CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Pembrolizumab (Keytruda) for metastatic Urothelial Carcinoma

March 2, 2018

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FUNDING

The pan-Canadian Oncology Drug Review is funded collectively by the provinces and territories with the exception of Quebec, which does not participate in pCODR at this time.

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TABLE OF CONTENTS

1 GUIDANCE IN BRIEF

This Clinical Guidance Report was prepared to assist the pCODR Expert Review Committee (pERC) in making recommendations to guide funding decisions made by the provincial and territorial Ministries of Health and provincial cancer agencies regarding pembrolizumab (Keytruda) for metastatic urothelial carcinoma. The Clinical Guidance Report is one source of information that is considered in the *pERC Deliberative Framework*. The *pERC Deliberative Framework* is available on the CADTH website (www.cadth.ca/pcodr).

This Clinical Guidance is based on: a systematic review of the literature regarding pembrolizumab (Keytruda) for metastatic urothelial carcinoma conducted by the Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; input from registered clinicians; and supplemental issues relevant to the implementation of a funding decision.

The systematic review and supplemental issues are fully reported in Section 6. A background Clinical Information provided by the CGP, a summary of submitted patient advocacy group Input on pembrolizumab (Keytruda) for metastatic urothelial carcinoma, a summary of submitted Provincial Advisory Group Input on pembrolizumab (Keytruda) for metastatic urothelial carcinoma, and a summary of submitted registered clinician input on pembrolizumab (Keytruda) for metastatic urothelial carcinoma, and are provided in Sections 2, 3, 4, and 5 respectively.

1.1 Introduction

The objective of this review is to evaluate the efficacy and safety of pembrolizumab 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.

Health Canada issued a Notice of Compliance (NOC) without conditions for pembrolizumab (Keytruda) as indicated for 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 on September 20, 2017. The Health Canada indication aligns with the funding request under review by pCODR. Pembrolizumab is a selective humanized monoclonal antibody designed to block the interaction between programmed cell death receptor-1 (PD-1) and its ligands, PD-L1 and PD-L2. The recommended dose of pembrolizumab for previously treated urothelial carcinoma is 200 mg administrated as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression. According to the Health Canada Product Monograph, patients should be treated with pembrolizumab until disease progression or unacceptable toxicity. Atypical responses (i.e., an initial transient increase in tumour size or small new lesions within the first few months followed by tumour shrinkage) have been observed. Clinically stable patients with initial evidence of disease progression may remain on treatment until disease progression is confirmed.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

The pCODR systematic review included one randomized, open-label, phase III trial comparing pembrolizumab to chemotherapy (i.e. paclitaxel, docetaxel, or vinflunine) in patients with advanced or

urothelial cancer that recurred or progressed after platinum-based chemotherapy.[1,2] Patients were eligible to enroll into KEYNOTE-045 if they met the following criteria: 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.[1]In addition, only patients whose samples could be evaluated for PD-L1 expression were enrolled in the study.[1]

A total of 542 patients were randomly assigned on a 1:1 ratio to receive pembrolizumab at 200 mg every 3 weeks (n = 270) or to one of three chemotherapies (n = 272).[1] Patients could have been treated with paclitaxel (175 mg/m^2; N= 84), docetaxel (75 mg/m^2; N = 84) or vinflunine (320 mg/m^2; N = 87).[1] In Canada, docetaxel and paclitaxel have been approved for the treatment of MUC while vinflunine has not been approved for this indication as noted by Provincial Advisory Group Input in Section 4. Treatment beyond initial progression was allowed for both the pembrolizumab and chemotherapy treatment groups at the investigator's discretion. A protocol amendment allowed patients in the chemotherapy group to receive pembrolizumab beyond progression.[3]This amendment was based on a recommendation made by the independent Data Monitoring Committee (DMC) of KEYNOTE-045. Thus, eligible patients assigned to chemotherapy could receive subsequent pembrolizumab therapy in the Retreatment Phase.[3]

Efficacy

The co-primary outcomes in KEYNOTE-045 were overall survival (OS) and progression free survival (PFS). Efficacy outcomes were assessed in the whole patient population as well as in those with a tumour PD-L1 combined positive score (CPS) ≥ 10%. CPS was defined as the percentage of PD-L1 expressing tumour cells and infiltrating immune cells relative to the total number of tumour cells.[1]

The trial was stopped at the secondary interim analysis, which occurred on 7-September-2016 after 334 deaths had occurred in the total patient population as well as 104 deaths among those with a PD-L1 CPS of ≥10%.[1] The DMC recommended early termination because pembrolizumab met the threshold for superiority by demonstrating superior OS as compared to chemotherapy.[1] Two updated analyses were also included in this pCODR Review (18-Jan-2017 and 19-May-2017).[2,4]

At the 7-Sept-2016 data cut-off, treatment with pembrolizumab was associated with a reduced risk of death as compared to chemotherapy (HR: 0.73, 95% 0.59 to 0.91; P = 0.002) (Table 1).[1]Similar results were observed for those with a PD-L1 CPS ≥10% (HR: 0.57, 95% CI: 0.37 to 0.88; P = 0.005).[1]Similar results were observed for all patients at the later data cut-off of 19-May-2017 (HR: 0.70, 95% 0.57 to 0.86; P = 0.0003) (Table 1).[4] In contrast, there was no difference in treatment effect on PFS for the total patient population (HR: 0.98, 95% CI: 0.81 to 1.19; p = 0.42) or for those with a PD-L1 CPS ≥10% (HR: 0.89, 95% CI: 0.61 to 1.28; P = 0.24) (Table 1).[1]Similar results were observed at the 19-May-2017 data cut-off (Table 1).[4] The ORR for patients treated with pembrolizumab was significantly higher than those treated with chemotherapy (21.1% vs 11.4%) (Table 1).[1] At the 19-May-2017 data cut-off, the ORRs were similar (pembrolizumab ORR: 21.1% vs chemotherapy ORR: 11.0%).[4]

Health related quality of life (HRQoL) was measured using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and the EuroQol five dimensions questionnaire visual analog scale (EQ-5D) scales. The minimal important difference (MID) for the EORTC QLQ-C30 was a change in ≥10 point from baseline while the MIDs for the EQ-3D visual analog scale and the EQ-3D utlility score were a change in ≥7 points and ≥0.08 points, respectively.[5] Overall, in the pembrolizumab group, patients had a better HRQoL at week 15 as compared to patients in the chemotherapy arm (least squares [LS] mean difference: 9.05 (4.61 to 13.48); nominal 2-sided P < 0.01).[5] This was also observed using the EQ-5D at week 15 (LS mean difference, [5] This was also observed using the EQ-5D at week 15 (LS mean difference,

6.45 (95% CI: 2.75 to 10.16); nominal 2-sided P < 0.001) and EQ-5D utility scores at week 15 [LS mean difference, 0.07 (95% CI: 0.03 to 0.12); nominal 2-sided P = 0.002)].

Harms

In KEYNOTE-045, grade 3 to 5 treatment related adverse events were less frequent in the pembrolizumab group compared to the chemotherapy group (15.0% vs. 49.4%).[1] This was also similar for treatment-emergent serious adverse events (pembrolizumab: 10.2% vs. chemotherapy: 22.4%).[1] Bellmunt et al (2017) reported that one patient died from pembrolizumab-related pneumonitis.[1] The authors also noted that three deaths in the pembrolizumab group were attributed to the study treatment by the investigator compared to four deaths in the chemotherapy group. De Wit et al (2017) reported similar trends at the 19-May-2017 data cut-off.[4]

Limitations

- KEYNOTE-045 was an open-label RCT design. A double-blinded design would have been very difficult to implement due to the assignment of chemotherapy agents (i.e. paclitaxel, vinflunine or docetaxel). The assessment of OS will not be influenced by the open-label nature of the trial because it is an objective outcome.[6,7] In contrast, there is a greater risk of detection bias for subjective outcomes (i.e. disease progression, PROs and AEs) because patients and study investigators are aware of treatment assignment. However, the potential for this bias was mitigated by using an independent central review to assess key efficacy outcomes, such as PFS and ORR.

- Although there was a significant treatment effect for OS, the Kaplan-Meier plots for the two treatment arms crossed each other around months 2 and 3. This may increase the uncertainty in the effect estimates as it suggests the hazard for death is not constant over time, which is an assumption required for the Cox proportional hazards model. One option for addressing this issue is by stratifying the estimated hazard ratio. Here, Cox regression models are fit at different time frames to obtain different hazard ratios. However, these methods reduce the sample size, and increase the likelihood of type 2 error. In response to a pCODR request, the Submitter provided a test of the proportional hazards assumption and an analysis of OS stratified by time. Given this evidence, it is difficult to interpret the hazard ratio in the trial as an "average" of the curves over time (or the average of the different hazard ratios after stratifying by different time frames). Qualitatively, the overall analyses favour pembrolizumab over chemotherapy, but there is uncertainty associated with the actual effect size.

Table 1. Highlights of the Key Outcomes from KEYNOTE-045

	Pembrolizumab Arm N=270	Chemotherapy Arm N=272
September 7, 2016 Data Cut[1]		
Median OS	10.3 months (95% CI: 8.0 to 11.8)	7.4 months (95% CI:6.1 to 8.3)
	HR 0.73; (95% CI: 0.59 to 0.51) p=0.002	
Median PFS	2.1 months (95% CI: 2.0 to 2.2)	3.3 months (95% CI: 2.3 to 3.5)
	HR 0.98; (95% CI: 0.81 to 1.19) p=0.42	
ORR	21.1% (95% CI: 16.4 to 26.5)	11.4% (95% CI: 7.9 to 15.8)
Median Follow-up	14.1 months (95% CI: 9.9 to 22.1)	
January 18, 2017 Data Cut[2]		
Median OS	10.3 months (95% CI: 8.0 to 12.3)	7.4 months (95% CI: 6.1 to 8.1)
	HR 0.70; (95% CI: 0.57 to 0.86) p=0.0004	
Median PFS	2.1 months (95% CI: 2.0 to 2.2)	3.3 months (95% CI: 2.4 to 3.5)
	HR 0.96; (95% CI: 0.79 to 1.16) p=0.32	
ORR	21.1%	11.0%
Median Follow-up	18.5 months (95% CI: 14.2 to 26.5)	
May 19, 2017 Data Cut[4]		
Median OS	10.3 months (95% CI: 8.0 to 12.3)	7.4 months (95% CI: 6.3 to 8.3)
	HR 0.70; (95% CI: 0.57 to 0.86) p=0.0003	
Median PFS	2.1 months (95% CI: 2.0 to 2.2)	3.3 months (95% CI: 2.4 to 3.5)
	HR 0.96; (95% CI: 0.79 to 1.16) p=0.32	
ORR	21.1%	11.0%
Median Follow-up	22.5 months (95% CI: 18.5 to 30.5)	22.5 months (95% CI: 18.2 to 29.3)

1.2.2 Additional Evidence

See Section 3, Section 4, and Section 5 for a complete summary of patient advocacy group input, Provincial Advisory Group (PAG) Input, and Registered Clinician Input, respectively.

