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:** For the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or within 12 months of completing neoadjuvant or adjuvant platinum-containing chemotherapy	
Submitted By: Merck Canada Inc.	**Manufactured By:** Merck Canada Inc.
NOC Date: September 20, 2017	**Submission Date:** July 24, 2017
Initial Recommendation: January 5, 2018	**Final Recommendation:** March 2, 2018

Drug Cost	
Approximate per Patient Drug Costs, per Month (28 Days) Submitted list price of $2,200.00 per 50 mg vial Note: Costs are calculated based on an average weight of 70 kg and body surface area of 1.7 m^2	**Pembrolizumab regimen costs:** $11,733.33 per 28-day course

pERC RECOMMENDATION	pERC recommends reimbursement of pembrolizumab (Keytruda) conditional on cost-effectiveness being improved to an acceptable level. Reimbursement should be for the treatment of patients with locally advanced or metastatic urothelial carcinoma (MUC) who have disease progression during or following platinum-containing chemotherapy or within 12 months of completing neoadjuvant or adjuvant platinum-containing chemotherapy. Funding should be for patients with a good performance status. Treatment should continue until confirmed disease progression or unacceptable toxicity or after completing two years of pembrolizumab therapy, whichever comes first. pERC made this recommendation because it was satisfied that there is a net clinical benefit with pembrolizumab compared with chemotherapy, based on a clinically meaningful improvement in overall survival (OS), an acceptable toxicity profile, and high unmet need for effective treatments. The Committee also concluded that the therapy aligns with patient values in that it offers an improvement in OS and maintains quality of life (QoL). However, pERC noted that, at the submitted price, pembrolizumab could not be considered cost-effective compared with chemotherapy. pERC also highlighted that the potential budget impact of pembrolizumab may be underestimated and could be substantial.

POTENTIAL NEXT STEPS FOR STAKEHOLDERS

Pricing Arrangements to Improve Cost-Effectiveness
Given that pembrolizumab has a net overall clinical benefit compared with chemotherapy, jurisdictions may want to consider alternate pricing arrangements and/or cost structures to improve the cost-effectiveness and affordability of pembrolizumab to an acceptable level.

Factors Affecting Budget Impact and Adoption Feasibility
pERC noted that the budget impact of pembrolizumab resulted from the high cost of pembrolizumab, the unknown number of patients who would receive the full 35 cycles or re-treatment, and a large market share expected for the pembrolizumab indication. pERC concluded that a reduction in drug price would be required to improve affordability.

Pembrolizumab Dosing of 2 mg/kg up to a Flat Dose of 200 mg
The Committee acknowledged that, although KEYNOTE-045 assessed pembrolizumab at a dosage of 200 mg every three weeks up to two years (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 (dose capped at 200 mg).

Common Approach to Define Confirmed Disease Progression
pERC noted the unique mechanism of action of immunotherapeutic agents and acknowledged that in a small percentage of patients, standard Response Evaluation Criteria in Solid Tumors (RECIST)-defined radiologic disease progression may be due to immune-related inflammation and may not be reflective of true disease progression (i.e., pseudo-progression). pERC noted that there is no consistently accepted definition for pseudo-progression in the clinical community. pERC agreed that until such a definition becomes available, it is reasonable to use the definition from the pivotal trial, which defined true progression as an additional 20% in tumour burden and/or the development of new lesions since the time of initial disease progression. A confirmatory scan should be done four to six weeks after initial progression to assess patients for true progression. pERC acknowledged that a confirmatory scan within this timeline may not be feasible in all jurisdictions and noted that eight weeks after initial progression would also be reasonable.

Unknown Treatment Duration and Re-Treatment of Patients
pERC noted that (in the case of KEYNOTE-045) treatment with pembrolizumab continues until confirmed disease progression, unacceptable toxicity, or a maximum of two years, whichever comes first. In KEYNOTE-045, the median duration of therapy with pembrolizumab was 3.45 months (range: 0.03 to 20.04). pERC also discussed an amendment in the KEYNOTE-045 trial that allowed re-treatment with pembrolizumab in the trial protocol. In the trial, patients could receive re-treatment for an additional year of pembrolizumab if they (1) stopped initial treatment after investigator-determined confirmed complete response according to RECIST 1.1, patients had to be treated with at least 24 weeks of pembrolizumab and received two treatments of pembrolizumab beyond initial complete response; or 2) had stable disease, partial response, or complete response and stopped treatment after 24 months for reasons other than disease progression or intolerability. pERC noted that the number of patients who would receive the full 35 cycles or re-treatment with pembrolizumab is unknown, and jurisdictions will need to consider this during implementation of pembrolizumab reimbursement.

POTENTIAL NEXT STEPS FOR STAKEHOLDERS	**Patients with prior non-platinum-containing chemotherapy** pERC acknowledged that there may be a small number of patients that are ineligible for a platinum-based chemotherapy (i.e., have contraindications for platinum) and who would receive an alternative chemotherapy. pERC felt that these patients should be eligible for pembrolizumab. **Optimal Sequencing of Pembrolizumab and Other Therapies Unknown** pERC concluded that the optimal sequencing of pembrolizumab and other treatments now available to treat patients with MUC who have disease progression during or following platinum-containing chemotherapy or within 12 months of completing neoadjuvant or adjuvant platinum-containing chemotherapy is unknown. Therefore, pERC was unable to make an evidence-informed recommendation on sequencing. However, pERC recognized that the provinces would need to address this issue when implementing pembrolizumab reimbursement and noted that collaboration among provinces to develop an evidence-based guideline would be of value. **Please note:** The Provincial Advisory Group's (PAG's) questions have been addressed in detail in the Summary of pERC Deliberations and in a summary table in Appendix 1.

