# pCODR EXPERT REVIEW COMMITTEE (pERC)
# FINAL RECOMMENDATION

The CADTH pan-Canadian Oncology Drug Review (pCODR) was established by Canada's provincial and territorial Ministries of Health (with the exception of Quebec) to assess cancer drug therapies and make recommendations to guide drug reimbursement decisions. The pCODR process brings consistency and clarity to the assessment of cancer drugs by looking at clinical evidence, cost-effectiveness, and patient perspectives.

**pERC Final Recommendation**
This pERC Final Recommendation is based on a reconsideration of the Initial Recommendation and feedback from eligible stakeholders. This pERC Final Recommendation supersedes the pERC Initial Recommendation.

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| **Drug: Pembrolizumab (Keytruda) plus Axitinib (Inlyta)**<br>**Submitted Reimbursement Request:**<br>For the treatment of patients with advanced renal cell carcinoma (RCC) in combination with axitinib, as first-line treatment | |
| **Submitted By:**<br>Merck Canada Inc. | **Manufactured By:**<br>Merck Canada Inc. |
| **NOC Date:**<br>December 13, 2019 | **Submission Date:**<br>August 2, 2019 |
| **Initial Recommendation:**<br>January 30, 2020 | **Final Recommendation:**<br>April 2, 2020 |

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| **Approximate per Patient Drug Costs, per Month (28 Days)** | • Pembrolizumab costs $4,400 per 100 mg vial<br>• Axitinib costs $97.13 per 5 mg tablet<br><br>At the recommended dose of 200 mg intravenously every three weeks for pembrolizumab and 5 mg twice a day for axitinib for a maximum of 35 cycles (two years), pembrolizumab plus axitinib costs:<br><br>• $419.05 (pembrolizumab) + $194.26 (axitinib) = $613.31 per day<br>• $17,172.68 per 28-days<br><br>At the recommended dose of 5 mg twice a day, single agent axitinib costs $194.26 per day and $ 5,439.28 per 28-day course. |

**pERC RECOMMENDATION**

☐ **Reimburse**

☒ **Reimburse with clinical criteria and/or conditions***

☐ **Do not reimburse**

*If the condition(s) cannot be met, pERC does not recommend reimbursement of the drug for the submitted reimbursement request.

pERC conditionally recommends the reimbursement of pembrolizumab (Keytruda) plus axitinib for the treatment of patients with advanced renal cell carcinoma (RCC) as first-line treatment if the following conditions are met:

- cost-effectiveness being improved to an acceptable level
- feasibility of adoption (budget impact) being addressed.

Eligible patients should be previously untreated in the advanced or metastatic setting and have a good performance status. Pembrolizumab treatment should continue until confirmed disease progression or unacceptable toxicity to a maximum of 35 cycles (approximately two years), whichever comes first. Treatment with axitinib should continue until disease progression or unacceptable toxicity.

pERC made this recommendation because it was satisfied that there is a net clinical benefit of pembrolizumab plus axitinib compared with sunitinib based on statistically significant and clinically meaningful improvements in overall survival (OS) and progression-free survival (PFS) with manageable toxicities. pERC concluded that the combination of pembrolizumab plus

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| | axitinib aligns with patient values in that it offers an improvement in overall survival, delays disease progression, and it provides patients with an effective treatment option with manageable side effects.<br><br>pERC concluded that at the submitted price, pembrolizumab plus axitinib cannot be considered cost-effective compared with sunitinib. pERC also highlighted that the potential budget impact of pembrolizumab may be underestimated and could be substantial for this small patient population. |
| **POTENTIAL NEXT STEPS FOR STAKEHOLDERS** | **Pricing Arrangements to Improve Cost-Effectiveness and Affordability of Pembrolizumab plus Axitinib Compared with Sunitinib**<br>Given that pERC concluded there is a net clinical benefit with pembrolizumab plus axitinib in patients with advanced RCC, jurisdictions may want to consider pricing arrangements and/or cost structures that would improve the cost-effectiveness and the affordability of pembrolizumab plus axitinib compared with sunitinib.<br><br>**Factors Affecting Budget Impact and Adoption Feasibility**<br>pERC noted that the budget impact of pembrolizumab resulted from the high cost of pembrolizumab, the uncertainty in the number of patients who would receive the full 35 cycles of pembrolizumab, the potential for re-treatment with pembrolizumab, and a large market share. pERC concluded that a reduction in drug price would be required to improve affordability.<br><br>**Pembrolizumab Dosing of 2 mg/kg up to a Flat Dose of 200 mg**<br>Upon implementation of reimbursement of pembrolizumab plus axitinib, pERC recognized that jurisdictions will need to choose between administering pembrolizumab at a flat dose or at a dose of 2 mg/kg up to a flat dose cap of 200 mg. The Committee acknowledged that, although Keynote-426 assessed pembrolizumab at a dosage of 200 mg every three weeks up to two years (maximum of 35 cycles), there is no evidence to suggest that the dosing amount of 200 mg is superior to 2 mg/kg (the dose used in initial pembrolizumab trials). For many patients, the flat dose results in a larger dose and greater cost. Therefore, pERC felt it would be reasonable that pembrolizumab be administered at 2 mg/kg up to a total dose of 200 mg (a flat dose cap of 200 mg).<br><br>**Optimal Sequencing of Available Therapies After Progression on Pembrolizumab plus Axitinib**<br>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 pembrolizumab plus axitinib. pERC also noted that patients who progress on pembrolizumab plus axitinib are unlikely to be treated with another immunotherapy and may be offered other approved targeted drugs available in the second-line or be enrolled in a clinical trial.<br><br>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. |

# SUMMARY OF pERC DELIBERATIONS

| 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** |

Kidney cancer accounts for approximately 3% of all cancers in Canada. In 2019 the estimated Canadian incidence for kidney cancer was 7,200 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. About 75% of patients present with localized disease confined to the kidney, of which 50% will experience relapse and develop metastases and the other 25% of patients will already have metastatic disease at presentation. The most important prognostic factor for outcome is tumour stage. Among patients with metastatic disease, 75% will have intermediate or poor-risk disease as defined by the International Metastatic Renal-Cell Carcinoma Database Consortium's (IMDC) prognostic factors. Patients with metastatic disease have lower survival rates than those with localized tumours. Currently, sunitinib and pazopanib are 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 drugs. pERC noted that nivolumab plus ipilimumab has received a conditional reimbursement recommendation for the first-line treatment for intermediate or poor-risk advanced RCC and is a funded treatment option in most Canadian jurisdictions. Although, there are new funded options for mRCC, due to the low survival rates, pERC agreed that there is a need for more effective treatment options that prolong survival and have better toxicity profiles.

