pCODR EXPERT REVIEW COMMITTEE (pERC)
FINAL RECOMMENDATION

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

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

Drug: Pembrolizumab (Keytruda)

Submitted Reimbursement Request:
As a monotherapy for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 [Combined Positive Score (CPS) ≥ 10] as determined by a validated test, or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status.

Submitted By: Merck Canada	**Manufactured By:** Merck Canada
NOC Date: April 11, 2019	**Submission Date:** February 20, 2019
Initial Recommendation: July 18, 2019	**Final Recommendation:** October 3, 2019

Approximate Per-Patient Drug Costs, per Month (28 Days)	Pembrolizumab costs $2,200.00 per 50 mg vial and $4,400.00 per 100 mg vial. 200 mg every three weeks. Cost per 28-day cycle: $11,733.00.

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 does not recommend the reimbursement of pembrolizumab (Keytruda) for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy and whose tumours express programmed death-ligand 1 (PD-L1) (combined positive score [CPS] ≥ 10) as determined by a validated test, or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status.

pERC made this recommendation because it was not satisfied that there is a net clinical benefit of pembrolizumab compared with gemcitabine plus carboplatin or single-drug chemotherapy given the limitations in the evidence from the available phase II clinical trial. While pERC acknowledged that there is an unmet need for effective treatments in this setting, the Committee concluded that there was considerable uncertainty in the magnitude of clinical benefit of pembrolizumab compared with appropriate comparators with regard to outcomes important to decision-making such as overall survival (OS), progression-free survival (PFS), and quality of life (QoL).

pERC agreed that pembrolizumab aligned with patient values in that it has manageable side effects, has the potential to maintain QoL, and offers an additional treatment choice. However, the Committee was unable to make conclusions on the magnitude of the clinical benefit of pembrolizumab

	compared with other options. pERC could not draw a conclusion on the cost-effectiveness of pembrolizumab compared with gemcitabine plus carboplatin or single-drug chemotherapy due to the uncertainty surrounding the incremental survival benefits used in the economic model.
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	**Possibility of Resubmission to Support Reimbursement** **Cisplatin-Ineligible and PD-L1 CPS ≥ 10 Subgroup** pERC considered that a phase III randomized controlled trial is currently being conducted in patients with locally advanced or metastatic urothelial carcinoma (UC) who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 CPS ≥ 10 comparing pembrolizumab with currently available treatments in Canada. pERC noted that new clinical data comparing pembrolizumab with standard of care treatments could form the basis of a resubmission to pCODR if comparative efficacy data important to decision-making, such as PFS, OS, and QoL, are available. **Platinum-Ineligible, Irrespective of PD-L1 Expression Status Subgroup** pERC noted that higher-quality evidence, including efficacy data important to decision-making, such as PFS, OS, and QoL, could form the basis of a resubmission to pCODR. pERC noted that evidence from high-quality phase II trials may be considered as part of a resubmission, given that conducting a phase III trial with pembrolizumab compared with standard of care (palliative care or single-drug gemcitabine) would likely not be feasible in this patient subgroup.

SUMMARY OF pERC DELIBERATIONS

In 2017, 8,900 new cases of bladder cancer with 2,400 deaths were estimated to have occurred in Canada due to urothelial cancer. It is one of the top ten causes of cancer deaths and is considered the fourth and 10th most common cancer diagnosed in males and females, respectively. UC is the most common type of bladder cancer. Patients presenting with or developing metastatic disease remain incurable. The standard of care for these patients remains cisplatin combination chemotherapy. However, approximately 30% to 50% of patients are considered ineligible for cisplatin-based chemotherapy because of comorbidities. A subset of patients who are cisplatin ineligible will not be candidates for any platinum-based chemotherapy and will receive either gemcitabine or best supportive care only. OS in patients who are cisplatin ineligible is very poor, ranging from seven to 10 months with current treatment options. pERC recognized that there is a substantial unmet need for effective and tolerable treatments in patients who are cisplatin ineligible, especially in those who are not eligible for any platinum-based chemotherapy and have locally advanced or metastatic UC.