Patient Advocacy Group Input

From a patient perspective, muscle invasive bladder cancer moderately to severely affected patients' ability to work, travel and exercise. Respondents also reported ability to volunteer, perform household chores, spend time with family and friends and fulfill family obligations being moderately to severely impacted. Caregiver respondents stated that they were also most affected with respect to ability to work. With respect to controlling aspects of bladder cancer, patient respondents reported stress, emotional well-being and fatigue and sleep as the most important aspects to control. Patient respondents also reported ability to control mobility, appearance and diarrhea as being important to control. Patient respondents reported previous treatments included transuretheral resection of the bladder tumour, Bacillus Calmette-Guerin therapy, mitomycin C, surgical removal of the bladder, cisplatin chemotherapy, radiation and bladder preservation. Over half of the respondents reported that their current therapies did not control the bladder cancer. The most common side effects associated with the current therapies included fatigue, nausea, decreased appetite, skin rash, hair loss, pain, fever, shortness of breath,

bleeding, and pneumonia. Patient respondents reported that it was very important or extremely important to be able to access new treatments. For respondents who have not experience the drug under review expect that it would improve their physical condition, such as decreasing the size or stabilizing of the tumor, reducing pain, and improving breathing. In addition, it is also expected that the new drug would improve the quality of life and provide long-term stability or reduction of disease. Over half of these respondents reported that they would be willing to tolerate moderate side-effects if the new drug is proven to be effective. Of the three patient respondents that had experience with pembrolizumab, all indicated that pembrolizumab was effective at controlling the bladder cancer with two respondents mentioning decreased severity of side-effects compared to other therapies. The side effects that were experienced included fatigue, skin rash, itchiness and diarrhea. For those who had experience with other therapies, they also reported that the infusion period for pembrolizumab was shorter than other therapies.

Provincial Advisory Group (PAG) Input

Input was obtained from five provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact implementation:

Clinical factors:

- Unmet need for second line treatment of urothelial cancer
- Sequencing of treatments for urothelial cancer

Economic factors:

- Treatment until progression

Registered Clinician Input

The clinicians providing input noted that a modest proportion of patients with muscle-invasive urothelial cancer might develop disease progression after first-line chemotherapy. In these patients, second-line therapy with pembrolizumab has been shown to offer an improvement in OS and quality of life, as well as better tolerability. Pembrolizumab will be used after cisplatin-based chemotherapy or in patients who are not eligible to receive cisplatin. The drug may also be used as a third-line therapy after taxane chemotherapy in a relatively small group of patients. The drug will likely replace or displace second-line chemotherapy with taxanes (paclitaxel or docetaxel). The clinicians providing input indicated that retreatments with and restarts of pembrolizumab should be performed in continence with those of other immunotherapy agents (e.g. nivolumab). 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, from a clinical point of view, the clinicians providing input support the 200mg fixed dose suggested by the evidence.

Summary of Supplemental Questions

There were no supplemental questions identified for this review.

Comparison with Other Literature

The pCODR Clinical Guidance Panel and the pCODR Methods Team did not identify other relevant literature providing supporting information for this review.

1.2.3 Factors Related to Generalizability of the Evidence

Table 2 addresses the generalizability of the evidence and an assessment of the limitations and sources of bias can be found in Sections 6.3.2.1a and 6.3.2.1b (regarding internal validity).

Table 2: Assessment of generalizability of evidence for Pembrolizumab (Keytruda) for Metastatic Urothelial Carcinoma

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence (KEYNOTE-045 trial)</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td rowspan="4">Population</td><td>Performance Status</td><td>Patients were included if they had an ECOG of 0, 1 or 2.

Baseline characteristics<table><tr><td>ECOG</td><td>Pembrolizumab</td><td>Chemotherapy</td></tr><tr><td>0</td><td>119 (44.1)</td><td>106 (39.0)</td></tr><tr><td>1</td><td>143 (53.0)</td><td>158 (58.1)</td></tr><tr><td>2</td><td>2 (0.7)</td><td>4 (1.5)</td></tr></table>
Subgroup Analysis<table><tr><td>ECOG</td><td>HR (95% CI)</td></tr><tr><td>0 or 1</td><td>0.74 (0.59–0.92)</td></tr><tr><td>2</td><td>0.43 (0.04–4.20)</td></tr></table>Just to note 6 patients had an ECOG status of 2</td><td>Does performance status limit the interpretation of the trial results (efficacy or toxicity) with respect to the target population (e.g., Canadian clinical practice, patients without the factor, etc.)?</td><td>A minority of patients included in the trial were ECOG 2 and these patients could not have additional poor prognostic factors. The CGP concluded that the trial results were generalizable to ECOG 2 patients. Based on clinical opinion, the CGP considered selective use in ECOG 2 patients with poor prognostic factors was reasonable and best left at the treating clinician’s discretion.</td></tr>
<tr><td>Measurable disease</td><td>Patients were enrolled in the trial if they had measureable disease based on RECIST 1.1 as assessed by the investigator/site radiologist. Tumor lesions situated in a previously irradiated area are considered measureable if progression has been demonstrated in such lesions.</td><td>Are the results generalizable to patients without measurable disease?</td><td>The trial results are generalizable to patients without measureable disease.</td></tr>
<tr><td>Ethnicity or Demographics</td><td>Details on race, ethnicity and geographic location baseline characteristics were documented in the NICE Report. The majority of patients were white (71.8%) while a smaller percentage were Asian (22.5%).[3] Furthermore, more patients enrolled in the trial were from a non-East Asian region (80.4%) as compared to an East Asian region (19.6%).[3]</td><td>If the trial was conducted outside of Canada, is there a known difference in effect based on ethnicity that might yield a different result in a Canadian setting? Also, if the demographics of the study countries differ from Canada, the average treatment effect in the trial might not be representative of a Canadian setting.</td><td>The CGP considered the population quite similar to a Canadian population and therefore generalizable.</td></tr>
<tr><td>Biomarkers</td><td>PD-L1 status was measured using a combined positive score. This was defined as the percentage of PD-L1 expressing tumour cells and infiltrating immune cells relative to the total number of tumour cells.

Although pembrolizumab is an anti-PD-L1 inhibitor, PD-L1 expression was not a criterion for eligibility for the trial. However, patients were required to have adequate tissue for biomarker status testing.

Baseline characteristics</td><td>Is the biomarker an effect modifier (i.e., differences in effect based on biomarker status)? Are the results of the trial applicable to all subgroups equally? Is there a substantial group of patients excluded from the trial to whom the results could be generalized?</td><td>OS was analyzed for differential benefits by PD-L1 combined positive score, but these were not clearly identified in subgroup analyses, and the CGP did not support use of pembrolizumab based on PD-L1 combined positive score. The CGP considered the benefits of pembrolizumab generalizable regardless of PD-L1 combined score.</td></tr>
</table>

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence (KEYNOTE-045 trial)</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td></td><td></td><td>
<table>
<tr><td>PD-L1 CPS</td><td>Pembrolizumab</td><td>Chemotherapy</td></tr>
<tr><td>< 10%</td><td>186 (68.9)</td><td>176 (64.7)</td></tr>
<tr><td>≥ 10%</td><td>74 (27.4)</td><td>90 (33.1)</td></tr>
</table>
Subgroup Analysis
<table>
<tr><td>PD-L1 CPS</td><td>HR (95% CI)</td></tr>
<tr><td>< 10%</td><td>0.80 (0.61–1.05)</td></tr>
<tr><td>≥ 10%</td><td>0.57 (0.37–0.88)</td></tr>
<tr><td>< 1%</td><td>0.89 (0.66–1.20)</td></tr>
<tr><td>≥ 1%</td><td>0.61 (0.43–0.86)</td></tr>
</table>
</td><td></td><td></td></tr>
<tr><td rowspan="2">Intervention</td><td>Line of therapy</td><td>Second-line and beyond</td><td>Are the results of the trial generalizable to other lines of therapy</td><td>The CGP considered the results generalizable to patients treated with at least one line of prior platinum-based chemotherapy. It is unclear if the results are generalizable to patients treated with only prior non-platinum-based chemotherapy.</td></tr>
<tr><td>Administration of intervention</td><td>Pembrolizumab dose was 200 mg IV every 3 weeks</td><td>Are the results generalizable to a different dose or administration schedule?</td><td>Although the initial clinical trials of pembrolizumab used a dose of 2 mg/kg, the manufacturer is now promoting the use of a flat dose of 200 mg. There is no evidence to suggest fixed dosing is superior to weight-based dosing.</td></tr>
<tr><td>Comparator</td><td>Standard of Care</td><td>In the chemotherapy arm patients are treated with paclitaxel, docetaxel and vinflunine.

Vinflunine is not available for this indication in Canada. In the trial, 87 (34%) of patients received vinflunine in the chemotherapy group. Regardless, the amount of patients who could receive vinflunine was 35%. Vinflunine was only available as comparator in countries where it was approved for the treatment of MUC.</td><td>If the comparator is non-standard, are the results of the trial applicable in the Canadian setting?</td><td>Pembrolizumab benefit was slightly greater compared to vinflunine in subgroup analyses (HR: 0.69) perhaps potentially biasing results more favourably toward pembrolizumab than would be expected in a Canadian population. However, as the results were qualitatively similar with paclitaxel and docetaxel (HR: 0.76) the CGP considered the impact of this on the results minimal. The results remained positive when vinflunine patients were excluded.</td></tr>
<tr><td>Setting</td><td>Countries participating in the Trial</td><td>The trial was conducted in 120 sites in 29 countries, which includes: USA, Australia, Austria, Belgium, Canada, Chile, Denmark, France, Germany, Hungary, Ireland, Israel, Italy, Japan, Netherlands, New Zealand, Norway, Peru, Poland, Portugal, Puerto Rico, Romania, Singapore, South Korea, Spain, Sweden, Taiwan, Turkey and UK.</td><td>If the trial was conducted in other countries, is there any known difference in the practice pattern between those countries and Canada? Differences in the patterns of care might impact the</td><td>This was an international RCT that included Canadian participants. The CGP is unaware of any differences in practice patterns that would limit generalizability to a Canadian population.</td></tr>
</table>

Domain	Factor	Evidence (KEYNOTE-045 trial)	Generalizability Question	CGP Assessment of Generalizability
			clinical outcomes or the resources used to achieve the outcomes.	

