **Submitted Reimbursement Request:** Intermediate/poor risk patients with previously untreated, advanced or metastatic renal cell carcinoma	
Submitted by: Bristol-Myers Squibb	**Manufactured by:** Bristol-Myers Squibb
NOC Date: July 6, 2018	**Submission Date:** April 26, 2018
Initial Recommendation: August 30, 2018	**Final Recommendation:** November 1, 2018

Approximate per Patient Drug Costs, per Month (28 Days)	Nivolumab costs $1,956.00 per 100 mg vial and $782.22 per 40 mg vial. • At the recommended dose of 3 mg/kg every three weeks for the first four doses, over 12 weeks, nivolumab costs $195.56 per day and $5,475.57 per 28-day course. • At the recommended dose of 3 mg/kg every two weeks, nivolumab single-agent costs $293.33 per day $8,213.35 per 28-day course. Ipilimumab costs $23,200.00 per 200 mg vial and $5,800.00 per 50 mg vial. • At the recommended dose of 1 mg/kg every three weeks x four doses, ipilimumab costs $386.67 per day and $10,826.67 per 28-day course.

pERC RECOMMENDATION	pERC recommends the reimbursement of nivolumab (Opdivo) plus ipilimumab (Yervoy) in patients with intermediate or poor-risk advanced renal-cell carcinoma (RCC) based on the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) criteria only if the following condition is met: • Cost-effectiveness is improved to an acceptable level. If the aforementioned condition cannot be met, pERC does not recommend reimbursement of nivolumab plus ipilimumab. Eligible patients should be previously untreated in the metastatic setting and have a good performance status. Treatment should continue until disease progression or unacceptable toxicity. pERC made this recommendation because it was confident that there is a net clinical benefit of nivolumab plus ipilimumab compared with sunitinib based on statistically significant and clinically meaningful improvements in both overall survival and objective response rate. In addition, there was a manageable toxicity profile compared with sunitinib. pERC concluded that the combination of nivolumab plus ipilimumab aligns with patient values in that it offers an improvement in overall survival and it provides patients with another effective and tolerable treatment option. pERC concluded that, at the submitted price, nivolumab plus ipilimumab is

© 2018 pCODR | PAN-CANADIAN ONCOLOGY DRUG REVIEW

	not cost-effective compared with sunitinib.
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	**Pricing Arrangements to Improve Cost-Effectiveness of Nivolumab Plus Ipilimumab Compared with Sunitinib** Given that pERC concluded that there is a net clinical benefit with nivolumab plus ipilimumab in patients with intermediate or poor-risk advanced RCC, jurisdictions may want to consider pricing arrangements and/or cost structures that would improve the cost-effectiveness of nivolumab plus ipilimumab compared with sunitinib. **Optimal Sequencing of Available Therapies After Progression on Nivolumab Plus Ipilimumab** pERC noted that there is currently no clinical trial evidence to inform the optimal sequencing of available treatments following progression on first-line treatment with nivolumab plus ipilimumab. pERC also noted that patients progressing on nivolumab plus ipilimumab are unlikely to be treated with another immunotherapy and may instead be offered a targeted agent or be enrolled in a clinical trial. **Time-Limited Need for Nivolumab Plus Ipilimumab** When implementing a funding recommendation for nivolumab plus ipilimumab, jurisdictions may consider addressing the time-limited need for this combination treatment in patients currently receiving a targeted agent in the first-line setting and who have not experienced disease progression. pERC noted that this time-limited access should be for previously untreated patients with intermediate or poor-risk RCC with a clear-cell component and who would otherwise meet the eligibility criteria outlined in this recommendation. **Restart of Treatment in Patients Who Progress During a Treatment Break** pERC noted that treatment breaks are expected to occur more frequently in clinical practice compared with the CheckMate 214 trial, which did not allow treatment breaks. pERC therefore agreed that it is reasonable to restart treatment in patients who progress during a treatment break, and that the decision to restart should be left to the treating oncologist. The Committee further noted that this scenario was not explored in the submitted budget impact analysis model or cost-effectiveness analysis. Therefore, pERC noted that the impact of re-initiating treatment in patients who have had a treatment break and develop disease progression is unknown. The Committee agreed that jurisdictions will need to consider the uncertainty in these factors upon implementation. **Please note:** Provincial Advisory Group (PAG) questions are addressed in detail in the Summary of pERC Deliberations and in a summary table in Appendix 1.

© 2018 pCODR | PAN-CANADIAN ONCOLOGY DRUG REVIEW

SUMMARY OF pERC DELIBERATIONS

Kidney cancer accounts for approximately 3% of all cancers in Canada. In 2017, the estimated Canadian incidence for kidney cancer was 6,600 new cases, with approximately 1,900 deaths. pERC noted that the majority of kidney cancers (85%) are RCC. Among these, the majority (80%) are of clear-cell histology. The most important prognostic factor for outcome is tumour stage.

Among patients with metastatic disease, 75% will have intermediate or poor-risk disease. Patients with metastatic disease are rarely cured and have lower survival rates than those with localized tumours. Sunitinib and pazopanib are considered the standard treatment options in the first-line setting. pERC noted that considerable monitoring and dose adjustments are required to manage toxicities associated with targeted agents. pERC therefore agreed that there is a need for more effective treatment options that prolong survival and have better toxicity profiles.