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

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

pERC deliberated on one single-arm, open-label, phase II trial (KEYNOTE 052) that evaluated the safety and efficacy of pembrolizumab as a first-line therapy in patients who are cisplatin ineligible and have locally advanced or metastatic UC. pERC specifically deliberated the results of one subgroup and one post-hoc analysis within KEYNOTE 052. The subgroup analysis included patients who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 CPS ≥ 10. The post-hoc analysis was performed in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status. Although pERC considered that the magnitude and durable nature of objective tumour responses observed with pembrolizumab were important, the Committee discussed that there was a high level of uncertainty around the magnitude of the clinical benefit given the limitations in the evidence from the non-comparative phase II clinical trial. Specifically, the Committee was concerned about the lack of appropriate sample size determination with no pre-specified threshold for clinical significance, the exploratory nature of the post-hoc subgroup analysis, and the descriptive data analyses with no formal hypothesis testing. In addition, pERC noted that overall response rate (ORR) is an uncertain surrogate for survival in most solid tumours and that the trial did not provide any comparative evidence on PFS, which is the main deciding factor in treatment selection in the current era in which multiple anti-PD-1, anti-PD-L1, or anti-PD-L2 drugs for locally advanced or metastatic UC are being investigated in clinical trials.

Upon reconsideration of the pERC Initial Recommendation, the Committee discussed the feedback provided by the sponsor stating that there is a strong suggestion that ORR acts as a surrogate outcome for OS in patients treated with PD-1 inhibitors. To support this position, the sponsor referred to literature that reported that patients treated with a PD-1 inhibitor (i.e., pembrolizumab or nivolumab) who achieved a complete or partial response had a better OS as compared with patients with no tumour response. pERC agreed with the response provided by the pCODR Methods Team in the pCODR Clinical Guidance Report (CGR) that based on several limitations identified in the provided evidence, it is challenging to confirm the appropriateness of ORR as a surrogate outcome for OS in the target patient population of the present reimbursement request. Specifically, pERC agreed that (1) the analyses provided by the sponsor may not provide sufficient statistical evidence to validate ORR as a surrogate outcome for OS as it has been suggested in the literature that a surrogate outcome should demonstrate an "individual-level" and a "trial-level" association using a meta-analytic/correlation approach, (2) the results of the KEYNOTE-045 and CheckMate-040 trials may not be generalizable to the patient population of the KEYNOTE-052 trial due to several differences in the trial design and patient characteristics between the studies, and (3) the analyses were either exploratory or did not appear to be pre-specified as per protocol, and it was unclear if the analysis was adjusted for multiplicity or adequately powered.

pERC agreed that the magnitude of effect of pembrolizumab compared with available therapies was uncertain, given the lack of comparative data and long-term outcomes important to patients, such as OS, PFS, and QoL. In addition, pERC discussed that phase II trials are mainly hypothesis-generating and their

intent is to determine whether there is sufficient promise to proceed to a phase III confirmatory trial. pERC noted that it is feasible to conduct a phase III randomized controlled trial in this setting. There are ongoing phase III trials with pembrolizumab in the two target patient populations that may provide clarity on the comparative effectiveness of pembrolizumab in relation to alternative treatment options. However, pERC agreed that conducting a phase III trial with pembrolizumab compared with standard of care (palliative care or single-drug gemcitabine) would likely not be feasible in the patient population that is platinum ineligible due to rapidly deteriorating patients and equipoise considerations. However, given the high level of uncertainty in the results from the available phase II trial, the Committee could not confidently conclude that pembrolizumab addresses the need for effective treatment options in this patient population.

Upon reconsideration of the pERC Initial Recommendation, the Committee discussed feedback provided by the sponsor, one patient advocacy group, and registered clinicians that suggested that while there is an urgent need for better treatment options for patients with cisplatin-ineligible disease, the need is especially high for patients with platinum-ineligible disease, as patients in the latter group have no effective treatment options. pERC agreed with the stakeholder feedback and acknowledged that there is an urgent unmet need for further treatment options for patients with cisplatin-ineligible disease, especially those with platinum-ineligible disease. However, given the high level of uncertainty in the results from the available phase II trial and the lack of robust comparative data with respect to outcomes important to decision-making, the Committee could not confidently conclude that pembrolizumab addresses the need for effective treatment options in this patient setting.

pERC considered the safety of pembrolizumab and agreed with the Clinical Guidance Panel (CGP) that incidence and severity of adverse reactions appear manageable and consistent with the safety profile of pembrolizumab in other cancer trials. The most frequently reported treatment-emergent adverse events (AEs) included fatigue, pruritus, rash, and decreased appetite. The most common grade 3 to 5 treatment-emergent AEs were fatigue, colitis, increased blood alkaline phosphatase level, muscle weakness, and hepatitis. No new safety signals were reported with regard to immune-mediated AEs. However, pERC noted that the non-randomized design of KEYNOTE 052 makes interpreting the safety events attributable to pembrolizumab challenging, given that all patients received the same treatment.