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. Patients with locally advanced or metastatic urothelial carcinoma (MUC) are typically treated with chemotherapy in the first-line setting; however, all patients eventually progress and are considered for therapy in the second-line setting. The current second-line options available for patients with MUC who have had platinum-containing chemotherapy include single-agent docetaxel and paclitaxel. Current treatment options have modest improvements in survival and response rates. pERC recognized that pembrolizumab for MUC is the first pCODR review for urothelial cancer and that there have been very few novel treatment options available for this group of patients. Furthermore, pERC noted the pCODR Clinical Guidance Panel's (CGP's) expert opinion that there is no established standard of care in Canada for this patient population, due to a lack of clinical evidence. Thus, pERC concluded that there is a high unmet need for more effective and tolerable treatments in this patient population.

pERC's *Deliberative Framework* for drug reimbursement recommendations focuses on four main criteria:	
CLINICAL BENEFIT	**PATIENT-BASED VALUES**
ECONOMIC EVALUATION	**ADOPTION FEASIBILITY**

pERC deliberated upon the results of one phase III, multi-centre, open-label randomized controlled trial, KEYNOTE-045. The trial assessed the efficacy and safety of pembrolizumab compared with the investigator's choice of chemotherapy (i.e., single-agent therapy with docetaxel, paclitaxel, or vinflunine) in patients with MUC that recurred or progressed after platinum-based chemotherapy. pERC noted that there was a clinically meaningful and statistically significant improvement in OS for patients treated with pembrolizumab compared with chemotherapy. pERC discussed that the OS curves for pembrolizumab and chemotherapy crossed each other early in the follow-up period, which increases the uncertainty in the effect estimates as it suggests that the hazard of death is not constant over time. pERC noted that, on average, patients treated with pembrolizumab compared with chemotherapy had improved survival. Therefore, despite some uncertainty, pERC agreed with CGP that there did appear to be a clinically meaningful difference in OS. pERC also observed that there was no statistically significant difference between pembrolizumab and chemotherapy for progression-free survival (PFS) and that objective response rates were similar between treatment groups.

pERC discussed the QoL data reported in the trial. The results of the KEYNOTE-045 study suggest that although the difference between treatment groups reached statistical significance in favour of pembrolizumab, the difference did not reach minimum important differences in any of the measurement scales (i.e., EORTC [European Organization for Research and Treatment of Cancer] QLQ-C30 and EQ-5D [EuroQol Five Dimensions questionnaire]). pERC noted the absence of a clear signal indicating an improvement in QoL; however, for patients in the pembrolizumab group, QoL was at least maintained. pERC also discussed the toxicity profile of pembrolizumab and noted that there were fewer overall treatment-related adverse events (TRAEs), grade 3 to grade 5 TRAEs, treatment-emergent serious adverse events, and treatment discontinuations due to TRAEs in patients treated with pembrolizumab compared with those treated with chemotherapy. Treatment-related events leading to death were similar between the treatment groups.

Therefore, based on the clinically meaningful and statistically significant improvements in OS, maintenance of QoL, and acceptable toxicities compared with chemotherapy, pERC concluded that there was an overall net clinical benefit of pembrolizumab in patients with MUC who have disease progression during or following platinum-containing chemotherapy or within 12 months of completing neoadjuvant or adjuvant platinum-containing chemotherapy.

pERC discussed the generalizability of the KEYNOTE-045 trial results and stated that the following groups of patients may also be eligible for pembrolizumab:

- patients with urothelial cancer of predominantly transitional histology of any primary site
- patients having an Eastern Cooperative Oncology Group (ECOG) performance status of 2

- patients who have received multiple lines of prior chemotherapy including a platinum-containing regimen (this does not include other immunotherapy agents)
- patients without formal measurable disease

First, pERC agreed with CGP that the diagnosis of urothelial cancer should not be limited to the renal pelvis, ureter, bladder, or urethra, as urothelial cancers of predominantly transitional histology of any primary site have similar tumour biologies and clinical behaviours and receive identical treatments. Second, pERC agreed with CGP that selective patients with an ECOG performance status of 2 may be eligible for this treatment because of its favourable toxicity profile and that treatment is best left at the treating clinician's discretion. Third, pERC noted that more than 55% and 20% of patients' settings of most recent prior therapy in the trial were first-line and second-line, respectively. Finally, pERC agreed with CGP that in clinical practice patients may not have measurable disease based on RECIST 1.1 and therefore, patients without formal measurable disease should qualify for treatment. pERC also discussed the effect of programmed death-ligand (PD-L1) testing in patients with MUC. They agreed with CGP that the results of biomarker analyses in KEYNOTE-045 were not definitive, and that there is insufficient evidence to support the use of PD-L1 testing for pembrolizumab.

pERC noted that the input from registered clinicians was consistent with the Committee's interpretation of the results of KEYNOTE-045 that pembrolizumab was more effective and better tolerated than chemotherapy. pERC acknowledged and agreed with clinician input that there is an unmet need in this setting and that pembrolizumab would provide an immunotherapy treatment option in this setting for patients with MUC. pERC also acknowledged that registered clinician input recommended that re-treatment with pembrolizumab should be managed consistently across all drugs with similar mechanisms of action (i.e., immunotherapies). Finally, pERC acknowledged that input from registered clinicians supported the 200 mg fixed dose suggested by the clinical evidence. The Committee acknowledged that, although KEYNOTE-045 assessed pembrolizumab at a dosage of 200 mg every three weeks up to two years (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, in line with previous pCODR recommendations for solid tumours, pERC felt it would be reasonable that pembrolizumab be administered at 2 mg/kg up to a total dose of 200 mg (dose capped at 200 mg).

pERC deliberated on the alignment of pembrolizumab with patient values. The Committee reviewed input from one patient group, Bladder Cancer Canada, which highlighted patient and caregiver experiences. The input provided by Bladder Cancer Canada gave pERC a broader understanding of patients' experience with MUC and its treatments. pERC noted that patients with MUC would like access to treatments that control symptoms such as stress, fatigue, disrupted sleep, and diarrhea as well as options to improve emotional well-being, mobility, and appearance. pERC observed that, compared with their current treatments, patients expect pembrolizumab to improve QoL and provide long-term stability or reduction of disease. Three patients had received treatment with pembrolizumab, and pERC noted that all these patients indicated that pembrolizumab was effective at controlling their MUC and had decreased the severity of side effects compared with other therapies. Side effects experienced with pembrolizumab included, no negative side effects, moderate fatigue, skin rash, itchiness, diarrhea, and low platelet counts. Thus, pERC concluded that pembrolizumab aligns with patient values, as it provides a significant improvement in survival (compared with chemotherapy), maintains QoL and has an acceptable toxicity profile.