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 randomized, open-label trial (CheckMate 214) comparing nivolumab plus ipilimumab to sunitinib monotherapy for previously untreated clear-cell advanced RCC. pERC concluded that there is a net clinical benefit of nivolumab plus ipilimumab over sunitinib based on statistically significant and clinically meaningful improvements in overall survival (OS) and objective response rate (ORR). Even though only a limited interpretation could be made on the available quality of life data, pERC agreed that nivolumab plus ipilimumab did not appear to result in deterioration of patients' quality of life. The Committee discussed the safety profile of nivolumab plus ipilimumab relative to sunitinib and noted that the incidence of grade 3 or higher toxicities was lower with the combination treatment. However, discontinuations due to adverse events and immune related adverse events were higher in the combination group. Overall, pERC agreed that nivolumab plus ipilimumab was better tolerated than sunitinib. Therefore, pERC concluded that there is a net overall clinical benefit with nivolumab plus ipilimumab, based upon statistically significant and clinically meaningful improvements in OS and ORR and a manageable toxicity profile compared with sunitinib.

pERC discussed the generalizability of the overall trial results in patients with advanced or metastatic RCC. Although the CheckMate 214 trial only compared nivolumab plus ipilimumab with sunitinib, pERC noted that the efficacy and safety outcomes with sunitinib are generalizable to those of pazopanib, a relevant comparator in the Canadian setting. Therefore, pERC agreed that the trial results are generalizable to the Canadian population. pERC also discussed that the CheckMate 214 trial included patients with clear-cell RCC and there was no evidence presented on the efficacy and safety of using nivolumab plus ipilimumab in patients with non-clear-cell histology. Upon reconsideration of the Initial Recommendation, pERC considered feedback from PAG related to the generalizability of the trial results to patients with non-clear-cell histology. pERC noted feedback from the Clinical Guidance Panel (CGP) clarifying that patients with non-clear-cell RCC are managed the same way as patients with clear-cell RCC. pERC therefore agreed that it is reasonable to generalize the CheckMate 214 trial results to patients with non-clear-cell RCC. pERC noted that the CheckMate 214 trial excluded patients with a Karnofsky Performance Status Scale score less than 70 (approximately Eastern Cooperative Oncology Group [ECOG] Performance Status [PS] 2) and that patients with ECOG PS 2 or greater are typically excluded from trials. Input from the CGP indicated that concerns related to the tolerability of agents in patients with poorer PS are of lesser concern with immunotherapies as the agents are well tolerated. pERC was therefore satisfied that patients with a poorer PS are likely to tolerate the combination treatment and should be included in the reimbursement population. pERC further agreed that the use of nivolumab plus ipilimumab should be restricted to patients who have not had previous treatment with an immunotherapy agent in the metastatic setting. Finally, the use of nivolumab plus ipilimumab in patients with pre-existing autoimmune disease should be left to the discretion of the treating oncologist.

pERC deliberated upon input from one patient advocacy group (Kidney Cancer Canada) concerning nivolumab plus ipilimumab and noted that patients value additional treatment options with fewer side effects, which delay disease progression and improve survival. Patients also emphasized the impact of RCC on their quality of life particularly as their disease progresses. Given that nivolumab plus ipilimumab

© 2018 pCODR | PAN-CANADIAN ONCOLOGY DRUG REVIEW

demonstrated statistically significant and clinically meaningful improvements in OS and ORR, a manageable toxicity profile and no deterioration in quality of life, pERC agreed that nivolumab plus ipilimumab aligned with patient values. Although few patients had direct experience using this combination agent, patients indicated that side effects associated with nivolumab plus ipilimumab were few or were very tolerable, which aligned with the results of the CheckMate 214 trial.

pERC deliberated upon the cost-effectiveness of nivolumab plus ipilimumab compared with sunitinib and concluded that, at the submitted price, nivolumab plus ipilimumab is not cost-effective. Uncertainty regarding the duration of treatment effect, cost of treatment/duration of treatment, estimates for utilities, and distribution of subsequent agents were considered in the reanalysis estimates by the pCODR Economic Guidance Panel (EGP). pERC noted that the observed treatment effect, based on a follow-up period of 25.2 months from the CheckMate 214 trial, was set to continue over a 15-year time horizon in the base-case results. Input from the CGP indicated that there is insufficient long-term follow-up data to support such a prolonged treatment effect. pERC therefore agreed with the EGP's reanalysis which reduced the amount of benefit accrued after the end of the trial period up to year five.

pERC also noted that treatment costs were based on the time to treatment discontinuation curve in the submitted analysis. Although this was reflective of treatment discontinuation observed in the trial (30% of patients discontinuing treatment due to study drug toxicity or adverse events unrelated to study drug), pERC noted that nearly 30% of patients had continued treatment beyond progression. Based on this, pERC agreed that using the time to treatment discontinuation curve to determine costs associated with treatment would not be an accurate representation of costs. Although there was no information on how long patients remained on treatment beyond progression, pERC agreed that the EGP's use of the progression-free survival curves, which account for a longer period of treatment, were a more reasonable estimate of treatment costs. pERC agreed that assumptions on the duration of treatment effect and duration of treatment had the largest impact on the incremental cost-effectiveness ratio. Furthermore, changes to the estimates of utilities and the distribution of subsequent treatments patients would receive also impacted the incremental cost-effectiveness ratio. Based on changes made to these inputs, pERC agreed that the true incremental cost-effectiveness ratio is likely closer to the upper range of the EGP's reanalysis estimates and concluded that nivolumab plus ipilimumab is not cost-effective compared with sunitinib.