1.2.4 Interpretation

Burden of Illness and Need

Although 1st-line platinum-based combination chemotherapy has reasonably high objective response rates and is associated with improved OS, there are currently no reliably effective 2nd-line treatment options for patients with incurable urothelial cancer. This includes patients who have had disease recurrence within 12 months of prior platinum-based neoadjuvant or adjuvant chemotherapy for localized muscle-invasive disease, as these patients do not seem to benefit from further platinum-based treatment.

Improved treatment options for these patients are needed and highly relevant, as urothelial cancer remains an important cause of cancer death in Canada with approximately 2400 deaths annually. Paclitaxel and docetaxel have shown modest efficacy as single agents or in combination with other drugs and are often offered to patients, but they have not demonstrated evidence of effectiveness in randomized trials. Vinflunine has been compared to supportive care in a randomized trial, but antitumor activity was low, toxicity significant, and survival results equivocal leading to failure of its regulatory approval outside of Europe.

Anti-PD-1 and anti-PD-L1 monoclonal antibodies have shown durable antitumor activity in urothelial cancer and are of high interest, but few other promising options are currently evident. Only docetaxel plus ramucirumab has shown promising activity in this setting but improvement in OS has not been demonstrated compared to docetaxel alone in a randomized trial.

Effectiveness

From this perspective the results of the KEYNOTE 045 RCT identify an important advance. Most important is the observation that patients receiving pembrolizumab lived longer on average than patients receiving investigators' choice chemotherapy. The risk of death was reduced 27% during the trial observation period (HR: 0.73, p=0.002) but perhaps as impressive was near 50% increase in the proportion of patients alive at 1 year from 30.7% to 43.9%. Although it did not meet the minimally important difference to confirm clinical superiority, HRQoL was statistically superior with pembrolizumab, indicating some degree of clinical benefit over chemotherapy. As well, the objective tumor response rate was nearly doubled (21.1% vs 11.4%, p=0.001), and the proportion of response lasting at least 12 months was 68% versus 35% confirmed durable benefit. Improvements in these endpoints are all potentially relevant to patients.

Safety

Severe adverse effects (grade 3 or higher) were more than one-third less common with pembrolizumab than with single agent chemotherapy, occurring in 15.0% of patients. The types and frequencies of autoimmune side effects seen with pembrolizumab were similar to those seen in other cancer trials. Specifically, severe autoimmune effects were seen in 4.5% of pembrolizumab treated patients, with pneumonitis and colitis comprising the majority of these events, both events which are treatable. Such reduced treatment toxicity is highly relevant to patients.

Limitations and Generalizability

Enrollment was limited to patients with urothelial carcinoma of the renal pelvis, ureter, bladder, or urethra that showed predominantly transitional-cell features and had 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. Patients had received two or fewer lines of systemic chemotherapy for advanced disease and had measurable disease by RECIST criteria. Patients also had ECOG performance status 0-2, however, ECOG 2 patients with one or more poor prognostic factors for second-line therapy (i.e., hemoglobin concentration of <10 g/dL, liver metastases, and receipt of the last dose of most recent chemotherapy <3 months before enrollment) were excluded. Patients could not have received prior checkpoint inhibitor treatment. The CGP considered these data generalizable to patients with urothelial cancer of predominantly transitional histology of any primary site and also to those without formally measureable manifestations of their cancer. As well, the favorable safety profile suggested that pembrolizumab was a reasonable choice in patients with ECOG 2 performance status. The trial design was pragmatic in allowing investigators' choice of control arm chemotherapy consisting either of paclitaxel, docetaxel, or vinflunine which are considered reasonable standard treatment options. However, as vinflunine is not available in Canada, this control arm lacks relevance. However, as the results were qualitatively similar with paclitaxel and docetaxel (HR: 0.76) the CGP considered the impact of this on the results minimal.

Strengths of the trial included OS as a co-primary endpoint and that treatment crossover at progression was not allowed before the primary analysis. The collection and reporting of HRQoL data is also a strength. A common practice in oncology trials but weakness of the trial design was lack of blinding of investigators and patients to treatment received. This raises potential for ascertainment bias that could lead to earlier discontinuation of chemotherapy compared to pembrolizumab. Often patients receiving immune checkpoint inhibitor therapy are continued on treatment despite evidence of tumor growth due to the possibility of "pseudoprogression" from tumor inflammation; whereas chemotherapy patients would always have treatment discontinued. The CGP considered the potential effect of this on the efficacy results uncertain.

1.3 Conclusions

The Clinical Guidance Panel concluded that there is a net clinical benefit to pembrolizumab in the treatment of incurable advanced or metastatic urothelial cancer with evidence of cancer progression on or after prior platinum-based chemotherapy for incurable disease or within 12 months of treatment for localized muscle-invasive disease and no prior immune checkpoint inhibitor therapy based on one high-quality randomized controlled trial that demonstrated a clinically and statistically significant benefit in OS benefit for pembrolizumab compared with investigators' choice of paclitaxel, docetaxel, or vinflunine. Adverse event profiles were better for pembrolizumab than control chemotherapy. In making this conclusion, the Clinical Guidance Panel considered:

- These results generalizable to patients without measureable disease, including those of slightly poorer performance status (ECOG 2), and those with multiple lines of prior chemotherapy.
- Ongoing clinical trials are comparing immune checkpoint inhibitors to 1st-line chemotherapy in cisplatin-eligible and –ineligible patients. Until the results of these trials are available, use of these drugs in chemo-naïve patients is not recommended.

- Patients in KEYNOTE-045 could not have received prior immune checkpoint inhibitor therapy and there is currently no evidence to suggest the use of a second-line immune checkpoint inhibitor following first-line use, given they work through similar mechanisms of action.
- There is currently no evidence of sequencing of immune checkpoint inhibitor therapy or direct head-to-head trials comparing immune checkpoint inhibitor therapies.
- It is unknown whether results are generalizable to patients with prior non-platinum based therapy only (e.g. single agent gemcitabine), however, only a minority of patients would be treated with prior non-platinum based therapy.

2 BACKGROUND CLINICAL INFORMATION

This section was prepared by the pCODR Genitourinary Clinical Guidance Panel. It is not based on a systematic review of the relevant literature.

2.1 Description of the Condition

Two-thousand four hundred Canadians are expected to die from urothelial cancer in 2017, making it one of the top ten causes of cancer death. It is the 4th most common cancer diagnosed in males. Urothelial cancer typically arises in the bladder but may develop in any location lined with urothelium including the renal pelvis, ureter, urethra, and prostatic urethra. In North America, urothelial cancer is often related to chronic tobacco exposure but may also occur due to chronic bladder irritation from conditions such as recurrent infections, indwelling catheters, and (in the developing world) schistosomiasis. Typically patients present with painless gross hematuria, and often initially have low grade superficial bladder tumors treated effectively with local excision and intravesical therapies. A minority of these patients progress with development of high grade muscle-invasive urothelial cancer requiring more definitive treatment such as radical cystectomy or chemoradiation with or without adjunctive systemic chemotherapy.

2.2 Accepted Clinical Practice

Patients may also present with incurable metastatic or locally advanced disease not amenable to curative local therapy, either de novo or following definitive local therapy. For these patients, treatment of symptomatic disease may require optimal analgesic therapy, palliative radiation, bisphosphonate therapy, and even surgery in rare cases. However, treating the underlying cancer usually requires systemic drug therapy. Urothelial cancer is often chemosensitive and many chemotherapy agents have demonstrated single-agent activity. Combination cisplatin-based chemotherapy is considered the standard of care and has been shown to improve OS. However, as many as 50% of patients may be considered "cisplatin ineligible" based on factors such as performance status, poor renal function, and neuropathy. Gemcitabine/cisplatin is the most commonly used combination chemotherapy in Canada, with substitution of carboplatin for cisplatin in some considered cisplatin ineligible. Single-agent gemcitabine may also be used in the latter scenario. Dose-intense methotrexate/vinblastine/doxorubicin/cisplatin (M-VAC) + G-CSF) and paclitaxel/gemcitabine/cisplatin have higher tumor response rates but greater toxicity than gemcitabine/cisplatin, they may be used in patients able to tolerate more rigorous treatment. Patients with non-bladder urothelial cancers are treated similar to bladder cancer although the prognosis is generally worse.

Objective tumor response rates are approximately 50% with gemcitabine/cisplatin, 40% with gemcitabine/carboplatin, and 30% with gemcitabine monotherapy. All patients eventually progress and some may be considered for second-line chemotherapy. Although modest activity has been observed with a number of chemotherapy agents,[8] none are reliably effective, resulting in variation in clinical practice. In a phase III study, vinflunine was compared to best supportive care and reported a survival benefit (after post-hoc adjustment for ineligible patients) that led to its approval for this indication by the EMA but not by the US FDA or Health Canada. In Canada, docetaxel or paclitaxel either as single agents or in combination with carboplatin are often used. Prognostic factors for 2nd-line urothelial cancer patients treated with chemotherapy include: performance status, anemia, the presence of liver metastases, and time from treatment with 1st-line chemotherapy.[9,10]

Urothelial cancers are associated with a high mutational burden, making them of interest for new immunotherapeutic approaches. Early phase clinical trials have shown activity of both single agent PD-1 (pembrolizumab, nivolumab) and PD-L1 inhibitors (atezolizumab, durvalumab) in patients with incurable urothelial cancer who are cisplatin ineligible or progressed after platinum-based chemotherapy.[11-14]

The modest effectiveness of 2nd-line chemotherapy for advanced urothelial cancer supports a rationale for testing immune checkpoint inhibitors in this population. Recently two randomized trials comparing standard 2nd-line chemotherapy to such drugs have been completed. The KEYNOTE-045 trial compared pembrolizumab to either paclitaxel, docetaxel, or vinflunine and reported improved OS and reduced toxicity with the experimental arm.[1]

2.3 Evidence-Based Considerations for a Funding Population

Considering the number of deaths due to bladder cancer annually, that over 90% of these are urothelial cancer, and the possibility that non-bladder primary urothelial cancers may not be included in these statistics, it is estimated that approximately 2,000 patients per year would receive 1st-line chemotherapy. Most of these patients would potentially be candidates for 2nd-line treatment with a modestly toxic immunotherapy drug. As well, patients with cancer recurrence within one year of curative intent perioperative chemotherapy are also considered as "2nd-line" patients. It is estimated that as many as 2,000 patients per year could be candidates for pembrolizumab as 2nd-line therapy for advanced urothelial cancer in Canada. To date, no tumor markers have been predictive for benefit from either chemotherapy or immunotherapy in this population.