pERC deliberated upon the cost-effectiveness of pembrolizumab and concluded that, at the submitted price, it was not cost-effective compared with chemotherapy. pERC considered estimates provided by the submitter and reanalyses performed by the pCODR Economic Guidance Panel (EGP). pERC noted that the following factors had an impact on the incremental cost-effectiveness ratio (ICER): cost of pembrolizumab, duration of treatment, time horizon, survival extrapolation methods used (which included adjustment for crossover), and cut-off point for OS. The factors that most influenced the incremental cost were the cost of pembrolizumab and the duration of treatment. The factors that most influenced the incremental effectiveness were the time horizon, the survival extrapolation methods used (which included adjustment for crossover), and the cut-off point for OS. pERC considered the uncertainty regarding the extrapolation for OS and PFS over a 10-year time horizon and the magnitude of benefit projected beyond the trial period. Upon reconsideration of the Initial Recommendation, pERC considered feedback from the submitter related to reducing the time horizon to five years, compared with 10 years in the base case. Given that the survival data from KEYNOTE-045 had a median follow-up of 80 weeks (18.5 months) with a median OS of 10.3 months in the pembrolizumab group, five-year survival rates are low in this setting. The EGP relied on the CGP's clinical opinion, which suggested using a five-year time

horizon as it is more clinically plausible in this patient population. The Committee agreed with the EGP's response to the submitter's concern regarding the time horizon and agreed that, in the case that extrapolation is required to estimate long-term effect, clinical expert judgment can be used to justify the plausibility of extrapolation. pERC also considered feedback from the submitter related to the survival extrapolation methods used by the EGP (which included adjustment for crossover). The EGP acknowledged that the OS for the comparator arm should be adjusted for the crossover of patients; however, the EGP noted that in KEYNOTE-045, there was no planned crossover at disease progression. As pERC agreed with the EGP that OS had the greatest impact on the ICER, the Committee reiterated its agreement with the EGP's conservative approach to consider a different extrapolation method (OS without adjustment for crossover) in the upper bound of the EGP's reanalysis to estimate the impact that the extrapolation method for long-term OS had on the ICER. pERC also noted that EGP was unable to evaluate the use of a 2 mg/kg dose of pembrolizumab. Although the use of a 2 mg/kg dose amount would likely not impact the effectiveness of pembrolizumab, there was uncertainty on how it would impact cost estimates, because for many patients, the use of the flat dose would result in a larger dose and greater cost. Upon reconsideration of the Initial Recommendation, pERC acknowledged feedback from the submitter that pembrolizumab was assessed at a 200 mg fixed dose and that there is no clinical evidence to support the use of pembrolizumab at a 2 mg/kg dose in the urothelial carcinoma population. pERC reiterated that, for many patients, the flat dose results in a larger dose and greater cost. Therefore, in line with previous pCODR recommendations for solid tumours, pERC felt it would be reasonable that pembrolizumab be administered at 2 mg/kg up to a total dose of 200 mg (dose capped at 200 mg). Overall, pERC agreed with the EGP's best estimates of the ICER when pembrolizumab was compared with chemotherapy. pERC concluded that the true ICER is likely near the middle to upper end of the EGP's reanalysis estimate. This estimate corresponds to an ICER based on the actual trial results of KEYNOTE-045 with no statistical adjustment for crossover. Consequently, pERC concluded that pembrolizumab was not cost-effective at the submitted price.

Upon reconsideration of the Initial Recommendation, pERC noted that patient group feedback was not provided, that both registered clinicians and the Provincial Advisory Group (PAG) feedback agreed with the Initial Recommendation, and that the submitter agreed only in part with the Initial Recommendation and did not support conversion to Final Recommendation. pERC recognizes that the Committee's decisions must be equitable, transparent, timely, and accountable to patients, health care funders, and the public to ensure that effective treatment options are considered for public funding. pERC noted that the submitter agreed with the clinical population for reimbursement but not the EGP reanalysis estimate. In light of this, pERC expressed dismay at receiving feedback that the submitter did not support early conversion to Final Recommendation due to differences in the interpretation of cost-effectiveness evidence, delaying timely access to public funding of effective treatment options such as pembrolizumab.

pERC considered the feasibility of implementing a funding recommendation for pembrolizumab. pERC agreed with EGP that the submitted budget impact analysis may be underestimated due to the number of patients eligible to be treated with pembrolizumab and due to market expansion. pERC noted that it is unlikely that patients and clinicians would choose a less effective and more toxic treatment over pembrolizumab. The Committee acknowledged that, although KEYNOTE-045 assessed pembrolizumab at a dosage of 200 mg every three weeks up to two years (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 (dose capped at 200 mg). Overall, due to the high cost of pembrolizumab, the unknown number of patients who would receive the full 35 cycles or re-treatment, and a large market share expected for this pembrolizumab indication, pERC concluded that a reduction in drug price would be required to improve cost-effectiveness and affordability to an acceptable level.

The Committee noted the input from the pCODR PAG, which requested information and clarification on whether results from KEYNOTE-045 are generalizable to patients who did not receive platinum-based chemotherapy. pERC noted that CGP considered it to be unknown whether results from KEYNOTE-045 are generalizable to patients who did not receive platinum-based chemotherapy in first-line treatment; however, only a minority of patients would be treated with prior non-platinum-based therapy. pERC acknowledged that there may be a small number of patients who are ineligible for a platinum-based chemotherapy (i.e., have contraindications for platinum) and who have received an alternative chemotherapy, pERC felt that these patients should be eligible for pembrolizumab.