pERC deliberated upon the results of one randomized, open-label trial (Keynote-426) comparing pembrolizumab plus axitinib to sunitinib monotherapy for previously untreated clear-cell advanced RCC. pERC discussed the clinical benefit of pembrolizumab plus axitinib compared with sunitinib based on statistically significant and clinically meaningful improvements in OS and progression-free survival (PFS). pERC noted that there were no meaningful differences observed in quality of life between patients who received pembrolizumab plus axitinib compared with sunitinib. However, pERC commented that for the symptom scale of diarrhea, worsening symptoms were observed in the pembrolizumab plus axitinib group compared with sunitinib. pERC discussed the safety profile of pembrolizumab plus axitinib compared with sunitinib and noted that the incidence of grade 3 or higher toxicities of hypertension, diarrhea, and alanine aminotransferase (ALT) elevations was higher in the pembrolizumab plus axitinib versus the sunitinib-treated patients. Overall, pERC concluded there is a net clinical benefit of pembrolizumab plus axitinib compared with sunitinib and that the combination of pembrolizumab plus axitinib had a manageable toxicity profile compared with sunitinib alone.

pERC discussed the sponsor's network meta-analysis (NMA) comparing pembrolizumab plus axitinib with other first-line therapies for advanced or metastatic RCC. As the treatments of nivolumab plus ipilimumab and pazopanib were the most relevant to Canadian practice, pERC noted these particular comparisons in their deliberations. pERC noted the limitations of the NMA including clinical heterogeneity, inconsistencies in outcome measurements and the inclusion of a mix of open-label and double-blind trials in the network. pERC commented that results from the NMA and the associated limitations make it difficult to draw conclusions about the comparison of pembrolizumab plus axitinib compared with nivolumab plus ipilimumab. pERC noted that the treatments with pembrolizumab plus axitinib and nivolumab plus ipilimumab are based on different International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) prognostic factors such that pembrolizumab plus axitinib would be used for patients with all IMDC factors (favourable, intermediate, poor) while ipilimumab plus nivolumab is used for patients with intermediate/poor risk factors. Additionally, pERC noted that the side effect profile of pembrolizumab plus axitinib compared with nivolumab plus ipilimumab differ as the latter is associated with more immunotherapy linked side effects while the former also has tyrosine kinase inhibitor (TKI)-associated side effects. Therefore, the side effect profiles of both drugs are different and treatment decisions would depend on clinical factors decided by the patient and the treating physician. Overall, pERC concluded that there is a net overall clinical benefit with pembrolizumab plus axitinib, based upon statistically significant and clinically meaningful improvements in OS and PFS and a manageable toxicity profile compared with sunitinib.

pERC discussed the generalizability of the overall trial results in patients with advanced or metastatic RCC. pERC noted that although the trial compared pembrolizumab plus axitinib to sunitinib, the efficacy and safety outcomes with sunitinib are considered generalizable to those of pazopanib, which is a relevant comparator in the Canadian setting. pERC also agreed with the clinical guidance panel (CGP) that the treatment of non–clear-cell histology is similar to that of clear-cell histology and patients are managed in the same way. Therefore, the results of the Keynote 426 trial, are generalizable to the non–clear-cell RCC patient population.

pERC deliberated upon input from one patient advocacy group (Kidney Cancer Canada) and noted that patients with advanced RCC 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. Of the seven patients and one caregiver that had direct experience with pembrolizumab plus axitinib, pERC noted that the patients experienced delayed disease progression and a generally well-tolerated side effect profile with pembrolizumab plus axitinib. Given that pembrolizumab plus axitinib demonstrated statistically significant and clinically meaningful improvements in OS and PFS and a manageable toxicity profile, pERC concluded that pembrolizumab plus axitinib aligns with patient values.

pERC deliberated upon the cost-effectiveness of pembrolizumab plus axitinib compared with sunitinib and concluded that at the submitted price, pembrolizumab plus axitinib is not cost-effective. pERC noted that median overall survival was not reached in either group of the Keynote 426 trial and therefore, the OS data were immature. Additionally, pERC noted that there is uncertainty in the long-term post-trial relative efficacy of pembrolizumab plus axitinib compared with sunitinib alone.

pERC noted that uncertainty regarding the duration of treatment effect, cost of treatment/duration of treatment, estimates for utilities, and distribution of subsequent drugs were considered in the reanalysis estimates by the pCODR Economic Guidance Panel (EGP). pERC noted that the observed treatment effect, based on a short follow-up period of 12.8 months from the Keynote 426 trial, was set to continue over a 15-year time horizon in the base case. pERC discussed the input from the CGP that indicated there is insufficient long-term follow-up data to support 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 to five years.

Upon consideration of the Initial Recommendation, pERC discussed feedback received from the sponsor, who disagreed with the five-year treatment-waning period in the EGP's reanalysis. The sponsor noted that there is no clinical data to support a limited period of benefit. pERC noted that the EGP maintained the reanalysis estimate because there was no data submitted during the review that demonstrated a benefit of pembrolizumab plus axitinib beyond the trial period and that there is uncertainty in allowing the treatment benefit to accrue until 10 years. pERC agreed with the EGP that treatment waning at five years is a reasonable approach given the short-term follow-up in the Keynote-426 trial and the insufficient long-term follow-up to support a prolonged treatment effect. pERC reiterated that, at the submitted price, pembrolizumab plus axitinib is not considered cost-effective.

pERC noted that the comparison of pembrolizumab plus axitinib to nivolumab plus ipilimumab and pazopanib was based on efficacy estimates from the sponsor's NMA. pERC noted the limitations identified by the review team including the heterogeneous trial populations and inconsistencies in outcome measurements and concluded that the results of the NMA should be interpreted with caution. pERC agreed with the limitations identified from the NMA and noted that limited conclusions could be drawn from the submitted economic analysis comparison of pembrolizumab plus axitinib versus nivolumab plus ipilimumab.