pERC discussed the feasibility of implementing a reimbursement recommendation for nivolumab plus ipilimumab for patients with intermediate or poor-risk and previously untreated RCC. pERC noted that the factors that influenced the budget impact analysis include the number of treatment lines considered (first-line only or up to three lines), eligible patient population, treatment duration of nivolumab-ipilimumab, and market share of nivolumab-ipilimumab. With the generalizability of the trial data into a number of additional patient populations, pERC acknowledged that the eligible patient population is likely to be bigger. It is unclear how much the budget impact analysis will be affected by this.

The Committee noted input from pCODR's PAG, which requested guidance and clarification on the implementation of nivolumab plus ipilimumab. pERC agreed that the outcomes observed with sunitinib can be generalized to treatment with pazopanib, a relevant comparator in the Canadian setting. For patients who are currently on first-line treatment with sunitinib or pazopanib and who have not experienced disease progression, pERC agreed that a decision to continue or switch treatment to nivolumab plus ipilimumab should be made with discussions between the treating oncologist and patient. Upon reconsideration of the Initial Recommendation, pERC considered feedback from PAG asking for clarity on criteria for restarting therapy after progression during a treatment break. pERC noted feedback from the CGP indicating that treatment breaks are expected to occur more frequently in clinical practice compared with the clinical trial, which did not allow treatment breaks. pERC therefore agreed that it is reasonable to restart treatment in patients who progress during a treatment break, and that the decision to restart should be left to the treating oncologist. pERC agreed that patients who have already been treated with an immunotherapy agent in the metastatic setting should not be eligible for reimbursement.

pERC agreed that it is reasonable to administer nivolumab as a 3 mg/kg dose up to a maximum of 240 mg every two weeks or 6 mg/kg up to a maximum of 480 mg every four weeks. pERC further agreed that the trial results did not demonstrate differing efficacy based on the programmed death-ligand 1 (PD-L1) expression levels and agreed that companion diagnostic testing is not required to determine patients' PD-L1 status for eligibility of treatment. pERC also recognized that provinces would need to address treatment sequencing upon implementation of nivolumab plus ipilimumab reimbursement and noted that collaboration among provinces to develop a common approach would be of value. Although there was some evidence

© 2018 pCODR | PAN-CANADIAN ONCOLOGY DRUG REVIEW

from the CheckMate 214 trial on outcomes with subsequent agents, pERC agreed that the data were not sufficient to make firm conclusions on treatment sequencing.

© 2018 pCODR | PAN-CANADIAN ONCOLOGY DRUG REVIEW

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 (Kidney Cancer Canada)
- Input from registered clinicians
- Input from pCODR's Provincial Advisory Group (PAG).

Feedback on the pERC Initial Recommendation was also provided by:

- One clinician group, (Cancer Care Ontario GU DAC)
- The PAG
- The submitter (Bristol-Myers Squibb).

The pERC Initial Recommendation was to recommend the reimbursement of nivolumab (Opdivo) plus ipilimumab (Yervoy) in patients with intermediate or poor-risk advanced renal-cell carcinoma (RCC) based on the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) criteria. Feedback on the pERC Initial Recommendation indicated that the manufacturer and registered clinician group agreed with the Initial Recommendation and PAG agreed in part with the Initial Recommendation.

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of the review is to evaluate the safety and efficacy of nivolumab plus ipilimumab vs. sunitinib monotherapy in the treatment of adult patients with previously untreated, advanced or metastatic RCC.

Studies included: One Phase III randomized multi-centre open-label trial

The pCODR systematic review included one Phase III randomized, multi-centre, open-label trial (CheckMate 214) of nivolumab plus ipilimumab followed by nivolumab monotherapy versus sunitinib monotherapy for previously untreated clear-cell advanced RCC.

Patient populations: Intermediate or poor-risk, clear-cell RCC, treatment beyond progression

Key eligibility criteria included that patients be 18 years or older, have histologically confirmed RCC with a clear-cell component, advanced or metastatic RCC and Karnofsky PS of at least 70%. Patients must not have received prior systemic therapy except with adjuvant or neoadjuvant therapy for completely respectable RCC, if such therapy did not include an agent that targets vascular endothelial growth factor (VEGF) or VEGF receptors and if recurrence occurred at least six months after the last dose of adjuvant or neoadjuvant therapy. Patients with a history of or current central nervous system metastases, prior systemic treatment with VEGF or VEGF receptor targeted therapy, prior treatment with an anti-PD1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint inhibitor pathways were not eligible for the trial. A total of 1,096 eligible patients were randomized into the study (547 in the nivolumab plus ipilimumab arm and 535 in the sunitinib arm in the intention-to-treat population; 423 and 416 patients, respectively, had intermediate or poor risk RCC). The vast majority (> 71%) of patients were male and there was an overall median age of 61 to 62 years in both treatment groups. A total of 79% of patients had a prognostic score of 1 to 2 (intermediate-risk) while the remaining 21% were within the poor-risk category. Approximately 35% of enrolled patients were from Canada or Europe.