PAG also requested clarification on whether patients who have been treated with two or more lines of chemotherapy, where the most recent chemotherapy was not platinum-based chemotherapy, be eligible for pembrolizumab. pERC agreed with CGP that results from KEYNOTE-045 are generalizable to patients treated with at least one line of prior platinum-based chemotherapy.

pERC noted that there is no consistently accepted definition for pseudo-progression in the clinical community. pERC agreed that until such a definition becomes available, it is reasonable to use the definition from the pivotal trial, which defined true progression as an additional 20% in tumour burden and/or the development of new lesions since the time of initial disease progression. A confirmatory scan should be done four to six weeks after initial progression to assess patients for true progression. pERC acknowledged that a confirmatory scan within this timeline may not be feasible in all jurisdictions and noted that eight weeks after initial progression would also be reasonable. pERC also discussed that more frequent scans to assess patients for true progression may be less costly than additional cycles of treatment with pembrolizumab. Therefore, more frequent scans may improve the cost-effectiveness and decrease the budget impact of pembrolizumab.

Finally, in KEYNOTE-045, the median duration of therapy with pembrolizumab was 3.45 months (range, 0.03 to 20.04). pERC also discussed an amendment in the KEYNOTE-045 trial that allowed re-treatment with pembrolizumab in the trial protocol. In the trial, patients could receive re-treatment for an additional year of pembrolizumab if they 1) stopped initial treatment after investigator-determined confirmed complete response according to RECIST 1.1, patients had to be treated with at least 24 weeks of pembrolizumab and received two treatments of pembrolizumab beyond initial complete response; or 2) had stable disease, partial response or complete response and stopped treatment after 24 months for reasons other than disease progression or intolerability. pERC noted that the number of patients who would receive the full 35 cycles or re-treatment with pembrolizumab is unknown, and jurisdictions will need to consider this during implementation of pembrolizumab reimbursement.

EVIDENCE IN BRIEF

The CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) deliberated upon the following:

- 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 pCODR clinical and economic review panels
- Input from one patient group: Bladder Cancer Canada
- Input from registered clinicians
- Input from pCODR's Provincial Advisory Group (PAG).

Feedback on the pERC Initial Recommendation was also provided by:

- Registered clinicians
- The PAG
- The submitter Merck Canada Inc.

The pERC Initial Recommendation was to recommend reimbursement of pembrolizumab (Keytruda) for locally advanced or metastatic urothelial carcinoma (MUC). Feedback on the pERC Initial Recommendation indicated that PAG and registered clinicians agreed with the Initial Recommendation. The submitter agreed in part with the Initial Recommendation. There was no feedback from the patient group on the Initial Recommendation.

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of the review is to evaluate the safety and efficacy of pembrolizumab (Keytruda) compared with an appropriate comparator for the treatment of patients with locally advanced or metastatic urothelial carcinoma (MUC) who have disease progression during or following platinum-containing chemotherapy or within 12 months of completing neoadjuvant or adjuvant platinum-containing chemotherapy.

Studies included: One randomized controlled trial

The pCODR systematic review included one randomized, open-label, phase III trial, KEYNOTE-045, which evaluated the efficacy and safety of pembrolizumab compared with the investigator's choice of chemotherapy in patients with MUC that recurred or progressed after platinum-based chemotherapy. Patients were randomized in a 1:1 ratio to pembrolizumab (n = 270) or to one of three chemotherapies (n = 272).

Pembrolizumab was administered at a fixed dosage of 200 mg every three weeks. The three chemotherapy regimens used in the study were paclitaxel, docetaxel, or vinflunine. pERC noted that the comparator of chemotherapy of paclitaxel and docetaxel was applicable to the Canadian treatment landscape; however, vinflunine has not been approved for this indication.

Key inclusion criteria were as follows: 18 years of age or older; histologically or cytologically confirmed urothelial carcinoma of the renal pelvis, ureter, bladder, or urethra that showed predominantly transitional-cell features on histologic testing; progression after platinum-based chemotherapy for advanced disease or recurrence within 12 months after the receipt of platinum-based adjuvant or neoadjuvant therapy for localized muscle-invasive disease; had received two or fewer lines of systemic chemotherapy for advanced disease previously; at least one measurable lesion according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1; and an Eastern Cooperative Oncology Group (ECOG) performance status score of 0, 1, or 2. Patients whose tumour specimen was not evaluable for programmed death-ligand (PD-L1) expression were excluded.

Patient populations: Prior first-line therapy, crossover allowed

Patients (n = 542) were randomly assigned and stratified by performance status (0, 1, or 2), presence of liver metastases (yes, no), hemoglobin concentration (< 10 g per deciliter, ≥ 10 g per deciliter), and time since last dose of chemotherapy (< 3 months, ≥ 3 months). Treatment continued until RECIST-defined

progression, intolerable toxic effects, withdrawal of consent, investigator's decision to withdraw or after completing two years of pembrolizumab therapy. For the re-treatment phase, patients who had radiological disease progression were eligible for an additional year of re-treatment with pembrolizumab if they 1) stopped initial treatment after investigator-determined confirmed complete response according to RECIST 1.1, patients had to be treated with at least 24 weeks of pembrolizumab and received two treatments of pembrolizumab beyond initial complete response; or 2) had stable disease, partial response or complete response and stopped treatment after 24 months for reasons other than disease progression or intolerability. The trial did not initially permit crossover; however, based on the results of the second interim analysis, it was recommended that the study be stopped early to allow patients in the chemotherapy group to cross over and receive pembrolizumab. Subsequent cancer therapy was received by 22% of patients in the chemotherapy group and 2% of patients in the pembrolizumab group. In the chemotherapy group, the majority of patients were treated with pembrolizumab (10%), followed by atezolizumab (4%) and nivolumab (3%); all patients in the pembrolizumab arm were treated with atezolizumab.