pERC noted that the EGP's reanalysis of the incremental cost-utility ratio (ICUR) was higher than the sponsor's submitted ICUR of pembrolizumab plus axitinib versus sunitinib. pERC agreed with the EGP reanalysis of waning the treatment effect from 15 years to five years and anchoring the utilities of health states. pERC noted that to achieve an ICUR of approximately $100 000 per quality-adjusted life-year (QALY) for the entire patient population (all IMDC risk categories) of advanced RCC, a price reduction of 75% of pembrolizumab would be required when compared with sunitinib. Therefore, pERC concluded that at the submitted price, pembrolizumab plus axitinib could not be considered cost-effective.

pERC discussed the feasibility of implementing a reimbursement recommendation of pembrolizumab plus axitinib for patients with previously untreated advanced RCC. pERC noted that the eligible patient population, treatment duration of pembrolizumab plus axitinib and market share of pembrolizumab plus axitinib would be the factors which influence the budget impact analysis. pERC acknowledged that the eligible patient population is likely to be larger if clinicians choose to generalize treatment with pembrolizumab and axitinib to other patient populations outside of the Keynote 426 trial's eligibility criteria. pERC commented on the considerable budget impact for the small number of patients. pERC also noted the key limitations of the budget impact analysis including the lack of data on market share assumptions as well as the overestimates of the nivolumab plus ipilimumab dose intensities used in the model. Therefore, pERC concluded that the budget impact of pembrolizumab plus axitinib would be underestimated for this small patient population and that a reduction in drug price would be required to improve affordability.

pERC noted input from pCODR's PAG, which requested guidance and clarification on the implementation of pembrolizumab plus axitinib. For patients who are currently on first-line treatment with sunitinib or pazopanib and who have not experienced disease progression, pERC agreed with the CGP that patients should continue treatment with their current therapy. However, pERC noted that if patients have just started their first-line therapy, and are unable to tolerate the therapy, a decision to continue or switch treatment to pembrolizumab plus axitinib should be between the treating oncologist and patient. pERC also noted that in the Keynote 426 trial, patients were allowed to receive single-drug pembrolizumab or single-drug axitinib if they were unable to tolerate axitinib or pembrolizumab, respectively. pERC noted that the study protocol for Keynote-426 allowed patients to continue pembrolizumab until a maximum of 35 cycles (approximately two years) after randomization and axitinib monotherapy could be continued afterwards until progressive disease or toxicity. pERC noted that this would be a reasonable approach.

Upon reconsideration of the Initial Recommendation, pERC discussed feedback received from PAG that stated that the duration of therapy of pembrolizumab should align with the Keynote-426 trial. pERC discussed that patients in the Keynote-426 trial could continue treatment with pembrolizumab until a maximum of 35 cycles (approximately two years) and agreed that this would be a reasonable approach to follow in clinical practice.

In addition, pERC agreed that it is reasonable to administer pembrolizumab as a 2 mg/kg dose up to a maximum of 200 mg flat dose. pERC also agreed that trial results demonstrated efficacy irrespective of the programmed death-ligand 1 (PD-L1) status and thus companion diagnostic testing is not required to determine patients' PD-L1 status for the eligibility of treatment with pembrolizumab plus axitinib. Finally, pERC noted that provinces would need to address treatment sequencing upon implementation of pembrolizumab plus axitinib and noted that the collaboration among provinces to develop a common approach would be of value.

# 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 [KCC])
- 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, CCO Genitourinary DAC
- the PAG
- the sponsor Merck Canada Inc.

The pERC Initial Recommendation was to conditionally recommend pembrolizumab in combination with axitinib for the treatment of patients with advanced RCC as first-line treatment. Feedback on the pERC Initial Recommendation indicated that the sponsor and registered clinician group agreed with the Initial Recommendation, whereas PAG agreed in part with the Initial Recommendation. No feedback was received from the patient advocacy group.

## OVERALL CLINICAL BENEFIT

### pCODR review scope

The purpose of the review is to evaluate the safety and efficacy of pembrolizumab (Keytruda) in combination with axitinib as a first-line treatment for patients with advanced RCC.

### Studies included: KEYNOTE-426—a phase III, open-label, global, multi-centre randomized controlled trial

The pCODR systematic review included one phase III, open-label, global, multi-centre, randomized controlled (RCT) trial (KEYNOTE-426 [NCT02853331]), which assessed the safety and efficacy of pembrolizumab (Keytruda) in combination with axitinib as a first-line treatment for advanced RCC. The study was conducted across 124 centres in 16 countries including four sites in Canada. A total of 1,062 patients were screened, and 861 patients were randomized in a 1:1 ratio into the pembrolizumab and axitinib treatment arm (n = 432) and sunitinib comparator arm (n = 429) between October 24, 2016 and January 24, 2018. Pembrolizumab was intravenously administered as 200 mg every three weeks in combination with axitinib which was orally administered 5 mg twice daily. Treatment with pembrolizumab was administered for a maximum of 35 doses (approximately two years). Sunitinib was orally administered 50 mg once daily for the first four weeks of a six-week cycle.

The pCODR review also included a summary and critical appraisal of the sponsor-submitted NMA and sensitivity analysis, which compared pembrolizumab and axitinib with competing interventions for the first-line treatment of metastatic RCC. Namely, the sensitivity analysis compared outcomes between pembrolizumab and axitinib and relevant treatments in the Canadian perspective, which included: sunitinib, pazopanib, axitinib, sorafenib, interferon (IFN), ipilimumab plus nivolumab, temsirolimus, avelumab plus axitinib, cabozantinib, and tivozanib.

### Patient populations: newly diagnosed or recurrent stage IV clear-cell RCC patients who have not received systemic therapy for advanced disease

Key eligibility criteria of KEYNOTE-426 included the following: age of 18 years or older, newly diagnosed or recurrent stage IV clear-cell RCC, measurable disease as per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 ( ≥ 1 measurable lesion), provision of a tumour sample for biomarker assessment, Karnofsky performance status score of ≥ 70, adequate organ function, and no prior systemic therapy for advanced disease. Patients were excluded based on the following criteria: symptomatic central nervous

system metastases, active autoimmune disease, systemic immunosuppressive treatment, poorly controlled hypertension (systolic blood pressure
≥ 150 mm Hg or diastolic blood pressure ≥ 90 mm Hg), and an ischemic cardiovascular event or New York Heart Association class III or IV congestive heart failure within one year before screening.