2.4 Other Patient Populations in Whom the Drug May Be Used

Multiple clinical trials are currently underway comparing checkpoint inhibitor drugs to chemotherapy in the 1st-line treatment of incurable urothelial cancer. The US FDA has approved both atezolizumab and pembrolizumab for the treatment of 1st-line cisplatin ineligible and 2nd-line incurable urothelial cancer, in addition to nivolumab for the latter indication. Other uncommon non-urothelial histologies of bladder cancer can occur, and pembrolizumab may be considered for their treatment, but evidence of benefit is much more limited.

3 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

One patient advocacy group, Bladder Cancer Canada, provided input on pembrolizumab (Keytruda) 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.

Bladder Cancer Canada collected information from 57 respondents with muscle-invasive bladder cancer via an online survey between the dates of July 14 and July 27 2017. Bladder Cancer Canada sent the survey to their database of approximately 4000 e-newsletter subscribers as well as posted the survey on the website and social media channels affiliated with bladder cancer. In addition to the survey, Bladder Cancer Canada conducted telephone interviews with two patients who were completing their pembrolizumab treatments after being on a trial for approximately two years. A third patient with pembrolizumab experience was corresponded with via email.

An online discussion forum, Inspire where subscribers are registered to the Bladder Cancer Advocacy Network Discussion Forum, was also visited to obtain patient experience with pembrolizumab.

Of the respondents to the patient survey, 50 were patients and 7 were caregivers, who responded on behalf of patients who were unable to respond or had passed away. There were in total 3 respondents with direct experience with pembrolizumab. The remaining 54 respondents had experience with advanced (muscle-invasive) disease but not with pembrolizumab.

One respondent was from Australia, one from the UK, and 3 from the US. The remainder of the respondents were from Canada, with 49% coming from Ontario.

From a patient perspective, muscle invasive bladder cancer moderately to severely affected patients' ability to work, travel and exercise. Respondents also reported ability to volunteer, perform household chores, spend time with family and friends and fulfill family obligations being moderately to severely impacted. Caregiver respondents stated that they were also most affected with respect to ability to work. With respect to controlling aspects of bladder cancer, patient respondents reported stress, emotional well-being and fatigue and sleep as the most important aspects to control. Patient respondents also reported ability to control mobility, appearance and diarrhea as being important to control. Patient respondents reported previous treatments included transuretheral resection of the bladder tumour, Bacillus Calmette-Guerin therapy, mitomycin C, surgical removal of the bladder, cisplatin chemotherapy, radiation and bladder preservation. Over half of the respondents reported that their current therapies did not control the bladder cancer. The most common side effects associated with the current therapies included fatigue, nausea, decreased appetite, skin rash, hair loss, pain, fever, shortness of breath, bleeding, and pneumonia. Patient respondents reported that it was very important or extremely important to be able to access new treatments. For respondents who have not experience the drug under review expect that it would improve their physical condition, such as decreasing the size or stabilizing of the tumor, reducing pain, and improving breathing. In addition, it is also expected that the new drug would improve the quality of life and provide long-term stability or reduction of disease. Over half of these respondents reported that they would be willing to tolerate moderate side-effects if the new drug is proven to be effective. Of the three patient respondents that had experience with pembrolizumab, all indicated that pembrolizumab was effective at controlling the bladder cancer with two respondents mentioning decreased severity of side-effects compared to other therapies. The side effects that were experienced included fatigue, skin rash, itchiness and diarrhea. For those who had experience with other therapies, they also reported that the infusion period for pembrolizumab was shorter than other therapies.

Please see below for a summary of specific input received from Bladder Cancer Canada. Quotes are reproduced as they appeared in the survey, with no modifications made for spelling, punctuation or grammar. The statistical data that was reported have also been reproduced as is according to the submission, without modification.

3.1 Condition and Current Therapy Information

3.1.1 Experiences Patients have with Metastatic Urothelial Carcinoma

Patients were asked how having muscle-invasive bladder cancer has affected their day to day activities including ability to travel, work, exercise, volunteer, perform household chores, spend time with family and friends and fulfill family obligations. Patients used a scale of one to five (1 – no impact at all, 2 – slightly impacted, 3 – moderately impacted, 4 – significantly impacted and 5 – very significantly impacted) to answer these questions. Bladder Cancer Canada noted that the most affected were patients' ability to work, ability to travel and ability to exercise. For 46% (26/56) of the respondents, ability to work was affected moderately to severely. Ability to exercise was similarly affected with 47% (27/57) respondents being moderately to severely impacted and 40% (23/57) of the respondents indicated that ability to travel was moderately to severely affected. In addition, ability to volunteer (34% of respondents), perform household chores (37% of respondents), spend time with family and friends (25% of respondents) and fulfill family obligations (29% of respondents) were somewhat lower and ranged from 29%-37% of respondents reported as being moderately to severely affected. Bladder Cancer Canada noted that the highest reported problem was the ability to work which severely affected 17.9% of respondents in his or her daily life.

The following are quotes reported by Bladder Cancer Canada to help illustrate the impact of metastatic urothelial carcinoma on patients:

> Patient 1
>
> "*I have had a radical cystectomy so my concerns are dealing with an ostomy pouch. It limits my daily activity as I cannot do strenuous chores or activities. I am always concerned about sudden leaks and must carry with me, at all times, spare pouches and clothes. I do use a leg bag for long trips and that helps with a lot of problems but as the bag fills you are hindered with walking and other activities so you must always be looking for a way to empty the bag. With experience I am able to cope as long as I am conscious of the potential problems. I have a CT scan every six months to see if the cancer has spread. This was decided when after the surgery some of the lymph nodes tested positive.*"
>
> Patient 2
>
> "*Most of my consequences have resulted from RC surgery - lymphodema restricts long periods of being on my feet or sitting with legs down. Adhesions from the RC gave me digestive issues for many months until I had a small bowel obstruction surgery. I cannot easily commit to plans with others very far into the future- my health hasn't quite stabilized yet. That is very limiting.*"
>
> Patient 3
>
> *"Have to always be near a bathroom, have to visit doctors a lot, feel like a burden to caregiver, little to no quality of life."*
>
> Patient 4
>
> "*The impact of cancer has had the greatest impact on life. The long term treatment of removing the bladder is very difficult to deal with.*"

Caregiver who responded on behalf of patient 1(now deceased)

"*The encroachment of a worsening situation for my late wife means the affect on day-to-day living evolved like the disease. In the early time period, life was somewhat normal between appointments, treatments, and a transition away from the work place. But as time passed, her ability to have a 'normal' life became impossible. The treatments, fatigue, and worry altered the energy capacity necessary to have a normal life. In the end, this disease cut her life short.*"

Caregiver who responded on behalf of patient 2

"*After undergoing RC, my father has been diagnosed with pt3b n1 stage bladder cancer. His battle is just beginning really. He will require further treatment given the stage of the cancer. He was not recommended to undergo chemotherapy prior to surgery as his kidney function was not optimal and he wears hearing aids and the oncologist was concerned for his hearing. We're waiting for a post surgery meeting with the urologist to review the results and develop a plan for treatment although there don't appear to be many options.*"

Respondents were also asked to rate on a scale of 1-5 how important it is to control various aspects of bladder cancer (1 – not important, 2 – slightly important, 3 – moderately important, 4 – very important, 5 – extremely important). Patient respondents reported that they were most affected with stress, emotional well-being and fatigue. Of the responses received, 62% (34/56) of respondents ranked controlling stress as moderately to severely important. Sleep was ranked third with 57% of patient respondents ranking it as moderately to severely important. In addition, controlling mobility, appearance and diarrhea were ranked t 50%, 49% and 40%, respectively. Respondents noted that controlling pain (35%) and shortness of breath (28%) was not as much of an issue for patients and less were affected by this aspect than other aspects.

Patient 1

"Hair thinning, due to chemo was stressful. Reflux, and gagging were extremely difficult to control. Breathlessness, fatigue & fluid retention were also extremely difficult."

Caregiver on behalf of patient 2

"My father is currently adjusting to his Illeal Conduit. He is extremely anxious about leakage and stays close to home because of his fear of leakage. Also, he has difficulty falling asleep again because of his anxiety of leakage"

Patient 3

"Being aware of & taking appropriate steps to deal with incontinence, due to neo-bladder diversion, is extremely important"

Patient 4

"Eating has changed, due to diarrhea- always need to be close to a bathroom. Always worried - especially what next tests show. Poor appetite. Don't like to go to pool when it's of people."

Patient 5

"I was in excruciating pain until the bladder was removed."

Patient 6

"Emotional Well being and stress. Especially the anxiety that comes with testing/scans and their results. Waiting for the next shoe to drop."

It was also noted that patients remarked that they did not rank something as important if they were not currently experiencing it.

3.1.2 Patients' Experiences with Current Therapy for Metastatic Urothelial Carcinoma

Bladder Cancer Canada noted that very few innovative treatments have emerged in the past few decades for bladder cancer. Symptoms of bladder cancer can worsen with metastases and from the high toxicity of chemotherapy.

According to Bladder Cancer Canada, approximately half of patients with advanced bladder cancer do not respond to their initial therapy and only 10-15% respond to second line chemotherapy. For patients whose advanced bladder cancer is progressing after platinum-based chemotherapy, there are little or no therapeutic options. For patients who are treated with chemotherapy, they have reported severe side-effects, which may reduce their quality of life. After chemotherapy the remaining option would be palliative care.