The pCODR Clinical Guidance Panel (CGP) and Methods Team noted that the baseline characteristics of the patient populations were well balanced across the treatment groups, except for smoking status, tumour PD-L1 combined positive score (CPS), setting of most recent prior therapy, and ECOG performance status. A reanalysis by the submitter with these selected baseline characteristics had minimal impact on the primary estimates of overall survival (OS) and progression-free survival (PFS). Overall, the median ages of patients in the trial in the pembrolizumab and chemotherapy groups were 67 and 65 years of age, respectively; the majority of patients were male (61.1% and 54.0%, respectively), white (overall 71.8%), current or former smokers (61.3% and 69.1%), and ECOG performance of 1 (53.0% and 58.1%). The percentage of patients with a PD-L1 CPS ≥ 10% was 28.5% in the pembrolizumab group and 33.8% in the chemotherapy group. Most patients had received prior cisplatin, were at or beyond three months since completion or discontinuation of the most recent prior therapy, and the setting of their most recent prior therapy was first line.

After discussing the generalizability of the KEYNOTE-045 trial results, CGP stated that given that the favourable toxicity profile of pembrolizumab compared with chemotherapy, pembrolizumab could be considered for patients with urothelial cancer of predominantly transitional histology of any primary site, patients with declining performance status (i.e., ECOG performance status of 2), those with multiple lines of prior chemotherapy (second-line and beyond), and those without formal measurable manifestations of their cancer. pERC noted CGP's justification for using clinical judgment when offering pembrolizumab to patients with an ECOG performance status of 2. The Committee agreed that patients with a good performance status (ECOG PS 0 to 2) who can tolerate this treatment may derive benefit. pERC also noted that KEYNOTE-045 was restricted to patients with a diagnosis of urothelial cancer of the renal pelvis, ureter, bladder, or urethra. pERC agreed with CGP that patients with urothelial cancer of predominantly transitional histology of any primary site, those with at least one line of prior platinum-based chemotherapy, and those without formal measurable disease should be included in the reimbursement population.

Key efficacy results: Clinically meaningful improvement in overall survival

The key efficacy outcome deliberated on by pERC was OS (co-primary outcome). After a median follow-up of 22.5 months, the median OS in the pembrolizumab group was 10.3 months and in the chemotherapy group was 7.4 months. pERC noted that the OS gain of 2.9 months with pembrolizumab was clinically meaningful and statistically significant (hazard ratio, 0.70; 95% confidence interval, 0.57 to 0.86; $P = 0.0003$). pERC discussed the fact that the OS curves for pembrolizumab and chemotherapy crossed each other early in the follow-up period, which increases the uncertainty in the effect estimates as it suggests that the hazard of death is not constant over time. pERC also acknowledged that even with crossover of patients from chemotherapy to pembrolizumab, an OS benefit was observed for pembrolizumab. PFS and objective response were not significant. pERC noted that the median duration of response was not reached in the pembrolizumab group and was 4.4 months in the chemotherapy group. Although CGP stated that the trial did not provide sufficient evidence to demonstrate an association between PD-L1 levels on disease risk and treatment response to pembrolizumab, pERC commented that more research is required to explore the effect of this biomarker in patients with MUC.

Patient-reported outcomes: Maintenance of quality of life

Patient-reported QoL was assessed using (European Organization for Research and Treatment of Cancer) QLQ-C30 and EQ-5D (EuroQol Five Dimensions questionnaire). The minimum important difference (MID) for the QLQ-C30 was a change from baseline of 10 points or greater, with lower scores indicative of

improvement in symptoms and side effects. The MIDs for the EQ-5D visual analogue scale and utility changes were 7 points or greater and 0.08 points or greater, respectively.

At week 15, differences in the mean change from baseline on the QLQ-C30 showed numerical improvements (i.e., less deterioration) of the Global Health Status Score in patients treated with pembrolizumab compared with chemotherapy. Although the difference in mean change in QLQ-C30 between treatment groups reached statistical significance, the difference did not reach the MID of 10 points or greater. Overall, for patients in the pembrolizumab treatment group, quality of life (QoL) was at least maintained.

EQ-5D scores generally increased over time for patients in the pembrolizumab group but not those in the chemotherapy group; scores improved at week 3 and the benefit was maintained through week 27. Similar to QLQ-C30, although the difference in mean change in EQ-5D (visual analogue scale score and utility score) between treatment groups reached statistical significance, the difference did not reach the MID of 7 or 0.08 points or greater, respectively.

pERC noted that CGP stated that although the MID was not met, QoL was statistically superior with pembrolizumab, which indicated some degree of clinical benefit over chemotherapy. pERC noted the absence of a clear signal indicating an improvement in QoL and noted that for patients in the pembrolizumab group, QoL was at least maintained. pERC agreed with the pCODR Methods Team that the open-label design of the study increased the risk of bias in the interpretation of the QoL data.

Limitations: Open-label design, hazard of death not constant over time, crossover allowed

The trial was open-label, which can introduce bias and threaten the internal validity of the trial. pERC recognized, however, that the potential for bias was minimized given the independent central review of key efficacy outcomes. The pCODR Methods Team noted that OS curves for pembrolizumab and chemotherapy crossed each other early in the follow-up period, which increases the uncertainty in the effect estimates as it suggests that the hazard of death is not constant over time. However, on average, patients treated with pembrolizumab compared with chemotherapy had improved survival. Despite the uncertainty, pERC agreed with CGP that there did appear to be a clinically meaningful difference between the survival curves. The OS results (co-primary end point) of the trial are likely confounded by the crossing over of patients in the chemotherapy group to the pembrolizumab group. However, pERC recognized that crossover at progression was not allowed before the primary analysis and OS results remained statistically significant, although one would expect that crossover would confound the observed treatment effect in favour of chemotherapy. pERC agreed with the pCODR Methods Team that crossover did not impact the primary analysis of OS but might have influenced later analyses.

Safety: Meaningful reductions in toxicities

pERC discussed the toxicity profile of pembrolizumab as observed in KEYNOTE-045. Compared with chemotherapy, pembroliozumab was associated with fewer treatment-related adverse events (TRAEs) of any grade (60.9% versus 90.2%), grade 3 to 5 TRAEs (15.0% versus 49.4%), and treatment-emergent serious adverse events (10.2% and 22.4%). Treatment-related events leading to death occurred in 1.5% of patients treated with pembrolizumab and in 1.6% of patients treated with chemotherapy.