pERC discussed the exploratory patient-reported outcomes data from KEYNOTE 052 and noted that the results suggested that pembrolizumab has the potential to maintain QoL. The Committee noted that QoL scores remained stable, with some patients reporting improvements. However, pERC concluded that given the open-label design of the trial, the lack of a comparator group, and the insufficient follow-up time, there is considerable uncertainty in the QoL results.

Overall, pERC was not satisfied that there is a net clinical benefit of pembrolizumab compared with gemcitabine plus carboplatin or single-drug chemotherapy given the limitations in the evidence from the available phase II clinical trial. While pERC acknowledged that there is an unmet need for effective treatments in this setting, the Committee concluded that there was considerable uncertainty in the magnitude of clinical benefit of pembrolizumab compared with appropriate comparators with regard to outcomes important to decision-making such as OS, PFS, and QoL.

Upon reconsideration of the pERC Initial Recommendation, the Committee discussed feedback provided by the sponsor that pERC has recognized a net clinical benefit in previous pCODR submissions that were based on non-comparative studies with ORR as the primary outcome. In acknowledging the sponsor's feedback, pERC agreed that the Committee has accepted evidence from non-comparative studies in previous pCODR reviews for reasons that are context (drug and disease) specific. As a principle, the Committee considers a review based on its own merits and the evidence presented for the drug under consideration. pERC agreed that there are considerations beyond the response rate and the study design that go into making recommendations, such as — but not limited to — the feasibility of conducting a randomized trial and the availability of alternative treatments. pERC reiterated that in this instance the Committee was not satisfied that there is a net clinical benefit of pembrolizumab compared with gemcitabine plus carboplatin or single-drug chemotherapy given the limitations in the evidence from the available phase II clinical trial.

pERC deliberated input from one patient advocacy group, noting that, according to patients, key symptoms of locally advanced or metastatic UC included blood in urine, fatigue, and urination problems. pERC considered that few patient respondents had direct experience using pembrolizumab and those who did reported that pembrolizumab gave rise to milder side effects compared with standard chemotherapy

and improved disease control, symptoms, and general QoL. pERC considered that patients value treatments that will achieve disease control, extend life expectancy, and maintain QoL. pERC agreed that pembrolizumab aligned with patient values in that it has manageable side effects, has the potential to maintain QoL, and offers an additional treatment choice. However, the Committee was unable to make conclusions on the magnitude of the benefit of pembrolizumab compared with standard of care treatment options in terms of tumour responses, PFS, OS, or QoL.

Upon reconsideration, pERC discussed feedback from the patient advocacy group (Bladder Cancer Canada) that the US FDA and the European Medicines Agency had approved the use of pembrolizumab in the present setting. pERC noted that the role of regulatory agencies in providing approval is limited to determining whether the benefit-risk ratio is favourable. pERC stressed that its role as a health technology assessment body is broader than the previously mentioned bodies in that it examines the comparative effectiveness of different treatment strategies, looking at multiple dimensions while aiming to provide a balance between the values, needs, preferences, and perspectives of patients and those of society.

pERC deliberated on the cost-effectiveness of pembrolizumab compared with gemcitabine plus carboplatin and gemcitabine monotherapy. Because of the considerable limitations in the available clinical data for pembrolizumab from the non-comparative phase II study and the lack of robust indirect comparative effectiveness estimates for PFS and OS, pERC concluded that it was not possible to draw meaningful conclusions on the cost-effectiveness of pembrolizumab. pERC noted that the sponsor provided indirect treatment comparisons (ITCs) to present relative treatment effect estimates between comparators in the absence of head-to-head data. pERC agreed with the pCODR Methods Team and the pCODR Economic Guidance Panel (EGP) that, given several limitations, including an unknown amount of bias in the unanchored effect estimates, the comparative effectiveness of pembrolizumab versus its comparators remains uncertain. The estimates of incremental effectiveness are largely based on a key clinical assumption that the efficacy results observed in KEYNOTE 052 and the submitted ITCs translate into real and meaningful improvements in PFS and OS for pembrolizumab compared with other currently available therapies. However, given the limitations in the treatment effect estimates from the available phase II clinical trials and the ITC analyses, and the inability of the submitted economic model to account for the resulting uncertainty in the parameter estimates, pERC agreed that the clinical effectiveness estimates could not be used to inform credible incremental cost-utility ratio (ICUR) estimates. Therefore, pERC was unable to draw a conclusion on cost-effectiveness and could not determine the ICURs for pembrolizumab compared with gemcitabine plus carboplatin and gemcitabine monotherapy for the treatment of adult patients with locally advanced or metastatic UC who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 CPS ≥ 10 as determined by a validated test, or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status.