The median age of patients was similar in the pembrolizumab plus axitinib (62, range: 30 to 89) and sunitinib arm (61, range: 26 to 90) with the majority of patients being younger than 65 years of age (pembrolizumab and axitinib at 60.2% and sunitinib at 64.8%). Patients were predominantly male, 71.3% and 74.6% in the pembrolizumab plus axitinib and sunitinib arm, respectively. Region of enrolment was categorized into North America (pembrolizumab and axitinib at 24.1% and sunitinib at 24.0%), Western Europe (pembrolizumab and axitinib at 24.5% and sunitinib at 24.2%), and the remaining parts of the world (pembrolizumab and axitinib at 51.4% and sunitinib at 51.7%). Enrolment was greatest in the remaining parts of the world and similar for all regions across both treatment groups. The majority of patients had an IMDC prognostic risk of intermediate (pembrolizumab and axitinib at 55.1% and sunitinib at 57.3%), followed by favourable (pembrolizumab and axitinib at 31.9% and sunitinib at 30.5%), then poor (pembrolizumab and axitinib at 13.0% and sunitinib at 12.1%). In both arms, more patients had ≥ 2 organ sites with metastases (pembrolizumab and axitinib at 72.9% and sunitinib at 77.2%) compared with those having one organ site with metastases. The lung (pembrolizumab and axitinib at 72.2% and sunitinib at 72.0%) followed by the lymph node (pembrolizumab and axitinib at 46.1% and sunitinib at 45.9%) were the two most common metastatic sites. Moreover, a similar number of patients in both arms received previous radiotherapy (pembrolizumab and axitinib at 9.5% and sunitinib at 9.3%) and previous nephrectomy (pembrolizumab and axitinib at 82.6% and sunitinib at 83.4%).

### Key efficacy results: Statistically significant PFS in favour of the pembrolizumab and axitinib group but median OS was not reached in either treatment arm

The key efficacy outcomes deliberated on by pERC included PFS and OS from the first interim analysis, (data cut off of August 24, 2018) and data from an unplanned cut off of January 2, 2019, which was requested by the European Medicines Agency (EMA). Key secondary outcomes included objective response rate (ORR) and duration of response (DOR).

Progression-Free Survival (PFS)

The median PFS improved by four months (15.1 months, 95% CI, 12.6 to 17.7) in the pembrolizumab plus axitinib group compared with the sunitinib group (11.1 months, 95% CI, 8.7 to 12.5). There was a statistically significant improvement for disease progression or death in favour of the pembrolizumab and axitinib group compared with sunitinib in the intention-to-treat (ITT) population (hazard ratio [HR] = 0.69, 95% CI, 0.57 to 0.84, $P < 0.001$). The first interim analysis for PFS crossed the pre-specified boundary for statistical significance of 0.0013.

Overall Survival (OS)

The median OS was not reached in either group. There was a statistically significant improvement for OS in favour of the pembrolizumab plus axitinib group compared with the sunitinib group in the ITT population (HR = 0.53,95% CI, 0.38 to 0.74; $P < 0.0001$). The first interim analysis for OS crossed the pre-specified boundary for statistical significance of 0.0001.

Objective Response Rate (ORR)

Since the coprimary end points of PFS and OS assessed by a blinded independent review committee (BICR) met the thresholds in the first interim analysis, the key secondary outcome of ORR was assessed. The ORR was higher in the pembrolizumab plus axitinib group of 59.3% (95% CI, 54.5 to 63.9) compared with 35.7% (95% CI, 31.1 to 40.4) in the sunitinib group. A complete response was reported in 25 patients (5.8%) in the pembrolizumab plus axitinib group and eight patients (1.9%) in the sunitinib group. Partial response was observed in 231 patients (53.5%) in the pembrolizumab plus axitinib group versus 145 patients (33.8%) in the sunitinib group.

### Patient-reported outcomes: No clinically meaningful differences reported in the FKSI-DRS and EORTC QLQ-C30

Pembrolizumab-axitinib did not result in meaningful changes in the FKSI-DRS compared with sunitinib. The median time to true deterioration was not reached in either treatment group. There was no statistically significant difference in the time to true deterioration assessed by the FKSI-DRS (i.e., time to first onset of three or more decreases from baseline with confirmation under the right-censoring rule) between the pembrolizumab and axitinib group and sunitinib group.

There were no clinically meaningful differences from baseline to week 30 in the EORTC QLQ-C30 global health status/QoL score in both groups. From baseline to week 30, for the EORTC QLQ-C30 functional scales (i.e., physical functioning and role functioning) and the symptom scales (i.e., nausea and vomiting), there was no statistically significant difference between the pembrolizumab plus axitinib group compared with sunitinib. However, worsening symptoms of diarrhea were observed in the pembrolizumab plus axitinib group compared with sunitinib from baseline to week 30. The sponsor conducted an exploratory adjustment for treatment exposure, which resulted in a similar event rate of diarrhea between the pembrolizumab plus axitinib and sunitinib group.

**Limitations: No direct comparison to other first-line available treatments such as pazopanib and nivolumab plus ipilimumab, short duration of follow-up, and median OS was not reached**

pERC noted the limitations and sources of bias of the KEYNOTE-426 trial as follows: the open-label study design and the lack of internal validity may have been affected by the lack of blinding, pre-specified interaction tests for subgroup analyses were not performed, and formal hypothesis testing and multiplicity adjustments were not performed for the patient-reported outcomes (PROs). The main limitation from the Keynote 426 trial was the short duration of follow-up and thus the median OS was not reached.