Patients received nivolumab (3 mg/kg) and ipilimumab intravenously (1 mg/kg) every three weeks for four doses (induction phase), followed by nivolumab monotherapy at a dose of 3 mg/kg every two weeks (maintenance phase). Sunitinib was administered at a dose of 50 mg orally once daily for four weeks of each six-week cycle. pERC noted that nivolumab may also be administered up to a dose of 240 mg every two weeks or 480 mg every four weeks for more than 30 to 60 minutes when administered as a single agent. Although the Health Canada regulatory approval did not specify the use of 6 mg/kg up to a maximum of 480

© 2018 pCODR | PAN-CANADIAN ONCOLOGY DRUG REVIEW

mg, pERC agreed with the Clinical Guidance Panel (CGP) that it would be reasonable to administer nivolumab at a dose of 3 mg/kg up to a max of 240 mg every two weeks or 6 mg/kg up to a max of 480 mg every four weeks in the monotherapy phase.

Treatment was continued until RECIST 1.1 defined progression or unacceptable toxicity. Patients were allowed to continue study therapy after initial investigator-assessed RECIST v1.1-defined progression if the subject had an investigator-assessed clinical benefit and was tolerating the study drug. A total of 28.5% (157 of 550) of treated subjects in the nivolumab plus ipilimumab group and 23.6% (129 of 546) of treated subjects in the sunitinib group were treated beyond progression (defined as a last dosing date after investigator-assessed RECIST v1.1 progression date). The duration of time patients continued on assigned treatment varied for each individual and continued as long as investigator-assessed clinical benefit was achieved, treatment was well tolerated and there was no further radiological progression of 10% or greater.

Key efficacy results: statistically significant improvement in OS and ORR

The key efficacy outcomes deliberated on by pERC included progression-free survival, OS and ORR in the intermediate/poor-risk patients, which were the co-primary end points in the CheckMate 214 trial.

For all treated patients, the median follow-up period was 25.2 months. pERC noted that nivolumab plus ipilimumab had a statistically significant OS benefit compared with sunitinib (hazard ratio for death, 0.63; 99.8% CI, 0.44 to 0.89; $P < 0.001$); the 12-month OS rate was 80% versus 72%, and the 18-month OS rate was 75% versus 60% in the nivolumab plus ipilimumab versus sunitinib groups, respectively. The median OS was not reached with nivolumab plus ipilimumab versus 26.0 months with sunitinib. Nivolumab plus ipilimumab was associated with a significantly higher ORR than sunitinib, as assessed by Independent Radiology Review Committee, with 42% of patients achieving ORR criteria in the nivolumab plus ipilimumab group versus 27% in the sunitinib group. Median progression-free survival (PFS) was 11.6 months for nivolumab plus ipilimumab, compared with 8.4 months for sunitinib. Although it was not statistically significant (did not meet the pre-specified threshold of $P = 0.009$), median PFS with nivolumab plus ipilimumab was more than three months longer than with sunitinib.

Patient-reported outcomes: Exploratory descriptive analysis

Health-related quality of life was an exploratory outcome in the CheckMate 214 trial and only descriptive statistics were reported. The National Comprehensive Cancer Network Functional Assessment of Cancer Therapy–Kidney Symptom Index (FKSI-19) in intermediate- and poor-risk patients was used. FKSI-19 scores range from 0 to 76, with higher scores indicating fewer symptoms. Patients' general health-related quality of life was assessed using the EuroQol EQ-5D and the Functional Assessment of Cancer Therapy-General (FACT-G). There was no information on whether minimally important differences were met.

The nivolumab plus ipilimumab group reported numerically higher scores with the FKSI-19 score compared with baseline scores and versus the sunitinib group for all assessments during the first six months. Although only descriptive statistics were reported, statistical improvements were reported for the mean change from baseline in FACT-G total score at approximately half of the assessment time points, time to deterioration (TTD) in FKSI-19 total score and in the TTD for both FACT-G total and EQ-5D VAS scores all in favour of the nivolumab plus ipilimumab group. pERC noted that only limited interpretations could be made on the available quality of life data. Overall pERC agreed that nivolumab plus ipilimumab did not result in deterioration of patient's quality of life.

Safety: Discontinuation due to toxicity and greater immune-mediated adverse events with nivolumab plus ipilimumab

The proportion of grade ≥ 3 treatment-related adverse events occurring in at least 15% of patients was lower in the nivolumab plus ipilimumab group (46%) compared with the sunitinib group (63%). However grade 3 or 4 drug related serious adverse events (AEs) (21.6% versus 12.0%) were greater in the combination group compared with sunitinib, respectively. Discontinuation due to study drug toxicity and immune related AEs were greater in the combination group. In the nivolumab plus ipilimumab group 24% of patients discontinued treatment due to study drug toxicity compared with 12% of patients in the sunitinib group. An additional 6% of patients in each treatment group discontinued treatment due to AEs unrelated to the study drug. Immune-mediated AEs occurred in 436 patients treated with nivolumab plus ipilimumab and included skin, endocrine, gastrointestinal, pulmonary, hepatic, and renal categories. There was no data available on the occurrence of immune-mediated AEs in the sunitinib group. The Committee discussed the safety profile of nivolumab plus ipilimumab relative to sunitinib and agreed that nivolumab plus ipilimumab was generally better tolerated than sunitinib.