pERC considered the feasibility of implementing a reimbursement recommendation for pembrolizumab for the treatment of adult patients with locally advanced or metastatic UC who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 CPS ≥ 10, or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status. The Provincial Advisory Group (PAG) identified that the continued availability of the 50 mg vial as well as the introduction of a 25 mg vial would be enablers for implementation given that vial sharing is not always possible. pERC also considered that pembrolizumab is a high-cost therapy and that the submitted Canada-wide budget impact was likely underestimated. Factors that affected the budget impact included the proportion of patients eligible for pembrolizumab under the current reimbursement request, the medication costs, and the rate of PD-L1 testing. pERC discussed that PD-L1 testing is not currently completed for patients with locally advanced or metastatic UC but would be required in patients who are cisplatin ineligible. pERC noted that short turnaround times (from the time the test is ordered to results reported) would be essential for the implementation of PD-L1 testing in this setting.

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: Bladder Cancer Canada (BCC)
- input from registered clinicians
- input from pCODR's PAG.

Feedback on the pERC Initial Recommendation was also provided by:

- one patient advocacy group, BCC
- registered clinicians
- PAG
- the sponsor, Merck Canada.

The pERC Initial Recommendation was to not recommend reimbursement of pembrolizumab (Keytruda) for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 (CPS ≥ 10) as determined by a validated test, or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status.

Feedback on the pERC Initial Recommendation indicated that PAG and the registered clinicians agreed with the Initial Recommendation. The patient advocacy group and sponsor disagreed with the Initial Recommendation.

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of the review is to evaluate the safety and efficacy of pembrolizumab for the treatment of adult patients with locally advanced or metastatic UC who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 (CPS ≥ 10) as determined by a validated test, or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status.

Studies included: One single-arm, open-label, phase II trial

The pCODR systematic review included one multicenter (including Canada), single-arm, open-label, phase II trial (KEYNOTE-052) (N = 374), which met the inclusion criteria for this review. KEYNOTE-052 assessed the safety and efficacy of pembrolizumab as a first-line therapy in patients who were cisplatin ineligible and had locally advanced and unresectable or metastatic UC. The pCODR requested reimbursement criteria were for two subgroups within the KEYNOTE-052 trial: patients with PD-L1 CPS ≥ 10 who were cisplatin ineligible, and patients who were ineligible to receive any platinum chemotherapy, irrespective of PD-L1 status. A subgroup analysis included patients who were not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 CPS ≥ 10. A post-hoc analysis was performed in patients who were not eligible for any platinum-containing chemotherapy regardless of PD-L1 status.

All patients who were enrolled in the trial were treated with a 200 mg dose of pembrolizumab every three weeks. Patients were treated with pembrolizumab until Response Evaluation Criteria in Solid Tumors (RECIST)-confirmed disease progression, intolerable toxic effects, doctor or patient decision to withdraw, inter-current illness preventing further treatment, confirmed pregnancy, non-compliance with trial procedures, loss to follow-up, or completion of 24 months of treatment. Investigators could continue to treat clinically stable patients beyond RECIST-confirmed disease progression if patients continued to derive a clinical benefit.

The median duration of treatment was 3.4 months (range: 0.03 to 27.89 months) among all patients enrolled in the trial.

Key trial inclusion criteria included patients with histologically or cytologically confirmed locally advanced and unresectable or metastatic UC of the renal pelvis, ureter, bladder, or urethra; and those who were ineligible for cisplatin-based therapy; had not previously received systemic chemotherapy for advanced disease; had centrally confirmed and measurable disease according to RECIST (version 1.1); had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2; and had adequate organ function. Patients who were considered platinum ineligible had an ECOG performance status of 2 and one or more of visceral metastasis, advanced age (80 years or older), or glomerular filtration rate lower than 60 mL per minute.