**Safety: Grade 3 or higher adverse events in pembrolizumab plus axitinib compared with sunitinib**

In the as-treated study population, among the 429 patients that received at least one dose of pembrolizumab plus axitinib, 98.4% experienced an adverse event (AE) of any cause compared with 99.5% of the 425 patients who received sunitinib. Grade 3 or higher AEs were slightly more common in the pembrolizumab plus axitinib group (75.8% of patients) compared with the sunitinib group (70.6% of patients). Hypertension was the most common grade 3 or higher AE that occurred in the pembrolizumab plus axitinib group (21.2%) and sunitinib (18.4%) followed by diarrhea in the pembrolizumab plus axitinib group (7.2%) versus the sunitinib group (4.5%). In the pembrolizumab and axitinib group, discontinuation of either drug due to AEs of any cause occurred in 30.5% of patients, discontinuation of both pembrolizumab and axitinib occurred in 10.7% of patients, interruption of either drug in 69.9% of patients, and a dose reduction of axitinib occurred in 20.3%. Four patients (0.9%) in the pembrolizumab and axitinib group died from AEs attributed to study treatment by the investigator (i.e., one patient died from each of the following: myasthenia gravis, myocarditis, necrotizing fasciitis, and pneumonitis). There were seven patients (1.6%) in the sunitinib group who died from AEs attributed to study treatment by the investigator (i.e., one patient each of acute myocardial infarction, cardiac arrest, gastrointestinal hemorrhage, intracranial hemorrhage, fulminant hepatitis, malignant neoplasm progression, and pneumonia). No deaths related to the study drug were reported.

**Comparator information: sponsor-submitted NMAs exhibited superiority of pembrolizumab plus axitinib over sunitinib for PFS and OS in the intermediate- and poor-risk subgroup; however, limitations of the NMA are cause for uncertainty**

The sponsor conducted a systematic literature review and an NMA to identify RCTs and systematic reviews that evaluated ORR, PFS, OS, and safety for patients with metastatic (mRCC). In the constant HR base-case analysis of PFS, pembrolizumab plus axitinib resulted in a statistically meaningful increase in the duration of PFS compared with most interventions, except nivolumab plus ipilimumab. In the constant HR base-case analysis of OS, treatment with pembrolizumab plus axitinib resulted in a statistically meaningful increase in the duration of OS compared with most competing interventions, except nivolumab plus ipilimumab. Among the intermediate- and poor-risk subgroups, the results of the PFS and OS constant HR analyses both showed that pembrolizumab plus axitinib was statistically superior to sunitinib, but not nivolumab plus ipilimumab. In appraising the NMA, the CADTH review team identified the following limitations: lack of clarity on the inclusion and exclusion criteria; sources of clinical heterogeneity; and lack of clarity of baseline characteristics of patients included in the trials; and missing data. Due to the limitations identified, results of the NMA should be interpreted with caution. The relative efficacy of pembrolizumab plus axitinib versus other competing interventions remains uncertain for the first-line treatment of mRCC.

**Need and burden of illness: need for effective novel therapies with improvement in OS due to progression on currently available therapies**

Long-term survival is rare for patients with mRCC; thus, there is an unmet need for novel therapies that are associated with increased efficacy and in particular increased OS. Presently, no predictive biomarkers

exist that would allow the rational selection of single-drug or combination therapy for individual patients. Until recently, the standard first-line treatment for mRCC consisted of either sunitinib or pazopanib. Although well-tolerated and effective, these treatments are not curative and most patients will progress, underscoring the urgent need for novel treatment approaches. The checkpoint inhibitors that target PD-1, such as nivolumab, have shown encouraging activity and are currently approved in the second-line mRCC setting. Interest has now shifted to treating with these drugs earlier in the disease-treatment process and exploring combination approaches, which have already shown early success. In the first-line setting, the combination of two checkpoint inhibitors, ipilimumab plus nivolumab, is currently funded and a Health Canada approved regimen for patients with intermediate- and poor-risk mRCC. Another strategy involves combining a checkpoint inhibitor with an angiogenesis inhibitor.

### Registered clinician input: the efficacy of pembrolizumab and axitinib combination therapy in the first-line setting for previously untreated advanced RCC, inclusive of all IMDC risk groups.

Joint input on behalf of three oncologists from Cancer Care Ontario (CCO) and joint input submitted on behalf of two oncologists from Kidney Cancer Research Network of Canada (KCRNC) were received. Based on the results of the KEYNOTE-426 trial, all clinicians agreed that pembrolizumab and axitinib would be beneficial as a first-line therapy for previously untreated advanced RCC, inclusive of all IMDC risk groups. The clinicians noted that compared with sunitinib, pembrolizumab and axitinib exhibited a significantly longer OS and PFS as well as a higher ORR with similar tolerance profiles. For this indication, pazopanib and sunitinib are currently used and funded in all provinces in the first-line setting. Recently, pERC granted nivolumab plus ipilimumab a positive conditional recommendation for intermediate or poor-risk patients with previously untreated, advanced RCC. Furthermore, all clinicians acknowledged that there is limited evidence to inform the sequencing of therapies following first-line pembrolizumab and axitinib. When asked whether there were clinical scenarios in which pembrolizumab plus axitinib, nivolumab plus ipilimumab, or targeted therapies would be the preferred treatment in first-line RCC, clinicians noted that pembrolizumab and axitinib would not replace the latter combination. The clinicians emphasized that pembrolizumab and axitinib would be used in previously untreated advanced or mRCC regardless of the IMDC risk group; alternatively, nivolumab and ipilimumab is indicated in IMDC intermediate and poor-risk patients. Further, PD-L1 status was noted to be clinically irrelevant for this indication; thus, monotherapy TKIs should only be used when patients are ineligible for any combination regimens. Moreover, clinicians were asked if patients who continue with single-drug axitinib after completion of 35 cycles of pembrolizumab should be eligible for single-drug nivolumab upon progression. CCO clinicians stated that there is a potential benefit of salvage therapy and re-initiation of PD-1 inhibition in a clinical scenario of delayed progression on axitinib alone after benefiting from 35 cycles of pembrolizumab. Input from KCRNC noted the importance of considering the duration between cessation of pembrolizumab therapy and disease progression; for instance, if the time exceeds six months another PD-1 inhibitor may have clinical efficacy. Further, when asked about evidence guiding the treatment duration of pembrolizumab, both inputs noted that administration should reflect the trial protocol (maximum of 35 cycles).