Bladder Cancer Canada noted that 48 patient respondents and 7 caregiver respondents (on behalf of patients) reported using the following therapies:

- Transuretheral resection of the bladder tumour (TURBT) – 61.8%
- BCG Treatments – 25.5%
- Mitomycin C – 12.7%
- Surgical Removal of the Bladder – 69.1%
- Cisplatin-based Chemotherapy – 58%
- Radiation – 21.8%
- Bladder preservation – 10.9%

Respondents reported that the following side effects were a**ssociated with the above listed** therapies:

- Fatigue – 84%
- Nausea – 51%
- Decreased Appetite – 41%
- Skin Rash – 18%
- Hair Loss – 39%
- Pain – 35%
- Fever -18%
- Shortness of Breath – 33%
- Pneumonia – 4%

Patients would have received more than one therapy and therefore may have selected more than one option for previous therapies. Respondents ranked the side-effects above as being moderately to severely intolerable in 73% of the responses, with 13.5 % ranking them as very intolerable. Of the responses received, 68% of respondents indicated that it was moderately to very significantly important to have a choice of drugs based on its known side-effects. In addition, 43% of patient respondents reported having experienced hardships accessing currently available treatments.

The following are quotes reported by Bladder Cancer Canada to help illustrate the effect current treatments for patients with metastatic urothelial carcinoma.

Patient 1

"*Had advance of bladder cancer with adjuvant chemo. Good margins reported with radical cystectomy and no involvement of lymph nodes. But at first 3 month CT scan post surgery, had new nodules in both lobes of lung. Then 11 month post surgery CT scan showed lesion to C7 vertebra*"

Patient 2

"*The creation of a Neo Bladder worked well for a while and provided hope. However, the intended normal functioning did not last too long and cancer re-appeared*."

Patient 3

"*Prior to bladder removal surgery, I had a series of "day surgeries" to remove the cancer, as well as several rounds of BCG treatments; however, the cancer kept recurring and bladder removal became necessary*."

Patient 4

"*The above response is related solely to the first line treatment of chemotherapy with cisplatin and gemcitabine . This treatment is almost as bad as the cancer itself*."

Patient 5

"*BCG treatment - fairly tolerable. Major surgery - Radical cystectomy, urethrectomy, hysterectomy, bilateral salpingo-oopherectomy and pelvic node dissection - long recovery time. Brachytherapy was tolerable due to expertise of the "Team". Very uncomfortable as the need to lie completely flat and could only move arms and head for three days, the delivery of radiation was relatively painless. Did not handle chemo very well, Extreme fatigue along with numerous other side effects*."

Patient 6

"*Chemo and surgery to remove the bladder were just not nice. Better than being dead though!*"

3.1.3 Impact of Metastatic Urothelial Carcinoma and Current Therapy on Caregivers

Bladder Cancer Canada also asked caregivers how muscle-invasive bladder cancer has affected his or her day-day activities including ability to work, travel, exercise, volunteer, perform household chores, spend time with family and friends and fulfill family obligations. Responses were provided on a scale of 1-5. There were 26 (45%) caregiver respondents (7 caregivers who had initially provided input on behalf of the patients and an additional 19 caregivers) who participated in this part of the survey. The most affected activities were the ability to work, ability to travel and ability to spend time with family and friends. Bladder Cancer Canada reported that the ability to work was affected moderately to severely for 57% (15/26) of respondents. Ability to travel and spend time with family and friends were equally affected at 56% (14/25) being moderately to severely affected. In addition, ability to exercise (46%), volunteer (48%), perform household chores (40%) and fulfill family obligations (48%) were lower and ranged from 40-48% being moderately to severely impacted. Bladder Cancer Canada noted that overall, caregiver respondents

appear to be more affected in their daily living than the patient themselves by the bladder cancer diagnosis. Below are comments reported by caregiver respondents:

> Caregiver 1
>
> "*At first I was in severe shock that ended up in a very deep depression - I ended up a mess and off work- it ended my career*."
>
> Caregiver 2
>
> "*As the cancer progresses, anything can happen and you have to be available to assist at all hours. You become withdrawn and stressed but have to keep a happy face. It is hard*."
>
> Caregiver 3
>
> "*I have been away from my husband and children very often to take my father to appointments. I stayed overnight with him at the hospital after his surgery as his hearing is impaired and English is not his first language. The emotional toll has been tremendous. It's extremely difficult to be told his diagnosis and all the information available indicates that his chances of survival are very low*."

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Expectations for and Experiences To Date with Pembrolizumab

Bladder Cancer Canada asked patients how important it was, on a scale of 1-5, to be able to access new treatment options for advanced bladder cancer (using the following scale: 1- Not important, 2 – Slightly important, 3 – Moderately Important, 4 – Very important, 5 – Extremely Important). Of the responses received, 80% of patient respondents reported that it was very important or extremely important to be able to access new treatments.

> Patient 1
>
> "*I have been told that because my MIBC is stage 3, I have no treatment options other than to remove my bladder, as archaic as this is*."
>
> Patient 2
>
> "*The chemo appears to have worked well, but remission may be temporary. If that turns out to be the case I would very much like to access new treatment options*."
>
> Patient 3
>
> "*Given the failure of a few of the treatment options, it is important to have an arsenal of treatment options available for the best chance at survival*."
>
> Patient 4
>
> "*Because of the nature of bladder cancer and the high recurrence rate, I would like to have the ability to access new treatment options*"

Caregiver on behalf of Patient 5

"*Given his current diagnosis, it is not known if he will be a candidate for chemo. His kidney function has likely improved, however, his hearing is still impaired so we still aren't sure if chemo will be an option and there is the fear of how he well will tolerate chemo*."

Forty-two respondents answered if they would consider taking a new therapy for their bladder cancer and how important it would be to:

1. Improve your physical condition such as: decreasing the size or stabilizing the tumour; reducing pain; improving your breathing – 93% of patients ranked this as very important or extremely important
2. Improve your quality of life – 90% of patients ranked this as very important or extremely important
3. Provide long-term stability or reduction of disease – 98% ranked this as very important or extremely important

In addition to the above, Bladder Cancer Canada asked patients if they were to consider taking a new therapy for their bladder cancer that is proven to be effective, what severity of side effects would they be willing to tolerate. In response to this question, 17% of respondents reported that they would be willing to tolerate none or just a few minor side effects, 57% of respondents reported that they would be willing to tolerate moderate side-effects; and 26% of respondents reported they would be willing to tolerate significant or very significant side-effects.

3.2.2 What Experiences Have Patients Had to Date with Pembrolizumab

Bladder Cancer Canada reported that three patients answered the survey who had specific experience with pembrolizumab. All three gained access through a clinical trial. Of the three patient respondents, two patients were from Canada (ON & NS) and one was from the US. Bladder Canada reported that two patient respondents have been on pembrolizumab for almost 2 years and the third was a Canadian patient on treatment for over 2 years. Of the three, one patient respondent has just finished treatment recently.

All three respondents ranked pembrolizumab as being extremely effective (5/5) at controlling his or her bladder cancer. When asked to compare the side effects from other therapies, only two respondents had experienced with other therapies. Two patient respondents reported that pembrolizumab was better than other therapies in terms of severity of side-effects. The third respondent could not compare to prior therapies; however, did comment that the respondent had no negative side-effects from pembrolizumab in any regard. Of the three respondents, one had moderate (somewhat tolerable) fatigue, skin rash, itchiness and diarrhea while one other had moderate diarrhea only. In addition one patient respondent reported low platelet counts near the end of the trial. Bladder Cancer Canada reported that no other side effects were reported by the three patient respondents surveyed. The comments noted below are with respect to the side-effects that were experienced:

> Patient 1
>
> "*The diarrhea was completely controlled with two teaspoons of syllium husks per day. The other side effect I had was the effect on my thyroid function. This was totally controlled with thyroid medication, one pill of 125 milligrams per day of synthroid medication.*"
>
> Patient 2
>
> "*OTC and prescription meds did not work for the diarrhea. It seems to come and go, so I try to pay more attention to what I am eating.*"
>
> "*The side effects really were minimal & tolerable. I chose to end the trial early though because I had complete response and the side effects were slowly becoming more prominent. I was beginning to show low platelet counts as another side effect.*"
>
> Patient 3
>
> "*I've been lucky (no side-effects were experienced)*"

Bladder Cancer Canada also asked patients on a scale of 1-5 how they would rate their quality of life while taking pembrolizumab. Two of the three respondents reported that they were very positively impacted and one reported that they were positively impacted. None of the respondents reported any negative impact. Below are the comments noted by the respondents with respect to their quality of life.

"*At time of RC (Apr/14), it was determined that 9 of 20 lymph nodes were cancerous. I was monitored for 1 year with only slight increases in node sizes & given existing hearing loss (I wear hearing aids), chemo was not a desirable option. Nodes continued to grow. Then Keytruda clinical trial, with 1st infusion July/15 - positive results achieved, with overall reduced node sizes after just 3 infusions. Further reductions realized. Keytruda/ pembrolizamab is a miracle drug , it made my life and my family's life normal again or better than normal. It is a matter of life and death being able to access new treatments for bladder cancer. The old first line treatment only delays death while pembrolizamab is a potential cure*."

Bladder Cancer Canada noted that hardships related to travel and time spent for treatments to access pembrolizumab was not addressed specifically in the survey but respondents were asked to respond via email in this regard. Comments from two respondents are noted below:

Patient 1

"*Treatment day was an all day event for me, because I had to travel approximately 1.5 hours away, making travel time three hours. The appointment always ran about three hours (between doc, research person, labs, infusion). The actual infusion was short, about one hour. Having a treatment one day every 3 weeks was easy compared to chemo. I never felt sick after a treatment. Keytruda treatment was much easier to go through than the radical cystectomy which has left me with permanent side effects like lymphedema. Because I was on a clinical trial, it was not a challenge to access the drug & I am grateful for that. Transportation to the infusion site would have been my biggest challenge, fortunately a friend offered to help*."

Patient 2

"*Travel time to receive chemotherapy and radiation at the local cancer centrewas about 15 minutes each way. Travel time to the clinical trial site where I received Keytruda was about 1.5 hours each way. The chemotherapy infusion took anywhere from a four to seven hours, whereas Keytruda required about one hour (½ hour infusion and ½ hour cleanse). The total time duration for each treatment was comparable overall between chemotherapy and Keytruda. The biggest challenge was to gain access to the trial. I inquired about trials after which my oncologist referred me to a centre where they were available and I was able to qualify. Overall the Keytruda infusions were much easier to tolerate than chemotherapy as there were no side-effects whereas on chemotherapy the side-effects were terrible*."

3.3 Additional Information

Bladder Cancer Canada noted a substantial need for treatment options that can meaningfully improve survival and quality of life in patients with advanced bladder cancer following chemotherapy or who are not eligible for chemotherapy

4 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

The Provincial Advisory Group includes representatives from provincial cancer agencies and provincial and territorial Ministries of Health participating in pCODR. The complete list of PAG members is available on the pCODR website (www.cadth.ca/pcodr). PAG identifies factors that could affect the feasibility of implementing a funding recommendation.