Patient population: Median age 73 years; main reasons for cisplatin ineligibility were renal dysfunction and ECOG performance status 2

Patients enrolled in the trial had a mean age of 73 years (standard deviation: 9.9), and the majority of patients were male (77.3%), white (88.6%), and had an ECOG performance stage of 1 (35.9%) or 2 (42.2%). The main reasons for cisplatin ineligibility were renal dysfunction (49.2%) and ECOG performance status of 2 (32.4%). The majority of patients had a predominant histology of UC (94%, N = 349).

Key efficacy results: Important but uncertain response rates

The primary outcome in the trial was ORR as assessed by an independent radiology review (IRR) using RECIST 1.1. Secondary outcomes included duration of response (DOR) as assessed by an IRR using RECIST 1.1, OS, PFS as assessed by an IRR using RECIST 1.1, and safety outcomes. Exploratory outcomes included health-related QoL.

Four data cut-offs were identified in the pCODR systematic review: September 01, 2016; March 09, 2017; November 30, 2017; and September 26, 2018. For the purpose of this Evidence in Brief section, the results of the November 30, 2017, database lock were presented, which represent a median follow-up of 11.5 months and aligns with the data cut used for the analyses in the submitted economic model.

The ORR for the overall trial population was 29.1% (95% confidence interval [CI], 24.3% to 33.8%) at the November 30, 2017, data cut-off. ORR was 47.3% (95% CI, 37.7 to 57.0) for patients with a PD-L1 CPS ≥ 10% and 26.2% (95% CI, 19.3 to 34.2) for patients who were platinum ineligible. The median DOR was not reached in the overall trial population and in patients with a PD-L1 CPS ≥ 10%. Data on median DOR as assessed by IRR using RECIST 1.1 for platinum ineligible patients were not reported.

At the November 30, 2017, data cut-off, 66.8% of patients had died (N = 247) and the median OS was 11.5 months (95% CI, 10.0 to 13.3). Of patients with a PD-L1 CPS ≥ 10%, 51.8% had died (N = 57), the median OS was 18.5 months (95% CI, 12.2 to not reported [NR]), 74.5% of the patients who were platinum ineligible had died (N = 108), and the median OS was 9.2 months (95% CI, 5.3 to 11.3).

The median PFS as assessed by IRR using RECIST 1.1 was 2.3 months (95% CI, 2.1 to 3.4); 81.4% of patients had progressed or died (N = 301). For those with a PD-L1 CPS ≥ 10%, 68.2% of patients had progressed or died (N = 75) and the median PFS was 4.9 months (95% CI, 3.8 to 10.8). Overall, 82.8% of patients who were platinum ineligible had progressed or died (N = 120) and the median PFS was 2.1 months (95% CI, 2.0 to 2.8).

Upon reconsideration of the pERC Initial Recommendation, the Committee discussed the feedback provided by the sponsor that noted that the CGR stated an incorrect median DOR of 2.1 months for the patient subgroup with platinum-ineligible disease. The sponsor clarified that the accurate median DOR for this patient subgroup was not reached (range: 2.8 to 27.6 + months). pERC and the pCODR Methods Team acknowledged the error and the pCODR Methods Team has corrected the DOR for the patient subgroup with platinum-ineligible disease in the CGR. While pERC noted that pembrolizumab showed durable responses in patients with cisplatin- and platinum-ineligible disease, the Committee reiterated that given the high level of uncertainty in the results from the available phase II trial and the lack of robust comparative data with respect to outcomes important to decision-making, pERC was not satisfied that there is a net clinical benefit of pembrolizumab compared with gemcitabine plus carboplatin or single-drug chemotherapy.

Patient-reported outcomes: Potential to maintain QoL

Patient-reported outcomes (PROs) were exploratory outcomes in KEYNOTE 052 and they were assessed using the European Organization for Research and Treatment of Cancer (EORTC) QoL Questionnaire C30

(QLQ-C30) and EuroQol Five-Dimensions Questionnaire 3-Levels (EQ-5D-3L). Overall, there were 367 patients included in the PRO analysis. At week 9, the majority of patients experienced an improvement of 10 or more points (29%) or stable global health status/QoL (43%). Similar results were observed at week 15. Scores after week 9 should be interpreted with caution because of the small sample sizes. The sponsor reported that both the EQ-5D-3L score and the EQ-5D Visual Analogue Score were stable over time. The Methods team noted that the primary health-related QoL end point was the change from baseline to week 9, which may not represent an accurate picture of patients' experiences with pembrolizumab for a prolonged period of time. As well, the trial was non-randomized and the impact of pembrolizumab on patient's QoL in relation to other therapies is unknown.