Treatment discontinuations due to TRAEs were also higher among patients treated with chemotherapy; 11.0% versus 5.6% of patients in the chemotherapy and pembrolizumab groups, respectively.

Immune-mediated events and/or infusion-related reactions (IMAEs) occurred in 16.9% of patients receiving pembrolizumab and 7.5% of patients receiving chemotherapy. The most frequent types of events of any grade (pembrolizumab versus chemotherapy) were hypothyroidism (6.4% versus 1.2%), pneumonitis (4.1% versus 0.4%), hyperthyroidism (3.8% versus 0.4%), and colitis (2.3% versus 0.4%). Severe skin reactions occurred more frequently in the chemotherapy group compared with the pembrolizumab group (1.2% versus 0.9%). Of these events, only pneumonitis, colitis, and severe skin reaction occurred at a severity of grade 3 or higher in the pembrolizumab and chemotherapy groups. All infusion reactions were graded as 1 or 2.

Overall, pERC agreed that the adverse event profiles were better for pembrolizumab than for the control group.

Comparator information: Vinflunine not approved in Canada for this indication

pERC noted that in the chemotherapy comparator arm, patients were randomized to docetaxel (30.9%), paclitaxel (30.9%), and vinflunine (32.0%). Paclitaxel and docetaxel have been approved for the treatment of MUC in Canada while vinflunine has not been approved for this indication. A subgroup analysis of OS stratified the effect of pembrolizumab by the investigator's choice of paclitaxel, docetaxel, or vinflunine. Although results of the subgroup analysis suggest that the effect of vinflunine may bias the overall results in favour of pembrolizumab, pERC agreed with CGP and the Methods Team that the impact on results were likely minimal and, therefore, OS estimates were unlikely to be biased.

Need and burden of illness: Treatment with improved survival and quality of life

In 2017, 2,400 deaths were estimated to have occurred in Canada from urothelial cancer. It is one of the top ten causes of cancer deaths and considered the fourth most common cancer diagnosed in males and 10th most common cancer diagnosed in females. Patients are treated with chemotherapy, including combination cisplatin-based chemotherapy such as gemcitabine/cisplatin (carboplatin in "cisplatin - ineligible" patients), single-agent gemcitabine, dose-intense methotrexate/vinblastine/doxorubicin/cisplatin (M-VAC), and paclitaxel/gemcitabine/cisplatin. All patients eventually progress and are considered for second-line chemotherapy.

Patients who have disease progression during or following platinum-containing chemotherapy or within 12 months of completing neoadjuvant or adjuvant platinum-containing chemotherapy do not seem to benefit from further platinum-based treatment. Second-line treatments in Canada include docetaxel or paclitaxel either as single agents or in combination with carboplatin. This choice is based on modest improvements in survival and response rates.

pERC noted that the goals of treatment for patients with MUC are primarily palliative, namely, to prolong life while maintaining or improving QoL. Given the toxicity associated with available chemotherapy, pERC agreed that there is a need for alternative options that reduce toxicity and prolong survival.

Registered clinician input: Effective and better tolerated than chemotherapy

The Committee deliberated on input from a joint submission from three oncologists on behalf of the Genitourinary Drug Advisory Committee at Cancer Care Ontario. According to this input, current standard options in the Canadian setting include platinum-based chemotherapy (cisplatin/carboplatin plus gemcitabine, or chemotherapy with methotrexate, vinblastine, Adriamycin, and cisplatin). pERC noted that docetaxel and paclitaxel are the most commonly used second-line agents. pERC agreed with the clinician input that pembrolizumab was more effective and better tolerated than chemotherapy. pERC noted that pembrolizumab would provide an immunotherapy option in the second-line setting for MUC. pERC acknowledged and agreed with clinician input that there is an unmet need in this setting as there are currently no drugs approved by Health Canada in the second-line setting for patients with MUC. Pembrolizumab represents a new class of treatment (i.e., immunotherapy) in this setting for MUC. Clinician input indicated that pembrolizumab would likely replace or displace second-line chemotherapy. Clinician input also acknowledged that pembrolizumab would be used after cisplatin-based chemotherapy, for patients not eligible for cisplatin, or as third-line treatment after a taxane (paclitaxel or docetaxel). Clinician input recommended that re-treatment with pembrolizumab should be managed consistently across all drugs with similar mechanisms of action (i.e., immunotherapies such as nivolumab). The input also noted that that although pharmacokinetic evidence suggests no advantage to either fixed dose (200 mg) or weight-based (2 mg/kg) regimens, a number of patients may experience overdoses with a 200 mg fixed dosing schedule. However, clinician input supported the 200 mg fixed dose suggested by the trial evidence.

PATIENT-BASED VALUES

Values of patients with metastatic urothelial carcinoma: Symptom management, quality of life

One patient group, Bladder Cancer Canada, provided input on pembrolizumab for the treatment of patients with MUC. Patient input indicated that MUC moderately to severely impacted their day-to-day activities including ability to work, exercise, travel, followed by their ability to volunteer, perform household chores, spend time with family and friends, and fulfill family obligations. Patients with MUC indicated that they would like to improve the following: stress, emotional well-being, fatigue, sleep,

mobility, appearance, and diarrhea. pERC noted that these problems and issues affect patients' QoL and ability to enjoy life.

Patient values on treatment: More effective treatment options, disease control, quality of life

Input from Bladder Cancer Canada indicated that current therapies include transurethral resection of the bladder tumour, Bacillus Calmette-Guérin therapy, mitomycin C, surgical removal of the bladder, cisplatin chemotherapy, radiation and bladder preservation. Of patients surveyed, 56% said treatments controlled their bladder cancer while 30% said they did not. Common side effects include fatigue, nausea, decreased appetite, skin rash, hair loss, pain, fever, shortness of breath, bleeding, and pneumonia. Patients and caregivers say there is a significant unmet need for treatment options for this patient population. Patients expected pembrolizumab to improve their physical condition, such as by decreasing the size of the tumour or stabilizing it, reducing pain, and improving breathing. Patients also expected pembrolizumab to improve QoL and provide long-term stability or reduction of disease. Of the patients who provided input, 57% were willing to tolerate moderate side effects and 26% were willing to tolerate significant or very significant side effects.