Overall Summary

Input was obtained from five provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact implementation:

Clinical factors:

- Unmet need for second line treatment of urothelial cancer
- Sequencing of treatments for urothelial cancer

Economic factors:

- Treatment until progression

Please see below for more details.

4.1 Factors Related to Comparators

PAG identified that there is no standard of care for patients with locally advanced or metastatic urothelial carcinoma who have received platinum-containing chemotherapy. The comparators in the KEYNOTE-045 trial were investigator's choice of paclitaxel, docetaxel or vinflunine. PAG noted that if the patient is fit enough for chemotherapy, paclitaxel or docetaxel would be used. Vinflunine is not available in Canada.

4.2 Factors Related to Patient Population

The funding request is for patients previously treated with platinum-based chemotherapy and the KEYNOTE-045 trial is for second-line treatment. PAG noted that first-line treatment with pembrolizumab would be out of scope of this review. However, PAG is seeking guidance on whether patients who could not receive platinum-based chemotherapy and are given an alternative chemotherapy regimen first line, be eligible for pembrolizumab second line.

PAG also noted that pembrolizumab in third or later lines of therapy is also out of scope of this review. However, 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 time limited need basis.

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. PAG noted that the KEYNOTE-045 trial excluded patients previously treated with PD-1/PD-L1 inhibitors and CTLA-4 inhibitors. 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 also noted that Health Canada has approved a PD-L1 inhibitor for urothelial cancer in May 2017, although at the time of this PAG input, there is no review at pCODR.

PAG is also seeking guidance on re-treatment with pembrolizumab in patients who have disease progression while on a treatment break.

4.3 Factors Related to Dosing

The dose is 200mg for urothelial cancer in the funding request and the KEYNOTE-045 trial. PAG noted trials suggest that weight based dose of 2mg/kg and 200mg fixed dose are similar. Although fixed dose would minimize drug wastage, PAG is seeking guidance on weight based dose for urothelial cancer given the high cost of fixed dose compared to weight based dose for patients weighing less than 100kg.

4.4 Factors Related to Implementation Costs

PAG noted that the infusion is 30 minutes which is less than chemotherapy.

4.5 Factors Related to Health System

Pembrolizumab, being an intravenous drug, would be administered in an outpatient chemotherapy center for appropriate administration and monitoring of toxicities. Intravenous chemotherapy drugs would be fully funded in all jurisdictions for eligible patients, which is an enabler for patients.

PAG noted that there is experience with pembrolizumab in the treatment of other cancers. However, as pembrolizumab is a high cost drug and requires monitoring of immune-mediated reactions throughout the course of therapy and beyond, PAG noted that smaller outpatient cancer centres may not have the expertise and resources to administer pembrolizumab or monitor for and treat serious adverse events.

4.6 Factors Related to Manufacturer

None identified.

5 SUMMARY OF REGISTERED CLINICIAN INPUT

One clinician input was received as a joint submission by three oncologists on behalf of the Genitourinary Drug Advisory Committee at Cancer Care Ontario.

The clinicians providing input noted that a modest proportion of patients with muscle-invasive urothelial cancer might develop disease progression after first-line chemotherapy. In these patients, second-line therapy with pembrolizumab has been shown to offer an improvement in OS and quality of life, as well as better tolerability. Pembrolizumab will be used after cisplatin-based chemotherapy or in patients who are not eligible to receive cisplatin. The drug may also be used as a third-line therapy after taxane chemotherapy in a relatively small group of patients. The drug will likely replace or displace second-line chemotherapy with taxanes (paclitaxel or docetaxel). The clinicians providing input indicated that retreatments with and restarts of pembrolizumab should be performed in continence with those of other immunotherapy agents (e.g. nivolumab). 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, from a clinical point of view, the clinicians providing input support the 200mg fixed dose suggested by the evidence.

Please see below for details from the clinician input(s).

5.1 Current Treatment(s) for MUC

The clinicians providing input identified that the current standard first-line treatment for patients with metastatic and/or unresectable loco-regionally advanced urothelial cancers includes platinum-based chemotherapy (cisplatin/carboplatin plus gemcitabine, or chemotherapy with methotrexate, vinblastine, Adriamycin, and cisplatin).

They also noted that, for patients whose disease progress after first-line therapy, there is a lack of evidence on treatment options with significant survival benefits, and that clinical decisions to use second-line chemotherapy are often made based on the results of phase II clinical trials. Docetaxel or paclitaxel are the most commonly used second-line agents.

5.2 Eligible Patient Population

The clinicians providing input indicated that muscle-invasive urothelial cancer is relatively uncommon. They also noted that advanced disease occurs in one-third to one-half of patients with this disease but only a relatively modest proportion of patients (one-third to one-half again) will be well enough to receive second line treatment. The physicians suggested that there would be a modest incident and/or prevalent population applicable for this request.

5.3 Identify Key Benefits and Harms with Pembrolizumab

Referring to the results of KEYNOTE-045 trial, the clinicians providing input noted that pembrolizumab could lead to a clinically relevant and statistically significant improvement in OS and quality of life, when compared with chemotherapy regimens. They noted that pembrolizumab improved quality of life and better-tolerated than chemotherapy options. In addition, the clinicians predicted that there would not be an increase in chair time requirements

for pembrolizumab, and that depending on the chemotherapy regimen used (e.g. weekly paclitaxel), the chair time could be decreased.

5.4 Advantages of Pembrolizumab Over Current Treatments

The clinicians providing input acknowledged that there is currently no drug approved by Health Canada, in the second-line setting, for the treatment of patients with progressive metastatic urothelial cancers, and that new treatments are urgently needed. Referring to the results of the randomized KEYNOTE-045 study, the clinicians indicated that pembrolizumab was the first (and only) agent with meaningful survival benefits in patients with advanced urothelial cancers. Therefore, they suggested that pembrolizumab is a very high priority for these patients with no second line treatment options.

5.5 Sequencing and Priority of Treatments with Pembrolizumab

The clinicians providing input stated that pembrolizumab would be used after cisplatin-based chemotherapy or in patients who are not eligible to receive cisplatin. They feel that pembrolizumab would also be used as third line treatment after treatment with taxane (paclitaxel or docetaxel) (in a relatively small group of patients. The physicians noted that pembrolizumab would likely replace or displace second-line chemotherapy.

5.6 Companion Diagnostic Testing

The physicians providing feedback identified no companion diagnostic testing for the drug under review.

5.7 Additional Information

The following additional information was also provided:

- Retreatments/ restarts – retreatments or restarts should be managed consistently across drugs with similar mechanisms of action (i.e., immunotherapies, including nivolumab)

- Dosing – Pharmacokinetic evidence suggests that 200 mg fixed dosing provides similar exposure to pembrolizumab, when compared to 2 mg/kg dosing. The problem from a cost containment point of view is that a lot of patients would by comparison be overdosed at 200mg, which is equivalent to the dose for a 100kg patient under the 2mg/kg dosing schedule. There is a drug wastage issue which is addressed by fixed dosing, however when the fixed dose is high that benefit tends to be nullified. From a clinical point of view, however, the evidence we have is with the 200mg dose and that needs to be taken into account.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the efficacy and safety of pembrolizumab in 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.

Note: Supplemental Questions most relevant to the pCODR review and to the Provincial Advisory Group were not identified while developing the review protocol.

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the CGP and the pCODR Methods Team. Studies were chosen for inclusion in the review based on the criteria in the table below. Outcomes considered most relevant to patients, based on input from patient advocacy groups are those in bold. The literature search strategy and detailed methodology used by the pCODR Methods Team are provided in Appendix A.