Safety: Manageable toxicity profile

Overall, 97.6% of patients had AEs and 62.7% had grade 3 to 5 AEs at the November 30, 2017, data cut-off. Sixty-eight per cent of patients experienced a treatment-related adverse event (TRAE) of any grade and 20.3% experienced a grade 3 to 5 TRAE. The most common types of AEs were fatigue (18%), pruritus (18%), and rash (12%). Seventeen per cent of patients discontinued the trial due to an AE while 11.6% discontinued due to a serious AE. Serious AEs were experienced by 50.5% of patients and 11.1% had a serious TRAE. Immune-mediated AEs occurred in 29% of patients and the most common grade 3 or 4 immune-mediated AEs were colitis (2%), pneumonitis (1%), and adrenal insufficiency (1%). There was one drug-related death due to a myositis.

Limitations: No direct comparative data to current treatment options

A critical appraisal was performed for the submitted network meta-analysis (NMA), which provides evidence on the efficacy of first-line pembrolizumab as compared with other anticancer drugs in patients with advanced or unresectable or metastatic UC who were ineligible for cisplatin-based chemotherapy. Although the results of the NMA overall support the efficacy of pembrolizumab in patients who are cisplatin ineligible and have advanced or metastatic UC, there are several limitations that were identified. First, the use of unanchored comparisons in the NMAs is a serious limitation due to the presence of unknown or unmeasured prognostic factors. It should be noted that the bias resulting from missing prognostic factors is very difficult to quantify and, as a result, it is unclear what impact the missing prognostic factors have on the results of the NMA. Second, not all of the trials included in the NMA reported baseline values for the factors that were included in the prediction models. Although these missing values were imputed using repeated bootstrap samples, this method may increase the uncertainty of the predicted outcomes for these trials. Third, the subgroup analysis assessing platinum-eligibility status should be interpreted with caution because the models only partially adjusted for known prognostic factors as a result of how platinum-eligibility status was defined. Due to these limitations, the comparative efficacy estimates obtained are likely biased, and it is not possible to quantify or identify the direction of the bias. As a result, the estimates may over- or underestimate the true treatment effect associated with pembrolizumab.

Need and burden of illness: Need for effective treatment options

In 2017, 8,900 new cases of bladder cancer with 2,400 deaths were estimated to have occurred in Canada due to urothelial cancer. It is one of the top ten causes of cancer deaths and is considered the fourth and 10th most common cancer diagnosed in males and females, respectively. UC is the most common type of bladder cancer. Patients presenting with or developing metastatic disease remain incurable. The standard of care for these patients remains cisplatin combination chemotherapy. However, approximately 30% to 50% of patients are considered ineligible for cisplatin-based chemotherapy because of comorbidities. A subset of patients with metastatic UC will not be candidates for any platinum-based chemotherapy and will receive either gemcitabine or best supportive care only. OS in patients who are cisplatin ineligible is very poor, ranging from seven to 10 months with current treatment options. Thus, there is a substantial unmet need for effective and tolerable treatments in patients who are cisplatin-ineligible and have metastatic UC.

Registered clinician input: Unmet need, suboptimal current treatment options, pembrolizumab can provide significant and durable benefits

pCODR received four registered clinician inputs. Three of the four inputs were prepared by individual clinicians while the other was jointly submitted by three clinicians from Cancer Care Ontario. Clinicians providing input indicated that advanced UC is an area of clear unmet need as a result of suboptimal treatment options. Many patients have comorbidities that preclude the use of toxic chemotherapy. In contrast, the clinician input indicated that they consider pembrolizumab less toxic and that it can provide

significant and durable benefits. There is general agreement among the clinicians giving input that pembrolizumab should be the preferred first-line treatment for the target population. Next in line would be chemotherapy should the patient become eligible. Contraindications for pembrolizumab are not as numerous as for chemotherapy, but autoimmune disorders should be considered and managed. Some clinicians mentioned that PD-L1 testing is not standard in all settings and should be made more broadly available.

PATIENT-BASED VALUES

Values of patients with locally advanced or metastatic UC: Achieving disease control, extending life expectancy, and maintaining quality of life

One patient input was provided to pCODR through a patient advocacy group submission from BCC for pembrolizumab for locally advanced or metastatic UC.