## PATIENT-BASED VALUES

### Experiences of patients with renal cell carcinoma: Unmet need for effective treatments for patients in the first-line setting

Patient input was obtained from KCC and included results from a survey conducted by Kidney Cancer UK (KCUK). KCC did not provide any direct insights into patients' experience with currently available treatments for mRCC but instead, advised pCODR to refer to KCC patient input submissions in which KCC reported extensively on various aspects of patient experience with current treatments. The recurring themes in those submissions included the high or unmet need for patients who become refractory to first-line treatment and the importance of having an informed choice of treatment based on known side effects as current treatment options are not effective for everyone and can be difficult to access.

### Patient values on treatment: availability of effective treatment options as many patients develop resistance to current first-line therapies for RCC and the ability to make informed treatment decisions based on known side effects

KCC acknowledged that although newer therapies have improved overall patient outcomes, there is a need for effective therapies with manageable side effects that are not resistant to antiangiogenic therapies. Additionally, effective predictive and prognostic biomarkers are needed to help detect the

disease at an earlier stage and guide treatments plans for patients, thus leading to improved patient outcomes. One patient respondent of the KCC survey accessed pembrolizumab and axitinib through enrolment to the KEYNOTE-426 trial and rated the treatment combination as extremely effective with a moderate impact on quality of life. The patient respondent noted side effects that were most commonly experienced were skin problems including itching (pruritus) and rash, redness and pain on the palm of the hand and sole of the foot (palmar plantar erythrodysesthesia), fatigue or lack of energy (asthenia), cough, hoarse or raspy or strained voice (dysphonia), and diarrhea. Notably, diarrhea and dysphonia were rated to be very tolerable; alternatively, skin problems, such as palmar plantar erythrodysesthesia were rated to be completely intolerable. Nonetheless, the patient noted that the treatment benefits outweighed the side effects. Moreover, the CKUK patient and caregiver survey respondents highlighted that pembrolizumab and axitinib elicited better control of the condition, shorter administration times, and minimal side effects that were manageable. Overall, patients value increased awareness and earlier detection of disease, delay in disease progression and increased support in helping manage the disease.

## ECONOMIC EVALUATION

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

The submitted economic model assessed the cost-effectiveness and cost-utility for pembrolizumab in combination with axitinib as first-line treatment for advanced RCC. Comparators included sunitinib monotherapy, pazopanib monotherapy, and nivolumab plus ipilimumab combination therapy. The target population are patients with previously untreated advanced RCC.

### Basis of the economic model: partitioned survival model

The economic analysis used a partitioned survival model to estimate health and cost outcomes. The partitioned survival model allocated a cohort of patients across three health states: progression-free, progressed disease, and death. The model was based on a median follow-up of 12.8 months from the KEYNOTE-426 trial and extrapolated the treatment effect of pembrolizumab plus axitinib over a 15-year time horizon and assumed the relative treatment effect would continue indefinitely over the entire time horizon.

### Drug costs: treatment cost of pembrolizumab plus axitinib and comparators in the submitted model

Pembrolizumab

Pembrolizumab costs $4,400 per 100 mg vial, while axitinib costs $97.13 per 5 mg tablet. At the recommended dose of 200 mg intravenously every three weeks for pembrolizumab and 5 mg orally twice a day for axitinib for a maximum of 35 cycles (approximately two years), pembrolizumab plus axitinib costs:

- $419.05 + $194.26 = $613.31 per day
- $17,172.68 per 28-day dose

At the recommended dose of 5 mg twice a day, single agent axitinib costs $194.26 per day and $5,439.28 per 28-day course.

Sunitinib

Sunitinib costs $257.66 per 50 mg capsule. At the recommended dose of 50 mg orally once a day for four weeks and two weeks off treatment, sunitinib costs:

- $171.77 per day
- $4,809.56 per 28-day course

Pazopanib

Pazopanib costs $35.52 per 200 mg tablet. At the recommended dose of 800 mg orally once a day, pazopanib costs:

- $142.08 per day

Nivolumab plus Ipilimumab

Nivolumab costs $782.22 per 40 mg, while ipilimumab costs $5,800 per 50 mg. At the recommended dose of 3 mg/kg intravenously every three weeks for nivolumab and 1 mg/kg intravenously every three weeks for ipilimumab for up to four doses, nivolumab plus ipilimumab costs:

- $236.90 + $522.00 = $758.90 per day
- $21,249.2 per 28-day course for the first four cycles

A total of 245 mg of nivolumab (6.36 vials) and 82 mg (1.89 vials) of ipilimumab would be administered once per 21-day cycle for an average body weight of 81.52 kg

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.

### Clinical effect estimates: Keynote-426 and sponsor's network meta-analysis

Patient-level survival data from KN426 was extrapolated with consideration of six potential parametric models. In the base case, the piecewise exponential distribution was used to model PFS in both arms by visual inspection of data plots and formal statistical tests. The choice of distribution was made using goodness of fit as assessed by Bayesian Information Criterion (BIC), Akaike information criterion (AIC), visual fit to observed Kaplan–Meier data, clinical plausibility, and by validating against external trial sources. The other comparators, PFS and OS, were derived by applying time-constant HRs estimated through fixed-effects NMAs to the survival curves of pembrolizumab plus axitinib.

### Cost-effectiveness estimates: submitted model required a more appropriate estimate of long-term comparative effectiveness

The EGP made the following changes to the submitted economic model to explore uncertainty in the main assumptions and limitations of the sponsor's economic evaluation:

- Attenuating relative treatment effect given the short follow-up period and the immaturity of the data: a decline in the treatment effect beyond the end of the trial period (duration approximately 12 months) was felt to be more reasonable. For the EGP reanalysis of the base-case estimate, the treatment effect for pembrolizumab plus axitinib was assumed to wane from the end of the treatment (two years) up to 3 to 10 years, with no incremental benefit after five years used in the EGP base case (i.e., HR of both PFS and OS linearly converge toward those of sunitinib over a three-year period, starting at two years and ends at five years).

- Parametric assumption of sunitinib OS: the sponsor used the exponential parametric function to estimate sunitinib OS; however, the best fit was observed with the log-normal function. The log-normal function was tried for sunitinib in the EGP reanalysis. Nevertheless, CGP agreed that the OS was too high and optimistic at 15 years as 15% of the patients were still alive using the log-normal function, as such it was not included in the EGP base case.