Three patients who provided input had experience with pembrolizumab. All three patients indicated that pembrolizumab was effective at controlling their MUC. Of these patients, two respondents indicated that pembrolizumab decreased the severity of side effects compared with other therapies. One patients reported no negative side effects while the others experienced fatigue, skin rash, itchiness, diarrhea and low platelets. Input also noted that the infusion period for pembrolizumab was shorter than that for other chemotherapies.

ECONOMIC EVALUATION

Economic model submitted: Cost-utility analysis, partitioned-survival analysis

The pCODR Economic Guidance Panel (EGP) assessed a cost-utility analysis comparing pembrolizumab to standard-of-care chemotherapy (docetaxel and paclitaxel) for patients with MUC who have disease progression during or following platinum-containing chemotherapy or within 12 months of completing neoadjuvant or adjuvant platinum-containing chemotherapy. The submitted model was a three-state partitioned-survival model.

Basis of the economic model: Ten-year time horizon, crossover adjustment

Costs included in the model were cost of PD-L1 testing (pembrolizumab group only), cost of treatment, cost of managing adverse events, resource costs for administration and disease follow-up, and cost of subsequent therapy. pERC noted that the cost estimates were based on KEYNOTE-045 and published literature.

Key clinical effects considered in the analysis included PFS, OS, and utilities by time-to-death approach.

Drug costs: High cost of drug

Pembrolizumab costs $44.00 per mg. At a recommended dosage of 200 mg every three weeks, pembrolizumab costs $419.05 per day and $11,733.33 per 28-day course.

Docetaxel costs $1.52 per mg. At the recommended dosage of 75 mg/m^2 IV every three weeks, docetaxel costs $9.20 per day and $257.72 per 28-day cycle. Paclitaxel costs $2.00 per mg. At the recommended dosage of 175 mg/m^2 IV every three weeks, paclitaxel costs $12.14 per day and $340.00 per 28-day cycle.

Cost-effectiveness estimates: Duration of treatment, adjustment for crossover

pERC discussed the submitter's and the EGP's best estimate of the incremental cost-effectiveness ratio (ICER) of pembrolizumab compared with chemotherapy for patients with MUC who have disease progression during or following platinum-containing chemotherapy or within 12 months of completing neoadjuvant or adjuvant platinum-containing chemotherapy. pERC considered estimates provided by the submitter and reanalysis estimates provided by EGP and noted uncertainty regarding the extrapolation for OS and PFS over a 10-year time horizon and the magnitude of benefit projected beyond the trial period. The factors that most influenced the incremental cost were the cost of pembrolizumab and the duration of treatment. The factors that most influenced the incremental effectiveness were the time horizon, the

survival extrapolation methods used (which included adjustment for crossover), and the cut-off point for OS.

pERC noted that EGP was unable to evaluate the use of a 2 mg/kg dose of pembrolizumab. Although the use of a 2 mg/kg dose amount would likely not impact the effectiveness of pembrolizumab, there was uncertainty on how it would impact cost estimates; for many patients, the use of the flat dose would result in a larger dose and greater cost. Furthermore, the proportion of patients who received subsequent treatments after treatment discontinuation varied between treatment groups.

Overall, pERC agreed with the EGP's best estimates of the ICER when pembrolizumab was compared with chemotherapy. pERC concluded that the true ICER is likely near the middle to upper end of the EGP's reanalysis estimate. This estimate corresponds to an ICER based on the actual trial results of KEYNOTE-045 with no statistical adjustment for crossover. Consequently, pERC concluded that pembrolizumab was not cost-effective at the submitted price.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: High drug cost, large budget impact
pERC considered the feasibility of implementing a funding recommendation for pembrolizumab.

pERC noted that the budget impact analysis was sensitive to the number of patients eligible to be treated with pembrolizumab and market expansion. Overall, due to the high cost of pembrolizumab, the unknown number of patients who would receive the full 35 cycles or re-treatment, and a large market share expected for the pembrolizumab indication, pERC concluded that a reduction in drug price would be required to improve cost-effectiveness and affordability to an acceptable level.

pERC noted that CGP considered it to be unknown whether results from KEYNOTE-045 are generalizable to patients who did not receive platinum-based chemotherapy in the first line; however, only a minority of patients would be treated with prior non-platinum-based therapy. pERC noted that in KEYNOTE-045, patients could not have received prior immunotherapy. CGP noted that there is currently no evidence to suggest the use of a second-line immune checkpoint inhibitor (i.e., pembrolizumab) following first-line use, given that they work through similar mechanisms of action. CGP also noted that there is currently no evidence of sequencing of immunotherapy treatments including pembrolizumab or direct head-to-head studies comparing immunotherapy in this setting.

PAG also requested clarification on whether patients who have been treated with two or more lines of chemotherapy, where the most recent chemotherapy was not platinum-based chemotherapy, would be eligible for pembrolizumab. pERC agreed with CGP that results from KEYNOTE-045 are generalizable to patients treated with at least one line of prior platinum-based chemotherapy.

pERC noted PAG's concern with pembrolizumab's fixed dosing schedule as opposed to a weight-based dosing schedule. The Committee acknowledged that, although KEYNOTE-045 assessed pembrolizumab at a dosage of 200 mg every three weeks up to two years (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 (dose capped at 200 mg).

pERC noted that there is no consistently accepted definition for pseudo-progression in the clinical community. pERC agreed that until such a definition becomes available, it is reasonable to use the definition from the pivotal trial, which defined true progression as an additional 20% in tumour burden and/or the development of new lesions since the time of initial disease progression. A confirmatory scan should be done four to six weeks after initial progression to assess patients for true progression. pERC acknowledged that a confirmatory scan within this timeline may not be feasible in all jurisdictions and noted that eight weeks after initial progression would also be reasonable.