From a patient's perspective, blood in urine was the most commonly reported symptom related to UC, followed by fatigue and urination problems. Almost all patients surveyed by BCC had experience with some form of chemotherapy that led to additional fatigue, nausea, constipation, and other well-known side effects, some of which were difficult to tolerate.

Patients valued having alternative treatment options which focused on achieving disease control, extending life expectancy, and maintaining QoL. Most patients with experience using pembrolizumab recommended the drug to other potential UC patients.

Patient values on treatment: Favourable experience; improved disease control, symptoms, and quality of life

BCC provided the perspective of 15 patients with experience with pembrolizumab. Pembrolizumab gave rise to milder side effects, an aspect that was strongly appreciated by patients. The net effect was a subjective improvement in disease control, symptoms, and general QoL in patients switching to pembrolizumab therapy. The less frequent and shorter duration of therapy with pembrolizumab was also cited by patients to be a benefit compared with other therapies they had experienced.

Upon reconsideration, pERC discussed feedback from the patient advocacy group (BCC) that the US FDA and the European Medicines Agency had approved the use of pembrolizumab in the present setting. pERC noted that the role of regulatory agencies in providing approval is limited to determining whether the benefit-risk ratio is favourable. pERC stressed that its role as a health technology assessment body is broader than the previously mentioned bodies in that it examines the comparative effectiveness of different treatment strategies, looking at multiple dimensions while aiming to provide a balance between the values, needs, preferences, and perspectives of patients and those of society.

ECONOMIC EVALUATION

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

The EGP assessed one cost-utility analysis (cost per quality-adjusted life-year gained) and one cost-effectiveness analysis (cost per life-year gained) of pembrolizumab compared with gemcitabine plus carboplatin and gemcitabine monotherapy in adult patients with locally advanced or metastatic urothelial cancer who are ineligible for cisplatin therapy.

Basis of the economic model: Clinical and economic inputs

The key clinical outcomes considered in the cost-utility analysis were PFS, OS, and utilities.

Costs considered in the analysis included those related to drug acquisition and administration, monitoring care, health care resource utilization, subsequent treatment, and terminal care.

Drug costs: Treatment cost of pembrolizumab and comparators

- Pembrolizumab costs $2,200.00 per 50 mg vial or $4,400.00 per 100 mg vial.
  Dosage schedule: Fixed dosing of 200 mg every three weeks.
  Cost per 28-day cycle: $11,733.00.

- Gemcitabine monotherapy costs $6.00 per 200 mg vial or $30.00 per 1,000 mg vial.
  Dosage schedule: 1,200 mg/m^2 for three times every four weeks.
  Cost per 28-day cycle: $216.00.

- Gemcitabine plus carboplatin: Gemcitabine costs $6.00 per 200 mg vial or $30.00 per 1,000 mg vial. Carboplatin costs $18.80 per 150 mg vial or $56.39 per 450 mg vial.
  Dosage schedule: 1,000 mg/m^2 for gemcitabine, once every three weeks; and AUC 5, once every 3 weeks for carboplatin.
  Cost per 28-day cycle: $326.39.

Cost-utility estimates: Substantial uncertainty in clinical effectiveness estimates

The sponsor-provided economic analysis assessed the cost-effectiveness of pembrolizumab in patients with locally advanced or metastatic UC who are ineligible for cisplatin therapy. The economic analysis included two base-case analyses based on patient characteristics: patients that are cisplatin ineligible and PD-L1 positive (CPS ≥ 10), and patients that are ineligible for platinum therapy, irrespective of their PD-L1 expression level. For the PD-L1–positive population, pembrolizumab was compared with both gemcitabine plus carboplatin and gemcitabine monotherapy. For the population that is platinum ineligible, pembrolizumab was compared with gemcitabine monotherapy.

The EGP's reanalyses of cost-utility presented ICURs as lower bounds with no upper bounds, given the uncertainty around the clinical comparative efficacy of treatments. The submitted base-case ICURs were lower than the EGP's lower-bound ICUR estimates (submitted probabilistic ICURs versus reanalyzed lower-bound probabilistic ICURs: $100,632 versus $108,468 compared with carboplatin plus gemcitabine for patients with CPS ≥ 10; and $68,179 versus $76,010 compared with gemcitabine monotherapy for patients who are platinum ineligible). This was primarily due to the following factors:

- A shorter time horizon (five years instead of 10 years): Considering expected survival duration in this population of patients, the CGP felt that a five-year time horizon was more appropriate.