- Utility values: the utility values in the sponsor's base-case analysis were based on number of days to death, which allowed for different utility values by treatment and health state. Although time-to-death health states are not an unreasonable approach to use in a model, it is currently not transparently modelled. The sponsor provided a deterministic scenario analysis using utility values anchored by health state, which was determined to be more transparent and consistent with previous reviews in RCC and was used for the EGP's best-case estimate.

- Cost of subsequent therapies: subsequent therapies were selected based on initial therapy in the sponsor's best-case estimate, and only the cost difference was modelled, not changes in effectiveness. The nature and distribution of subsequent therapies were taken from the KN426 trial for pembrolizumab plus axitinib and sunitinib. The EGP conducted a scenario analysis of their base-case estimate using the average cost of subsequent therapies that was assumed to occur for both treatment arms.

In the EGP base case (attenuating relative treatment effect to wane at two years and end after five years, and using utilities anchored in health states), the ICUR of pembrolizumab plus axitinib was $255,001 per QALY when compared with sunitinib. A scenario analysis of the EGP base case using average subsequent treatment costs in both arms increased the ICUR to $273,557 per QALY.

The sponsor provided a sequential analysis of additional comparators of pazopanib and nivolumab plus ipilimumab in the overall RCC population, the sequential ICUR of pembrolizumab plus axitinib is $333,528

per QALY when compared with the least expensive treatment (pazopanib). pERC noted the limitations associated with the different patient populations included in the model as nivolumab plus ipilimumab is currently approved in intermediate- and poor-risk patients and as such the results of the sequential analysis is uncertain.

## ADOPTION FEASIBILITY

**Considerations for implementation and budget impact: concerns with drug wastage and budget impact is underestimated**

PAG noted there will be drug wastage, as vial sharing may not be feasible in smaller outpatient cancer centres. The factors that most influence the budget impact analysis (BIA) include the peak share of the pembrolizumab plus axitinib combination, time to peak for the pembrolizumab and axitinib combination, shape of the pembrolizumab plus axitinib combination uptake curve, and nivolumab plus ipilimumab share at pembrolizumab plus axitinib's peak. Limitations of the BIA model include lack of data on the market share assumptions and possible overestimation of the assumption of relative dose intensity for nivolumab plus ipilimumab. Both inputs were modifiable and explored by the EGP.

# ABOUT THIS RECOMMENDATION

### The pCODR Expert Review Committee

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

Dr. Maureen Trudeau, Oncologist (Chair)
Dr. Catherine Moltzan, Oncologist (Vice-Chair)
Daryl Bell, Patient Member
Dr. Kelvin Chan, Oncologist
Lauren Flay Charbonneau, Pharmacist
Dr. Michael Crump, 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. W. Dominika Wranik, Health Economist

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

- Dr. Catherine Moltzan and Dr. Michael Crump who were not present for the meeting
- Dr. Maureen Trudeau, who did not vote due to her role as the pERC Chair.
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All members participated in deliberations and voting on the Final Recommendation, except:

- Dr. Avram Denburg and Dr. Christopher Longo, who were not present for the meeting
- Dr. Maureen Trudeau, who did not vote due to her role as the pERC Chair.

### Avoidance of conflicts of interest

All members of the 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 Pembrolizumab (Keytruda), through their declarations four members had a real, potential or perceived conflict and based on application of the *pCODR Conflict of Interest Guidelines*, but none of these members was excluded from voting. For the Final Recommendation, one member had a real, potential, or perceived conflict, and based on application of the pCODR Conflict of Interest Guidelines, none of the members were excluded from voting.

### Information sources used

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

### Consulting publicly disclosed information

pCODR considers it essential that pERC recommendations be based on information that may be publicly disclosed. All information provided to the pCODR Expert Review Committee for its deliberations was handled in accordance with the *pCODR Disclosure of Information Guidelines*. There was no non-disclosable information in this recommendation document.

### Use of this Recommendation

This Recommendation from pERC is not intended as a substitute for professional advice, but rather to help Canadian health systems leaders and policy-makers make well-informed decisions and improve the quality of health care services. While patients and others may use this Recommendation, it is for informational and educational purposes only, and should not be used as a substitute for the application of clinical judgment respecting the care of a particular patient, for professional judgment in any decision-making process, or for professional medical advice.

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

| PAG Implementation Questions | pERC Recommendation |
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| **Currently Funded Treatments**<br>PAG identified:<br>• For advanced or metastatic RCC, two oral targeted therapies, pazopanib and sunitinib, are funded in all provinces for first-line treatment.<br>• The immunotherapy combination of nivolumab and ipilimumab is currently funded in most provinces for intermediate- and poor-risk patients with previously untreated, advanced or metastatic renal cell carcinoma.<br>• Temsirolimus is funded in most provinces for poor-risk advanced or metastatic RCC but is rarely used. | • pERC agreed with the CGP that the benefits of pembrolizumab plus axitinib with respect to OS and PFS were observed in all IMDC risk groups and PD-L1 expression categories, and as such would be a first-line treatment option available to patients with advanced RCC. |
| **Eligible Patient Population**<br>• PAG is seeking clarity on the eligible patient populations. The reimbursement request is for patients with advanced RCC. KEYNOTE-426 trial included patients with clear-cell histology and all IMDC prognostic risk groups and PD-L1 expression categories. PAG is seeking information on pembrolizumab plus axitinib in patients with non–clear-cell histology or those with active central nervous (CNS) metastases.<br>• PAG is also seeking guidance on whether there are specific IMDC prognostic risk groups or PD-L1 expression categories where pembrolizumab plus axitinib is the preferred treatment in this setting.<br>• PAG is seeking guidance on whether patients who have started first-line treatment (e.g., sunitinib, pazopanib, or nivolumab plus ipilimumab), and have not yet progressed or who are unable to tolerate treatment, could switch to pembrolizumab plus axitinib combination as their first-line treatment. | • pERC agreed with the CGP that patients with non–clear-cell histology and all IMDC groups would be eligible to receive pembrolizumab plus axitinib.<br>• pERC agreed with the CGP that patients with stable brain metastases would be eligible to receive pembrolizumab plus axitinib.<br>• pERC agreed with the CGP that patients who have started first-line treatment and have not yet progressed should not be switched to pembrolizumab plus axitinib; however, patients who are unable to tolerate treatment early on in the therapy may be able to switch to pembrolizumab plus axitinib upon discussion with the patient and in consultation with the treating physician. |
| **Implementation Factors**<br>• The dose is 200 mg for RCC in the funding request and the KEYNOTE-426 trial. PAG noted trials suggest that weight-based dose of 2 mg/kg and 200 mg fixed dose are similar. Although a fixed dose would minimize drug wastage, PAG is seeking guidance on weight-based dose for RCC (i.e., 2 mg/kg up to 200 mg) given the high cost of a fixed dose compared with a weight-based dose for patients weighing less than 100 kg.<br>• PAG also identified emerging data of dosing pembrolizumab at 400 mg every 6 weeks, PAG is seeking guidance on the appropriateness of alternate dosing/schedule (i.e., 400 mg or 4 mg/kg up to a flat dose cap of 400 mg every 6 weeks).<br>• PAG noted that as pembrolizumab is currently used in a number of other indications, drug wastage could be minimized with vial sharing. However, vial sharing may not be feasible in smaller outpatient cancer centres. Furthermore, discontinuation of the 50 mg vial may result in wastage, particularly | • pERC agreed with the CGP that it would be reasonable to administer pembrolizumab at 2 mg/kg up to a total dose of 200 mg.<br>• pERC noted the emerging data for dosing pembrolizumab at 400 mg; however, the committee noted that there is limited evidence to inform on the 4 mg/kg up to a flat dose cap of 400 mg at every 6 weeks dosing, and as such was unable to comment.<br>• pERC noted that treatment with axitinib should be continued until disease progression, development, or unacceptable toxic effects or physician or patient decision to discontinue treatment.<br>• pERC agreed that treatment with pembrolizumab should continue until disease progression or unacceptable toxicity for a maximum of 35 cycles (approximately two years), as noted in the Keynote-426 protocol.<br>• pERC agreed that for patients who do not tolerate the pembrolizumab plus axitinib combination, treatment with single-drug pembrolizumab or |