© 2018 pCODR | PAN-CANADIAN ONCOLOGY DRUG REVIEW

Need and burden of illness: Need for treatment options with better toxicity profile

Kidney cancer accounts for approximately 3% of all cancers in Canada. In 2017, there were 6,600 new cases and 1,900 deaths due to the disease. About 85% of kidney cancers are RCC. About 80% of all RCCs are of clear-cell histology, whereas 20% are classified as non-clear-cell cancers. Among patients with metastatic disease (25% at presentation), 75% will have intermediate or poor prognosis. Of the patients diagnosed with localized disease (75% at presentation), 50% of patients will eventually relapse and develop metastatic disease. The most important prognostic factor for outcome is tumour stage. Survival rates in localized stages range from 70% to 90% for smaller tumours (stages I and II) but drop significantly to 50% to 60% for patients with more extensive tumours (stage III). Patients with metastatic disease are rarely cured. The most commonly used classification for mRCC in the early treatment era was the Memorial Sloan Kettering Cancer Center (MSKCC) criteria. The IMDC criteria describes a more extensive prognostic risk model and has been shown to improve in predicting prognosis as compared with the MSKCC, CCF(Cleveland Clinic Foundation) model and the IKCWG (international Kidney Cancer Working Group) model with tyrosine kinase inhibitor (TKI) therapy. Both, the MSKCC and IMDC models are used in Canada.

Sunitinib and pazopanib, both small molecule TKI of the VEGF receptor are considered the standard treatment options in the first-line setting. Although temsirolimus is considered an acceptable first-line treatment option in patients with poor-risk criteria, this agent is rarely used in the Canadian setting. Despite the availability of standard treatment options in this setting, pERC agreed that there is a need for more effective options that prolong survival and have better toxicity profile.

Registered clinician input: Better tolerated and effective treatment option

Input from registered clinicians indicated that nivolumab plus ipilimumab is superior to other therapies and is a “must have” treatment. Registered clinicians also indicated that nivolumab plus ipilimumab is better tolerated by patients and is the preferred first-line treatment option in patients with intermediate or poor-risk status. Input from clinicians also indicated that patients are likely to receive a TKI in the second-line setting after progressing on the combination. pERC agreed with the CGP that results in the subgroup of patients with favourable risk disease are not sufficiently powered to determine whether any observed treatment effect is meaningful.

PATIENT-BASED VALUES

Values of patients with mRCC: Quality of life, symptom control, improved survival, choice of treatment

Patient input emphasized the impact of mRCC on patient’s quality of life including great morbidity, and further deterioration as the disease progresses. Weakness, fatigue, and shortness of breath are symptoms reported by Kidney Cancer Canada to be the main drivers of poor quality of life whether it is due to the disease or the treatments provided to combat mRCC. Patients value having treatments that provides improved and meaningful OS benefit in the first-line setting. Patient input further noted that existing therapies are not effective for all patient subgroups. Specifically, patients identified as intermediate- and poor-risk face greater difficulty, as their OS is much lower than patients with favourable risk.

Most respondents thought current systemic treatments were generally tolerable, although approximately one-quarter of patients providing input rated current therapies as intolerable. Recurring themes from this submission and from Kidney Cancer Canada input for earlier pCODR reviews included a requirement for better treatment options, and when considering new therapy, having a choice in treatment options, including the opportunity to make an informed decision based on known side effects. For patients who experience drug intolerance, providing treatment alternatives within that line of therapy is extremely important.

Patient values on treatment: Few side effects, improved quality of life

The patient input rated a need for drugs or drug combinations with fewer side effects (compared with currently available treatments) as being the highest overall priority in choosing treatment options. It appears that respondents place greater priority on delaying disease progression and having drugs or drug combinations that have a greater effect at slowing or stopping the spread of cancer. Three respondents reported having experience with the combination of nivolumab plus ipilimumab. The rankings these patients assigned for the tolerability of nivolumab plus ipilimumab were higher than the rankings for tolerability

© 2018 pCODR | PAN-CANADIAN ONCOLOGY DRUG REVIEW

assigned by patients who had other treatments. Two of these patients indicated that the benefits of nivolumab plus ipilimumab outweighed the experience of side effects. All three patients indicated that this treatment was extremely effective. On a scale of 1 to 5, patients rated their quality of life on nivolumab plus ipilimumab as 4 out of 5. Although few patients had direct experience using this combination agent, patients indicated that side effects associated with nivolumab plus ipilimumab were few or were very tolerable, which aligned with the results of the CheckMate 214 trial. Given that nivolumab plus ipilimumab demonstrated statistically significant and clinically meaningful improvements in OS and ORR, a manageable toxicity profile and no deterioration in quality of life, pERC agreed that nivolumab plus ipilimumab aligned with patient values.

ECONOMIC EVALUATION

Economic model submitted: cost-effectiveness and cost-utility analyses

The pCODR Economic Guidance Panel assessed cost-effectiveness and cost-utility analyses comparing nivolumab plus ipilimumab with sunitinib for the treatment of adult patients with previously untreated, advanced or metastatic RCC.