- Costs for AEs (changing the cost of grade 3 and higher events to a medical oncologist consultation fee instead of hospitalization): The CGP noted that most of the AEs would be treated on an outpatient basis. The CGP noted that a proportion of febrile neutropenia AEs would likely require hospitalization. It was assumed that 10% were applied the cost of a hospitalization ($7,599) while the remaining 90% were assigned a consultation fee ($157).

The EGP noted several limitations in the submitted analysis, particularly the uncertainty in the clinical comparative efficacy data. The sponsor provided ITCs to present relative treatment effect estimates between comparators in the absence of head-to-head data. The pCODR Methods Team and the EGP agreed that, given several limitations, including an unknown amount of bias in the unanchored effect estimates, the comparative effectiveness of pembrolizumab versus its comparators remains uncertain (for more details on the ITCs, see paragraph on limitations). The estimates of incremental effectiveness are largely based on a key clinical assumption that the efficacy results observed in the KEYNOTE 052 trial and the submitted ITCs translate into real and meaningful improvements in PFS and OS for pembrolizumab compared with other currently available therapies. However, given the limitations in the treatment effect estimates from the available phase II clinical trials and the ITC analyses, and the inability of the economic model to account for the resulting uncertainty in the parameter estimates, the EGP's reanalyzed ICUR estimates were uncertain and the EGP elected to place no upper bounds on its best-case ICUR estimates.

Upon reconsideration of the pERC Initial Recommendation, the Committee discussed the feedback provided by the sponsor noting that the EGP's best-case scenario ICUR for the population with platinum-ineligible disease was overestimated as the EGP prolonged pembrolizumab's maximum treatment duration from 2 to 3 years, therefore increasing the treatment costs without increasing the expected clinical benefit. pERC noted the response provided by the EGP in the *pCODR Economic Guidance Report (EGR)* clarifying that the EGP did not actually undertake an analysis whereby the maximum duration of treatment with pembrolizumab was increased. Instead, this analysis had been considered in an earlier draft of the EGR but had subsequently been removed as per guidance from the CGP. However, the wording in Tables 11 and 43 of the EGR had been missed to be revised in the final version of the EGR. pERC and the EGP acknowledged the typo and the EGP has corrected the text in Tables 11 and 43 of the EGR accordingly.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: Budget impact likely underestimated

Considerations with regard to the feasibility of implementing a reimbursement recommendation for pembrolizumab for the treatment of adult patients with locally advanced or metastatic UC who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 CPS ≥ 10, or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status: PAG identified that the continued availability of the 50 mg vial as well as the introduction of a 25 mg vial would be enablers for implementation given that vial sharing is not always possible. Factors that affected the budget impact included the proportion of patients eligible for pembrolizumab under the current reimbursement request, the medication costs, and the rate of PD-L1 testing. PD-L1 testing is not currently completed for patients with locally advanced or metastatic UC but would be required in patients who are cisplatin ineligible. Short turnaround times (from the time the test is ordered to results reported) would be essential for the implementation of PD-L1 testing in this setting.

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

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

- Dr. Kelvin Chan, who was not present for the meeting
- Dr. Christian Kollmannsberger, who was excluded from voting due to a conflict of interest.
- Daryl Bell, who did not vote due to his role as a patient member alternate

pERC Membership During Deliberation of the Final Recommendation

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

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

- Dr. Matthew Cheung, who did not vote as he was absent from the meeting
- Dr. Christian Kollmannsberger, who was excluded from voting due to a conflict of interest
- Daryl Bell, who did not vote due to his role as a patient member alternate.

Avoidance of conflicts of interest

All members of pERC must comply with the *pCODR Conflict of Interest Guidelines*; individual conflict of interest statements for each member are posted on the pCODR website and pERC members have an obligation to disclose conflicts on an ongoing basis. For the review of pembrolizumab (Keytruda) for locally advanced or metastatic urothelial carcinoma, through their declarations, one member had a real, potential, or perceived conflict, and based on application of the *pCODR Conflict of Interest Guidelines*, one 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 the pCODR Expert Review Committee for its deliberations was handled in accordance with the *pCODR Disclosure of Information Guidelines*.

Use of this Recommendation

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