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| in low volume or rural institutions where vial sharing is not feasible and weight-based dosing is utilized. PAG identified that the re-introduction of the 50 mg vial by the manufacturer and introducing a 25 mg vial would be an enabler to implementation.<br>• PAG is seeking clarity on both treatment duration and treatment discontinuation as in the KEYNOTE-426 trial treatment "continued until disease progression, development of unacceptable toxic effects, or physician or patient decision to discontinue."<br>• As pembrolizumab was administered for a maximum of 35 cycles in the KEYNOTE-426 trial, PAG is seeking clarity on whether patients should receive a total of two years of treatment or 35 cycles, as treatment interruptions due to toxicity may lead to two years occurring before 35 cycles are administered.<br>• For patients who do not tolerate the pembrolizumab plus axitinib combination, PAG is seeking guidance on whether treatment with single-drug pembrolizumab or single-drug axitinib is appropriate.<br>• As pembrolizumab is an intravenous therapy, whereas axitinib, pazopanib and sunitinib are oral therapies, PAG noted that additional pharmacy resources are required to prepare and administer the infusion, in addition to chemotherapy chair time and additional clinic visits.<br>• Pembrolizumab, being an intravenous drug, would be administered in an outpatient chemotherapy centre for appropriate administration and monitoring of toxicities. Intravenous chemotherapy drugs would be fully funded in all jurisdictions for eligible patients, which is an enabler for patients. | single-drug axitinib is appropriate. pERC commented that patients in the Keynote 426 trial were able to continue with either single-drug pembrolizumab for a maximum of 35 cycles or single-drug axitinib until progressive disease.<br>• pERC agreed that patients who stop pembrolizumab after 35 doses without PD or stop pembrolizumab due to having achieved a complete response may be eligible for a second course of pembrolizumab treatment for up to 17 additional doses (approximately one year) upon experiencing PD as noted in the Keynote-426 protocol. |
| **Sequencing and Priority of Treatments**<br>• PAG is seeking guidance on the appropriate sequencing of first-, second-, and third-line treatment with VEGF and PD-1 checkpoint inhibitors (e.g., pazopanib, sunitinib, nivolumab plus ipilimumab, and nivolumab) for IMDC risk groups (favourable, intermediate, and poor). In particular:<br>  • Place in therapy for pembrolizumab plus axitinib and which patient population would benefit most from the combination and which patient population would be best suited for treatment with other available therapies.<br>  • Treatment options after progression on pembrolizumab plus axitinib combination therapy (e.g., would nivolumab, another PD-1 inhibitor, be used in the second- or third-line setting?).<br>  • Should patients who continue with single-drug axitinib, after completing 35 cycles of pembrolizumab, be eligible for single-drug nivolumab upon progression? | • pERC agreed with the clinician input that combination treatment with pembrolizumab plus axitinib would be for patients with previously untreated advanced or metastatic RCC, regardless of the IMDC risk group. pERC also noted that pembrolizumab plus axitinib would not replace nivolumab plus ipilimumab given that nivolumab plus ipilimumab is specific for the intermediate- or poor-risk patient population, and the treatment with pembrolizumab plus axitinib is for all IMDC prognostic risk groups.<br>• pERC agreed with the clinician input that treatment options after progression on pembrolizumab plus axitinib would depend on the duration between stopping pembrolizumab plus axitinib and when progression occurs. pERC noted that if the duration is greater than 6 months after pembrolizumab therapy, another PD1 inhibitor may be efficacious. |

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| **Companion Diagnostic Test/Other**<br>• PAG noted that the subgroup of patients with PD-L1 expression greater than 1% had better outcomes and is seeking clarity on whether PD-L1 testing is required. PD-L1 status is not currently being tested in renal cancer patients and is not required for use of nivolumab plus ipilimumab in the first-line setting or single-drug nivolumab in the second line. | • pERC agreed with the CGP and clinician input that PD-L1 testing should not be required for treatment with pembrolizumab plus axitinib in renal cancer patients. |

CNS= central nervous metastases, CGP = Clinical Guidance Panel; IMDC = International Metastatic RCC Database Consortium; mRCC = metastatic renal cell carcinoma; PAG = Provincial Advisory Group; PD1 = programmed cell death protein 1; pERC = CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee; PD = progressive disease; RCC = renal cell carcinoma; VEGF = vascular endothelial growth factor.