Basis of the economic model:

Costs included were drug acquisition costs, administration costs, wastage, duration of treatment, monitoring costs, AEs costs, costs of subsequent therapies, and costs of end of life care. pERC noted that the cost of treatment was based on the time to treatment discontinuation curve and the incremental cost-effectiveness ratio (ICER) was sensitive to this input.

Key clinical effect estimates considered in the analysis include OS, PFS or TTD, AEs, utilities and disutilities. pERC noted that there was uncertainty in the estimate of long-term treatment effect which was based on a trial follow-up period of 25.2 months and the assumption that this effect would continue over a 15-year time horizon.

Drug costs: Sensitive to duration of treatment, treatment beyond progression allowed

Nivolumab costs $1,956.00 per 100 mg vial and $782.22 per 40 mg vial. At the recommended dose of 3 mg/kg every three weeks for the first four doses, over 12 weeks, nivolumab costs $195.56 per day and $5,475.57 per 28-day course. At the recommended dose of 3 mg/kg every two weeks, nivolumab single-agent costs $293.33 per day and $8,213.35 per 28-day course.

Ipilimumab costs $23,200.00 per 200 mg vial and $5,800.00 per 50 mg vial. At the recommended dose of 1 mg/kg every 3 weeks for 4 doses, ipilimumab costs $386.67 per day and $10,826.67 per 28-day course.

Sunitinib costs $64.42 per 12.5 mg capsule. At the recommended dose of sunitinib of 50 mg once daily, the cost of sunitinib is $252.66 per day and $7,214.56 per 28-day course.

Cost-effectiveness estimates: time to treatment discontinuation and uncertainty in long-term treatment effect

pERC deliberated on the cost-effectiveness of nivolumab plus ipilimumab compared with sunitinib based on the submitted economic evaluation and reanalysis estimates provided by the pCODR Economic Guidance Panel. pERC noted that the factors that most influenced the ICER were assumptions based on the duration of treatment effect and duration of treatment. pERC noted that the observed treatment effect, based on a follow-up period of 25.2 months from the CheckMate 214 trial, was set to continue over a 15-year time horizon in the base-case results. Input from the CGP indicated that there is insufficient long-term follow-up data to support such a prolonged treatment effect. pERC therefore agreed with the pCODR Economic Guidance Panel's (EGP) reanalysis which reduced the amount of benefit accrued after the end of the trial period up to year five. pERC also noted that treatment costs were based on the time to treatment discontinuation curve in the submitted analysis. Although this was reflective of treatment discontinuation observed in the trial (30% of patients discontinuing treatment due to study drug toxicity or AEs unrelated to study drug), pERC noted that nearly 30% of patients had continued treatment beyond progression. Based on this, pERC agreed that using the time to treatment discontinuation curve to determine costs associated with treatment would not be an accurate representation. Although there was no information on how long patients remained on treatment beyond progression, pERC agreed that the pCODR EGP's use of the progression-free survival curves, which account for a longer period of treatment, were a more reasonable estimate of treatment costs.

© 2018 pCODR | PAN-CANADIAN ONCOLOGY DRUG REVIEW

Furthermore, changes to the estimates of utilities and the distribution of subsequent treatments to patients would receive also impacted the ICER. pERC noted that utilities derived from the trial were high and close to what is observed in the healthy population and were higher than those used in other studies conducted in the same population. pERC further noted that the quality of life data from the CheckMate 214 trial was an exploratory end point and only descriptive results were presented. The Committee agreed that lower utility values used by the EGP better reflected those of patients with advanced RCC. Lastly, pERC agreed with the CGP that patients progressing on sunitinib are unlikely to receive further sunitinib therapy in the second-line setting.

Based on the changes made to these inputs, pERC agreed that the true ICER is likely closer to the upper range of the EGP's reanalysis estimates and concluded that nivolumab plus ipilimumab is not cost-effective compared with sunitinib.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: unknown sequencing of subsequent agents

pERC considered the feasibility of implementing a reimbursement recommendation for nivolumab plus ipilimumab. pERC noted that the factors that influenced the budget impact analysis include the number of treatment lines considered (first-line only or up to three lines), eligible patient population, treatment duration of nivolumab plus ipilimumab, and market share of nivolumab plus ipilimumab. With the generalizability of the trial data into a number of additional patient populations, pERC acknowledged that the eligible patient population is likely to be larger than projected in the analysis. It is unclear how much the budget impact analysis will be affected by this.