Table 3: Selection Criteria

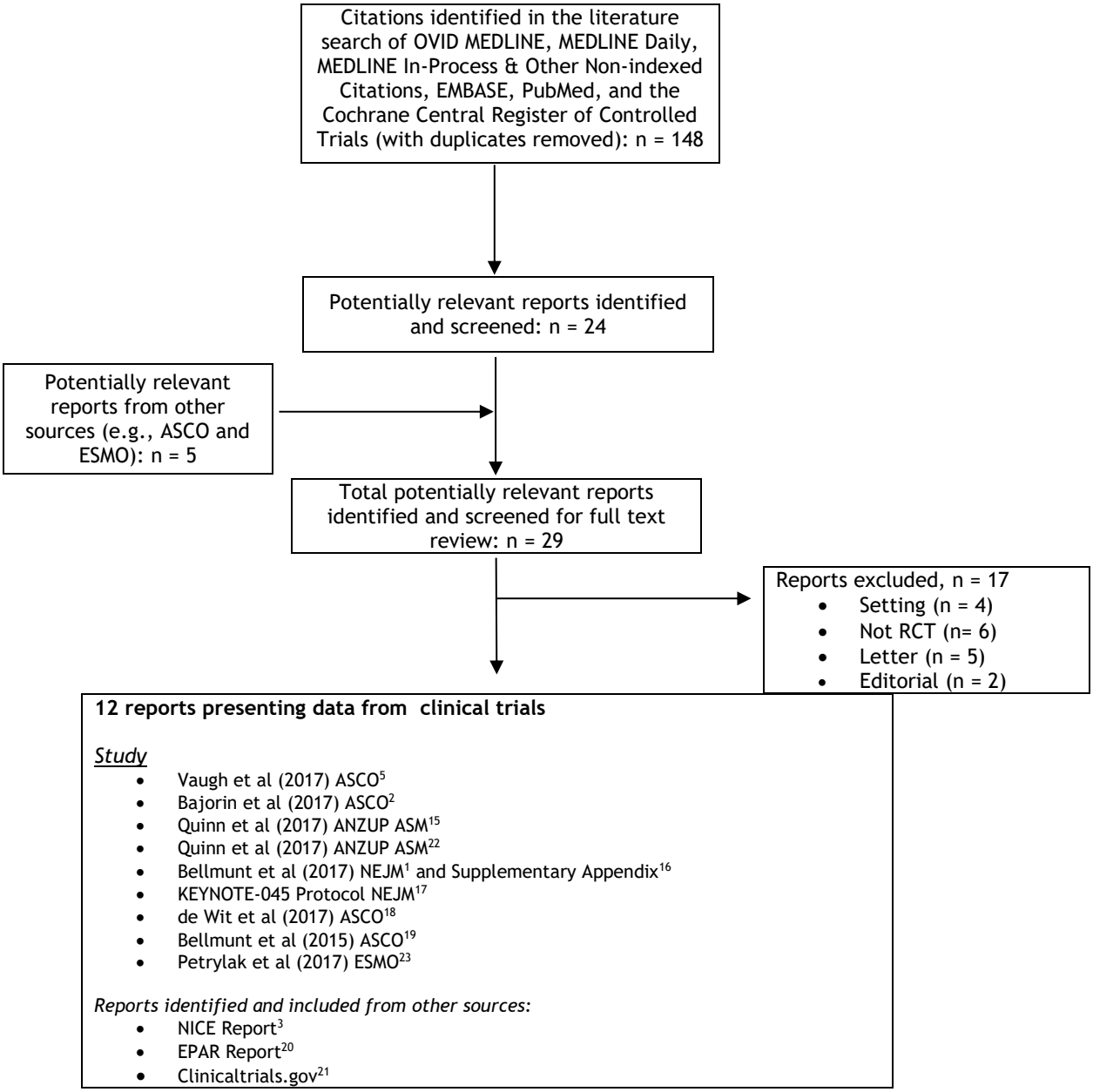
Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Published or unpublished RCTs In the absence of RCT data, fully published clinical trials investigating the safety and efficacy of pembrolizumab should be included.	Patients with locally advanced or MUC who have disease progression during or following platinum-containing chemotherapy or within 12 months of completing neoadjuvant or adjuvant platinum-containing chemotherapy Subgroups: • Age (<65 vs. ≥ 65 yrs) • ECOG PS (0 or 1 vs. 2) • Smoking status (current vs. former vs. never) • Histologic type (transitional cell vs. mixed) • PD-L1 status (<1% vs. ≥1%) or (<10% vs ≥10%) • Location of 1°tumour (upper vs. lower tract) • Location of metastases (lymph node only or visceral) • Liver metastases (yes vs. no) • Hemoglobin (<10 g/dl vs. ≥10 g/dl) • Context of most recent therapy (neoadjuvant vs. adjuvant vs. 1st therapy for metastases vs. 2nd therapy for metastases) • Time since most recent chemo (<3 mons vs. ≥3 mons) • Previous platinum therapy (cisplatin vs. carboplatin) • Investigator's choice (paclitaxel vs. docetaxel vs. vinflunine)	Pembrolizumab	Chemotherapy • Paclitaxel • Docetaxel • Vinflunine Checkpoint inhibitors • Nivolumab	Primary • **OS** • **PFS** • **HRQoL** Secondary • ORR • DOR • DCR Safety • AEs • SAEs • WDAEs
Abbreviations: MUC = metastatic urothelial carcinoma; HRQoL=Health related quality of life; RCT=randomized controlled trial; SAE=serious adverse events; AE=adverse events; WDAE=withdrawals due to adverse events; DCR=disease control rate; ORR=objective response rate; DOR=duration of response; ORR = overall response rate; yrs = years; ECOG PS = Eastern Cooperative Oncology Group Performance Status; vs. = versus; PD-L1 = Programmed death-ligand 1; g/dL = Grams Per Decilitre; mons = months				
Notes:* Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions).				

6.3 Results

6.3.1 Literature Search Results

Of the 232 potentially relevant reports identified, one study (KEYNOTE-045) in 12 citations was included in the pCODR systematic review (Figure 1).[1-3,5,15-23] Seventeen reports were excluded because six were not RCTs, five were letters, four were in a different setting and two were editorials. Additional reports related to the KEYNOTE-045 trial were obtained from the Submitter.[4,24,25]

Figure 1. QUOROM Flow Diagram for Inclusion and Exclusion of studies



Note: Additional data related to KEYNOTE-045 were also obtained through requests to the Submitter by pCODR [Health Canada Module 2.5, 2.7.1, 2.7.3, 2.7.4 and 2.7.6[24]; Checkpoint Responses[25]; de Wit et al (2017) ESMO[4]]

6.3.2 Summary of Included Studies

The pCODR systematic review included one phase III RCT that assessed the safety and efficacy of pembrolizumab as a second-line therapy in patients with advanced urothelial carcinoma (MUC) that progressed during or after the receipt of platinum-based chemotherapy, KEYNOTE-045. A total of 542 patients were randomly assigned to receive pembrolizumab at 200 mg every 3 weeks (n = 270) or to one of three chemotherapies (n = 272). Patients could have been treated with paclitaxel (175 mg/m^2; N= 84), docetaxel (75 mg/m^2; N = 84) or vinflunine (320 mg/m^2; N = 87).[1] It should be noted that vinflunine has not been approved for this indication in Canada.

6.3.2.1 Detailed Trial Characteristics

The summary of the trial and select quality characteristics are presented in Table 4 and Table 5.

Table 4: Summary of trial characteristics of the included study

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes

Study
KEYNOTE-045
NCT02256436
 	
Characteristics
International, randomized, open-label phase 3 trial
 	
Sample size
Randomized (N) = 542
Treated (N) = 521
 	
Number of centres and number of countries
120 sites in 29 countries
 	
Patient Enrolment Dates
5-Nov-2014 to 13-Nov-2015
 	
Second Interim data cut-off
7-Sept-2016
 	
Final Analysis Date
18-Jan-2017
 	
Funding
Merck
	Key Inclusion Criteria:
	• Diagnosis of UC of the renal pelvis, ureter, bladder, or urethra.
	• Progression or recurrence after first-line platinum-containing regimen (i.e. cisplatin, carboplatin):
	  • In the metastatic setting or for inoperable locally advance disease; or
	  • In the adjuvant setting following cystectomy for localized muscle-invasive UC (recurrence/progression <=12 months); or
	  • In the neoadjuvant setting following cystectomy for localized muscle-invasive UC (recurrence/progression <=12 months)
	• No more than 2 prior lines of systemic chemotherapy for MUC
	• Measureable disease
	• ECOG of 0, 1, or 2
	• Adequate organ function
	
	Key Exclusion Criteria:
	• UC that is suitable for local therapy administered with curative intent
	• Immunodeficiency or receiving systemic steroid therapy within 7 days prior of the first dose of study medication
	• Anti-cancer monoclonal antibody within 4 weeks prior to study Day 1
	• Prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks of study Day 1
	• Prior therapy with all choices of active comparator
	• Known additional malignancy that is progressing or requires active treatment with the exception of basal cell carcinoma of the skin, squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cancer; or incidental prostate cancer
	• Known active CNS metastases and/or carcinomatous meningitis, cardiac disease, ILD or non-infectious pneumonitis, infection requiring systemic therapy
	• Active autoimmune disease requiring systemic treatment within the past 3 months
	• Severe hypersensitivity reaction to paclitaxel, docetaxel, vinflunine
	• Prior therapy with PD-1 or anti-PD-Ligand 1 agent, or with an agent directed to another co-inhibitory T-cell receptor
	• Active HIV, HBV or HCV
		Intervention
		Pembrolizumab
		
		Comparator
		Paclitaxel
		Docetaxel
		Vinflunine
			Co-primary:
			OS
			
			PFS
			
			Secondary:
			ORR
			
			DOR
			
			Exploratory:
			HRQoL
			
			Safety

Abbreviations: CNS = central nervous system; HBV = hepatitis B; HCV = hepatitis C; HIV = Human immunodeficiency virus; ILD = interstitial lung disease; PD-1 = anti-programmed cell death 1; BSA = body surface area; MUC = metastatic urothelial cancer; UC = urothelial cancer; ECOG = Eastern Cooperative Oncology Group performance status; HRQoL=Health related quality of life; ORR=objective response rate; TTR = time to response; DOR = duration of response; PFS = progression-free survival; OS = OS			

Table 5: Select quality characteristics of included studies of pembrolizumab in patients with MUC who progressed during or after the receipt of platinum-based chemotherapy

Study	Treatment vs. Comparator	Primary outcome	Required sample size [A]	Sample size	Randomization method [B]	Allocation concealment	Blinding [C]	ITT Analysis	Final analysis [D]	Early termination	Ethics Approval
KEYNOTE - 045	Pembrolizumab vs. Chemotherapy	OS and PFS	470	542	IWRS, stratified	Yes	No	Yes	Yes	Yes	Yes

Abbreviations: ITT = intention to treat; IWRS = interactive web response service; OS = OS

Notes:
A: Based on a sample size of 470 patients, the trial had 88% power to detect 370 deaths in all patients and 86% power to detect 110 deaths in patients with a PD-L1 CPS ≥ 10% using a one-sided significance level of α=0.025. The study also had >99% power to detect 420 PFS events in all patients and 97% power to detect 137 PFS events in patients with a PD-L1 CPS ≥ 10%. The power calculation allowed for two interim analyses.[17]
B: Randomization was stratified by ECOG performance status (0 or 1 vs 2), liver metastases (yes vs. no), hemoglobin concentration (< 10 g per deciliter vs ≥ 10 g per deciliter) and time since last dose of chemotherapy (< 3 months vs ≥ 3 months).
C: Investigators and patients were not blinded to treatment assignment. In fact, chemotherapy treatment assignment was guided by the study investigator. PFS and ORR were confirmed by a blinded independent review committee.
D: At the first interim analysis, the OS data was reviewed by a Data Monitoring Committee (DMC) and the committee recommended that the trial continue. At the second interim analysis, 7-Sept-2016, the DMC reviewed the trial, which was based on 334 deaths in the total population and 104 deaths in the tumour PD-L1 combined positive score (CPS) of ≥ 10%. The DMC decided to determinate the trial early since pembrolizumab met the superiority thresholds for OS in both patient populations.[1]