Finally, in KEYNOTE-045, the median duration of therapy with pembrolizumab was 3.45 months (range, 0.03 to 20.04). pERC also discussed an amendment in the KEYNOTE-045 trial that allowed re-treatment with pembrolizumab in the trial protocol. In the trial, patients could receive re-treatment for an additional year of pembrolizumab if they 1) stopped initial treatment after investigator-determined

confirmed complete response according to RECIST 1.1, patients had to be treated with at least 24 weeks of pembrolizumab and received two treatments of pembrolizumab beyond initial complete response; or 2) had stable disease, partial response, or complete response and stopped treatment after 24 months for reasons other than disease progression or intolerability.

DRUG AND CONDITION INFORMATION

Drug Information	• Immunotherapy anti-PD-1 • 50 mg solution for infusion 100 mg/4 mL vial • 200 mg administered intravenously over 30 minutes every three weeks
Cancer Treated	• Metastatic urothelial carcinoma
Burden of Illness	• Approximately 2,400 Canadians will die from MUC in 2017 • Patients may be ineligible for platinum-containing chemotherapy due to poor performance status, advanced age, renal impairment, and peripheral neuropathy
Current Standard Treatment	• No standard of care • Chemotherapy options
Limitations of Current Therapy	• Modest improvements in survival with current therapies • Poor performance status of patients makes it difficult for many patients to tolerate toxicities from chemotherapy

ABOUT THIS RECOMMENDATION

The pCODR Expert Review Committee

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

Dr. Maureen Trudeau, Oncologist (Chair)
Dr. Catherine Moltzan, Oncologist (Vice-Chair)
Dr. Kelvin Chan, Oncologist
Lauren Flay Charbonneau, Pharmacist
Dr. Matthew Cheung, Oncologist
Dr. Winson Cheung, Oncologist
Dr. Avram Denburg, Pediatric Oncologist
Mike Doyle, Health Economist
Dr. Craig Earle, Oncologist
Leela John, Pharmacist
Dr. Anil Abraham Joy, Oncologist
Dr. Christine Kennedy, Family Physician
Cameron Lane, Patient Member Alternate
Valerie McDonald, Patient Member
Carole McMahon, Patient Member
Dr. Marianne Taylor, Oncologist

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

- Dr. Avram Denburg and Dr. Craig Earle, who were not present for the meeting
- Cameron Lane, 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)	Leela John, Pharmacist
Dr. Catherine Moltzan, Oncologist (Vice-Chair)	Dr. Anil Abraham Joy, Oncologist
Dr. Kelvin Chan, Oncologist	Dr. Christine Kennedy, Family Physician
Lauren Flay Charbonneau, Pharmacist	Cameron Lane, Patient Member Alternate
Dr. Matthew Cheung, Oncologist	Valerie McDonald, Patient Member
Dr. Winson Cheung, Oncologist	Carole McMahon, Patient Member
Dr. Avram Denburg, Pediatric Oncologist	Dr. Marianne Taylor, Oncologist
Dr. Craig Earle, Oncologist	

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

- Drs. Craig Earle, Matthew Cheung and Anil Abraham Joy, who were not present for the meeting
- Cameron Lane, who did not vote due to his role as a patient member alternate.

Avoidance of conflicts of interest

All members of the pCODR Expert Review Committee must comply with the *pCODR Conflict of Interest Guidelines*; individual conflict of interest statements for each member are posted on the pCODR website, and pERC members have an obligation to disclose conflicts on an ongoing basis. For the review of pembrolizumab (Keytruda) for metastatic urothelial carcinoma, through their declarations, no members had a real, potential, or perceived conflict, and based on application of the *pCODR Conflict of Interest Guidelines*, none of these members was excluded from voting.

Information sources used

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

Consulting publicly disclosed information

pCODR considers it essential that pERC recommendations be based on information that may be publicly disclosed. All information provided to 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: pERC RESPONSES TO PAG IMPLEMENTATION QUESTIONS

PAG Implementation Questions	pERC Recommendation
• PAG is seeking guidance on whether patients who could not receive platinum-based chemotherapy and are given an alternative chemotherapy regimen first line would be eligible for pembrolizumab second line. • PAG is seeking guidance on whether the use of pembrolizumab in patients who have been treated with two or more lines of chemotherapy and who are still fit for further treatment would be appropriate on a time-limited need basis. • PAG is also seeking guidance on re-treatment with pembrolizumab in patients who have disease progression while on a treatment break.	• Yes, patients with contraindications for platinum and who have received an alternative chemotherapy, should be eligible for pembrolizumab. • Yes, patients treated with at least one line of prior platinum-based chemotherapy should be eligible for pembrolizumab (this does not include other immunotherapy agents). • Yes, re-treatment according to amendment in KEYNOTE-045 trial protocol.
• PAG is seeking clarity on treatment duration. • PAG is seeking guidance on weight-based dose for urothelial cancer given the high cost of fixed dose compared with weight-based dose for patients weighing less than 100 kg.	• Treatment with pembrolizumab should continue until confirmed disease progression, unacceptable toxicity, or a maximum of two years (in the case of KEYNOTE-045), whichever comes first. In KEYNOTE-045, the median duration of therapy with pembrolizumab was 3.45 months (range, 0.03 to 20.04). • Yes, pERC felt it would be reasonable that pembrolizumab be administered at 2 mg/kg up to a total dose of 200 mg (dose capped at 200 mg).
• PAG is seeking advice on the appropriate treatments after progression on pembrolizumab. • PAG is requesting clarity in the pERC recommendation regarding patients who would have been treated with other immunotherapy drugs through clinical trials or special access programs (e.g., atezolizumab). • PAG is seeking guidance on the use of pembrolizumab in sequence with other immunotherapy treatments as well as comparison of pembrolizumab with other immunotherapy, if available.	• Optimal sequencing of pembrolizumab and other therapies is unknown.
• PAG is seeking confirmation that the recommendation that the benefits of pembrolizumab in locally advanced or metastatic urothelial cancer is independent of PD-L1 status and that PD-L1 testing is not required for this indication.	• Yes, there is insufficient evidence to support the use of PD-L1 testing for pembrolizumab.