The Committee noted input from pCODR's PAG, which requested guidance and clarification on the implementation of nivolumab plus ipilimumab. pERC agreed that the outcomes observed with sunitinib can be generalized to treatment with pazopanib, a relevant comparator in the Canadian setting; therefore, the CheckMate 214 trial results are likely generalizable to the Canadian context. For patients who are currently on first-line treatment with sunitinib or pazopanib and who have not experienced disease progression, pERC agreed that a decision to continue or switch treatment to nivolumab plus ipilimumab should be made with discussions between the treating oncologist and patient. pERC acknowledged that there may be instances where the treating oncologist may agree it is reasonable to keep the patient on ongoing first-line treatment with a TKI such as sunitinib or pazopanib because patients are responding well and it allows the oncologist to maximize the number of available treatment options for patients. Upon reconsideration of the Initial Recommendation, pERC considered feedback from PAG asking for clarity on criteria for restarting therapy after progression during a treatment break. pERC noted feedback from the CGP indicating that treatment breaks are expected to occur more frequently in clinical practice compared with the clinical trial, which did not allow treatment breaks. pERC therefore agreed that it is reasonable to restart treatment in patients who progress during a treatment break, and that the decision to restart should be left to the treating oncologist. The Committee further noted that re-initiating treatment following temporary discontinuation was not explored in the submitted budget impact analysis model or cost-effectiveness analysis. Therefore, pERC noted that the impact of re-initiating treatment in patients who have had a treatment break and develop disease progression is unknown. The Committee agreed that jurisdictions will need to consider the uncertainty in these factors upon implementation.

pERC agreed that patients who have already been treated with an immunotherapy agent in the metastatic setting should not be eligible for reimbursement. pERC agreed that it is reasonable to administer nivolumab as a 3 mg/kg dose up to a maximum of 240 mg every two weeks or 6mg/kg up to a maximum of 480 mg every four weeks. Similar to the risk score methodology used in the CheckMate 214 trial, pERC agreed that it is reasonable to use the IMDC score to determine patients` risk status. pERC agreed that the trial results did not demonstrate differing efficacy based on PD-L1 status and agreed that companion diagnostics are not required to determine eligibility for treatment. pERC also recognized that provinces would need to address treatment sequencing upon implementation of nivolumab plus ipilimumab reimbursement and noted that collaboration among provinces to develop a common approach would be of value. Although there was some evidence from the CheckMate 214 trial on outcomes with subsequent agents, pERC agreed that the data were not sufficient to make firm conclusions on treatment sequencing.

© 2018 pCODR | PAN-CANADIAN ONCOLOGY DRUG REVIEW

© 2018 pCODR | PAN-CANADIAN ONCOLOGY DRUG REVIEW

DRUG AND CONDITION INFORMATION

Drug Information	• Nivolumab is a PD-L1 immune checkpoint inhibitor and ipilimumab is a monoclonal antibody that blocks cytotoxic T lymphocyte-associated antigen 4 (CTLA-4). • Combination phase: Nivolumab 3 mg/kg is administered as an intravenous infusion over 30 to 60 minutes every three weeks for the first four doses in combination with ipilimumab 1 mg/kg administered intravenously over 90 minutes, followed by the single-agent phase. Ipilimumab can be administered intravenously over 30 minutes if there is no infusion reaction with the first dose. • Single-agent phase: Nivolumab 3 mg/kg is administered as an intravenous infusion over 30 to 60 minutes every two weeks or Nivolumab 6 mg/kg is administered as an intravenous infusion over 60 minutes every four weeks.
Cancer Treated	• Advanced renal cell carcinoma in the intermediate or poor risk category.
Burden of Illness	• In 2017, there were 6,600 new cases and 1,900 deaths. • Survival rates in localized stages are 70% to 90% (stages I and II), and drop to 50% to 60% for patients with more extensive tumours (stage III). • Patients with metastatic disease are rarely cured.
Current Standard Treatment	• Sunitinib • Pazopanib
Limitations of Current Therapy	• There is a need for more effective options that prolong survival and have better toxicity profiles.

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
Dr. Leela John, Pharmacist
Dr. Anil Abraham Joy, Oncologist
Dr. Christine Kennedy, Family Physician
Cameron Lane, Patient Member Alternate
Dr. 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:

- Dr. Anil Abraham Joy and Cameron Lane, who were not present for the meeting.

© 2018 pCODR | PAN-CANADIAN ONCOLOGY DRUG REVIEW

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. Avram Denburg, Pediatric Oncologist
Dr. Leela John, Pharmacist
Dr. Anil Abraham Joy, Oncologist
Dr. Christine Kennedy, Family Physician
Dr. Christian Kollmannsberger, Oncologist
Dr. Christopher Longo, Health Economist
Cameron Lane, Patient Member
Valerie McDonald, Patient Member
Dr. Marianne Taylor, Oncologist
Dr. Dominika Wranik, Health Economist

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

- Dr. Winson Cheung and Dr. Anil Abraham Joy who were not present for the meeting
- Daryl Bell, who did not vote due to his role as a patient member alternate.

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 plus ipilimumab for advance 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

pCODR does not assume any legal liability or responsibility for the accuracy, completeness or usefulness of any information, drugs, therapies, treatments, products, processes, or services disclosed. The information is provided "as is" and you are urged to verify it for yourself and consult with medical experts before you rely on it. You shall not hold pCODR responsible for how you use any information provided in this report. This document is composed of interpretation, analysis, and opinion on the basis of information provided by pharmaceutical manufacturers, tumour groups, and other sources. pCODR is not responsible for the use of such interpretation, analysis, and opinion. Pursuant to the foundational documents of pCODR, any findings provided by pCODR are not binding on any organizations, including funding bodies. pCODR hereby disclaims any and all liability for the use of any reports generated by pCODR (for greater certainty, "use" includes but is not limited to a decision by a funding body or other organization to follow or ignore any interpretation, analysis, or opinion provided in a pCODR document).

© 2018 pCODR | PAN-CANADIAN ONCOLOGY DRUG REVIEW

APPENDIX 1: CADTH PAN-CANADIAN ONCOLOGY DRUG REVIEW EXPERT REVIEW COMMITTEE RESPONSES TO PROVINCIAL ADVISORY GROUP IMPLEMENTATION QUESTIONS

PAG Implementation Questions	pERC Recommendation
• PAG is seeking information on comparison to pazopanib and temsirolimus and whether the trial results can be generalized to patients receiving other first-line therapies.	• pERC agreed that the outcomes observed with sunitinib can be generalized to treatment with pazopanib, therefore the CheckMate 214 trial results are generalizable to the Canadian context. Although temsirolimus is considered an acceptable first-line treatment option in patients with poor risk criteria, this agent is rarely used in the Canadian setting.
• PAG is seeking information on the use of nivolumab plus ipilimumab in previously treated patients and in patients with non-clear-cell histology, recognizing these may be out of scope of the current review. • Prior adjuvant or neoadjuvant immunotherapy.	• pERC noted feedback from the Clinical Guidance Panel clarifying that patients with non-clear cell RCC are managed the same way as patients with clear cell RCC. pERC therefore agreed that it is reasonable to generalize the CheckMate214 trial results to patients with non-clear cell RCC. • pERC agreed that patients who have already been treated with an immunotherapy agent in the metastatic setting should not be eligible for reimbursement.
• PAG is seeking clarity on the scoring (e.g., MSKCC/Motzer, Heng) for determining poor/intermediate-risk patients.	• Similar to the risk scoring used in the CheckMate 214 trial, pERC agreed that it is reasonable to use the IMDC score to determine patients' risk status.
• PAG is seeking guidance on whether patients with poor/intermediate-risk disease who have started oral targeted therapy and have not yet progressed could be switched to nivolumab plus ipilimumab combination as their first-line treatment.	• For patients who are currently on first-line treatment with sunitinib or pazopanib and who have not experienced disease progression, pERC acknowledged that there may be instances where the treating oncologist may agree it is reasonable to keep the patient on treatment because patients are responding well and it allows the oncologist to maximize the number of available treatment options for patients. pERC, however, agreed that a decision to continue or switch treatment to nivolumab plus ipilimumab should be made with discussions between the treating oncologist and patient.
• PAG is seeking information on alternate dosing schedules for nivolumab in the nivolumab monotherapy phase. ○ The use of nivolumab 3mg/kg up to maximum of 240 mg every two weeks in the monotherapy maintenance phase, given that this dosing schedule has been adopted in other indications. ○ The use of nivolumab 6 mg/kg up to a maximum of 480 mg every four weeks as the monthly administration schedule would reduce the frequency of clinic visits for the patients.	• Based on the Health Canada product monograph pERC noted that nivolumab may also be administered up to a dose of 240 mg every two weeks or 480 mg every four weeks over 30 to 60 minutes when administered as a single agent. Although the Health Canada regulatory approval did not specify the use of 6 mg/kg up to a maximum of 480 mg, pERC agreed with the CGP that it would be reasonable to administer nivolumab at a dose of 3 mg/kg up to a maximum of 240 mg every two weeks or 6mg/kg up to a maximum of 480 mg every four weeks in the monotherapy phase.
• PAG identified that in clinical practice there are patients who would have treatment breaks and have disease progression during the treatment break. PAG is seeking guidance on restarting nivolumab monotherapy in these patients. • Impact on cost-effectiveness and BIA.	• pERC noted feedback from the CGP indicating that treatment breaks are expected to occur more frequently in clinical practice compared with the clinical trial, which did not allow treatment breaks. pERC therefore agreed that it is reasonable to restart treatment in patients who progress during a treatment break and that the decision to restart should be left to the treating oncologist. The Committee further noted that this was not explored in the submitted BIA model or cost-effectiveness analysis. Therefore, pERC

© 2018 pCODR | PAN-CANADIAN ONCOLOGY DRUG REVIEW

	noted that the impact of re-initiating treatment in patients who have had a treatment break and develop disease progression is unknown. The Committee agreed that jurisdictions will need to consider the uncertainty in these factors upon implementation.
• PAG is seeking guidance on the appropriate sequencing of oral targeted therapies and immunotherapies. PAG is seeking information on the use of oral targeted therapies after progression on nivolumab plus ipilimumab combination therapy.	• pERC also recognized that provinces would need to address treatment sequencing upon implementation of nivolumab plus ipilimumab reimbursement and noted that collaboration among provinces to develop a common approach would be of value. Although there was some evidence from the CheckMate 214 trial on outcomes with subsequent agents, pERC agreed that the data were not sufficient to make firm conclusions on treatment sequencing.
• Wastage of nivolumab.	• pERC noted that wastage was incorporated for both nivolumab and ipilimumab into the economic model and BIA.
• Companion diagnostics — PD-L1 testing.	• pERC agreed that the trial results did not demonstrate differing efficacy based on PD-L1 status and agreed that companion diagnostic tests are not required to determine eligibility for treatment.

BIA = budget impact analysis; CGP = Clinical Guidance Panel; PAG = Provincial Advisory Group; pERC = CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee.

© 2018 pCODR | PAN-CANADIAN ONCOLOGY DRUG REVIEW