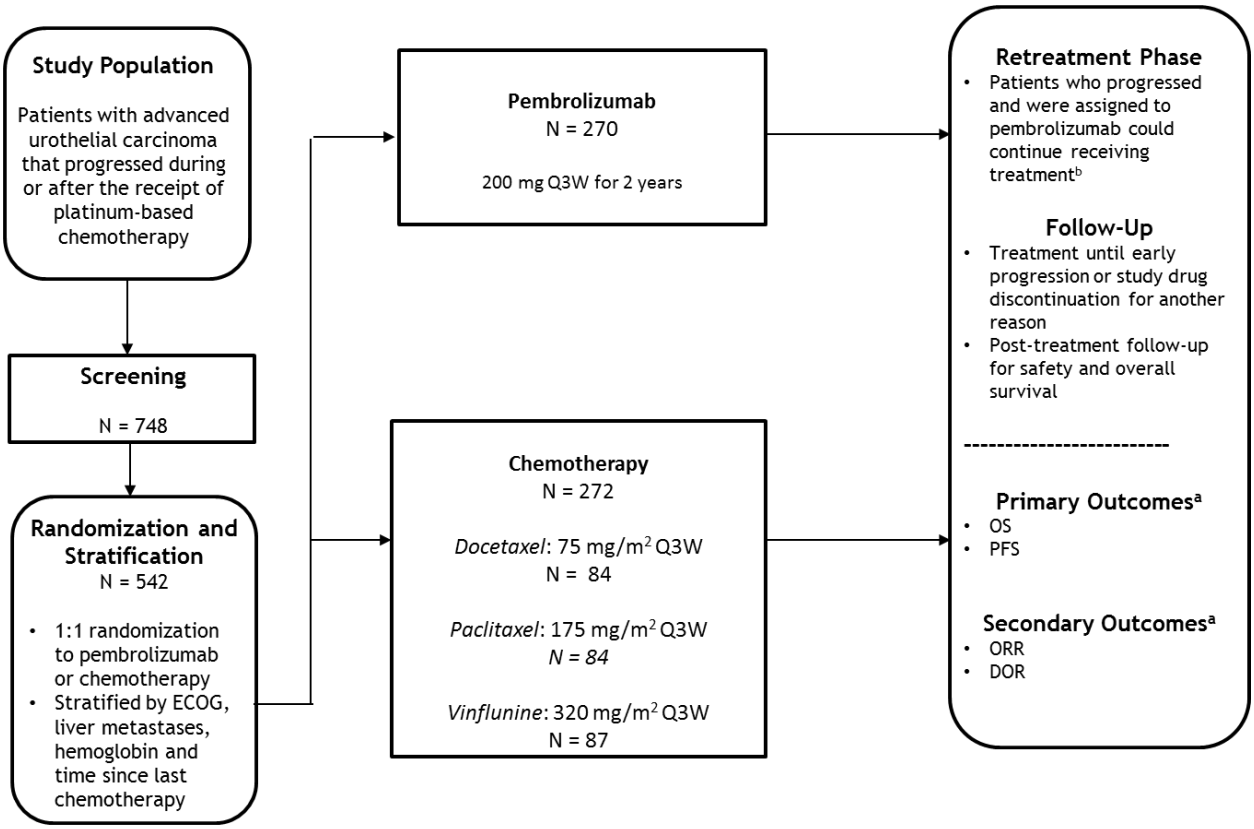
a) Trial

KEYNOTE-045 was a randomized, open-label, international phase III trial that assessed the efficacy and safety of pembrolizumab compared to chemotherapy (i.e. paclitaxel, docetaxel, vinflunine) in patients with advanced urothelial cancer that recurred or progressed after platinum-based chemotherapy.[1] The trial was conducted in 120 sites in 29 countries, which includes: USA, Australia, Austria, Belgium, Canada, Chile, Denmark, France, Germany, Hungary, Ireland, Israel, Italy, Japan, Netherlands, New Zealand, Norway, Peru, Poland, Portugal, Puerto Rico, Romania, Singapore, South Korea, Spain, Sweden, Taiwan, Turkey and UK.[20] The trial was sponsored by Merck.

Key inclusion criteria included: 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) criteria 1.1; and an Eastern Cooperative Oncology Group (ECOG) performance status score of 0, 1, or 2.[1,17]In addition, only patients whose samples could be evaluated for PD-L1 expression were enrolled in the study.[1] PD-L1 expression was measured in formalin-fixed tumour samples at a central lab with the use of a commercially available PD-L1 IHC 22C3 pharmaDx assay (Dako).[1]

Patients who had an ECOG performance status of 2 and exhibited one or more poor prognostic factors for second-line treatment (i.e. presence of liver metastases, hemoglobin concentration of <10 g per deciliter and <3 months since their last dose of chemotherapy) were excluded from the trial.[1] Patients were also excluded if they had received prior treatment with anti-PD-1, anti-PD-L1 or anti-CTLA-4 therapy.[1]

Figure 2: Study design of KEYNOTE-045



Abbreviations: ECOG= Eastern Cooperative Oncology Group; Q3W = every 3 weeks; OS = overall survival; PFS = progression free survival; ORR = objective response rate; DOR = duration of response
[a] Outcomes were assessed in the total and PD-L1 CPS ≥ 10% patient populations
[b] A protocol amendment made on 14-Dec-2016 incorporated the DMC recommendation to allow patients on chemotherapy to crossover to pembrolizumab if they meet eligibility requirements

Figure 2 represents the study design of KEYNOTE-045. It consisted of three phases: 1) the treatment phase, 2) the retreatment phase and 3) the follow-up phase.[17]These phases will be described in more detail, more specifically:

Treatment Phase[17]

- Eligible patients were randomized using a centralized interactive web response system.
- Patients were randomized on a 1:1 ratio to receive either pembrolizumab or chemotherapy based on the study investigator's choice (i.e. docetaxel, paclitaxel or vinflunine).
    - Study investigators used their clinical judgement to select which of the three chemotherapy drugs patients would receive and the protocol did not provide specific guidance.
    - Vinflunine was only provided to patients in countries where it had been approved for the treatment of MUC.
- Randomization was stratified by ECOG performance status (0 or 1 vs. 2), presence of liver metastases (yes vs. no), hemoglobin concentration (<10 g per deciliter vs. ≥10 g per deciliter), and time since last dose of chemotherapy (<3 months vs. ≥ 3 months).
- Tumour assessments occurred on week 9 followed by every 6 weeks during the first year and then every 12 weeks in the second year.
- Response to treatment was assessed radiologically using the RECIST criteria and it was performed by a blinded independent review committee (BIRC).

- Patients with initial radiological disease progression had repeated imaging occur ≥ 4 weeks later to confirm disease progression.
    - If repeat imaging demonstrated stable disease (SD), partial response (PR) or complete response (CR) then treatment was continued. Furthermore, if repeat imaging, as assessed by the investigator and site radiologist, met the threshold for disease progression (i.e. ≥ 20% increase in tumor burden compared to nadir) and did not show a further increase in tumor burden, then treatment could be continued.
    - Treatment continued until RECIST-defined disease progression, intolerable toxic effects, withdrawal of consent, investigator's decision to withdrawal or after completing two years of pembrolizumab therapy.

Retreatment Phase[17]

- Patients who had radiological disease progression were eligible for an additional year of pembrolizumab therapy.
    - Patients had to meet the following criteria to be eligible for retreatment:
        - Patient stopped their initial treatment with pembrolizumab after investigator-determined confirmed CR 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 CR
        - Patient had SD, PR or CR and stopped pembrolizumab treatment after 24 months for reasons other than disease progression or intolerability
- Patients received the same dose frequency of pembrolizumab as in the treatment phase.
- Initially, the trial did not permit crossover. However, based on the results of the second interim analysis, the DMC recommended that the study be stopped early to allow patients in the chemotherapy to crossover and receive pembrolizumab.[3]

Follow-up Phase[17]

- Patients who discontinued treatment for reasons other than disease progression had a radiological assessment every 6 weeks for the first year and then every 12 weeks in the second year.
- No restrictions were placed on the use of subsequent treatments and patients could have received more than one therapeutic agent.
- OS data was collected after the patient completed the 30 day follow-up visit and then every month until death or the study closed.
- Post-discontinuation information was documented, such as: date of disease progression, documentation of any subsequent anti-cancer and the date of death.

The co-primary endpoints measured in KEYNOTE-045 were OS (OS) and progression-free survival (PFS).[1] Secondary endpoints included: objective response rate (ORR), duration of confirmed response (DOR), time to response (TTR) and safety. Health-Related Quality of Life (HRQoL) was measured as an exploratory endpoint using the European Organisation for Research and Treatment of Cancer core 30 quality of life Questionnaire (EORTC QLQ-C30) and EuroQol EQ-5D.[17]

The trial was composed of two patient populations, the intention-to-treat (ITT) population (comprised of all randomized patients), and patients with a tumour PD-L1 combined positive score (CPS) ≥ 10%. PD-L1 CPS ≥ 10% was defined as the percentage of PD-L1 expressing tumour cells and infiltrating immune cells relative to the total number of tumour cells.[1]

The power calculation for the co-primary endpoints (i.e. OS and PFS) were based on a sample size of 470 patients. The prevalence of patients with a PD-L1 CPS ≥ 1% or ≥ 10% was estimated to be 55% and 33%, and therefore, the sample size would also require 260 patients with a PD-L1 CPS ≥ 1% and 156 patients with a PD-L1 CPS ≥ 10%.[17]The family-wise type I error rate was controlled using a one-sided alpha of 2.5% for OS, PFS and ORR. The trial was designed to include two interim analyses. A Hwang-Shih-DeCani alpha-spending function was implemented to control for type 1 error. [17]

The power calculation for OS was based on four assumptions, which include: 1) OS will follow an exponential distribution with a median of eight months in the chemotherapy arm; 2) the OS hazard ratios (HRs) are predicted to be 0.70, 0.50 and 0.60 for all patients, patients with a PD-L1 CPS ≥10% or a PD-L1 CPS ≥1%, respectively; 3) the enrollment period will occur over 12 months with a minimum of 18 months follow-up; and 4) there will be a yearly dropout rate of 2%.[17] Based on a sample size of 470 patients, the trial was designed to have 88% power to detect 370 deaths in all patients and 86% power to detect 110 deaths in patients with a PD-L1 CPS ≥ 10%.

The power calculation for PFS was based on four assumptions, which include: 1) PFS will follow an exponential distribution with a median of four months in the chemotherapy arm; 2) the PFS HRs are predicted to be 0.50, 0.45 and 0.50 for all patients, patients with a PD-L1 CPS ≥10% or a PD-L1 CPS ≥1%, respectively; 3) the enrollment period will occur over 12 months; and 4) there will be a yearly dropout rate of 5%.[17] The authors estimated that the study would have >99% power to detect 420 PFS events in all patients and 97% power to detect 137 PFS events in patients with a PD-L1 CPS ≥10%.

Protocol Amendments

There were global and country-specific amendments made to the protocol. However, for the purpose of this review, only the global amendments will be considered, more specifically:

- Amendment #2 (26-Aug-2014): Include docetaxel was a comparator.[20]
- Amendment #4 (not released): Include OS and PFS in patients with a PD-L1 CPS ≥10% as co-primary objectives.[20]
- Amendment #9 (27-Feb-2016): Include OS and PFS in patients with a PD-L1 CPS ≥1% as co-primary objectives.[20]
- Amendment #11 (26-May-2016): Include the number of events in patients with a PD-L1 CPS ≥1% into the interim and final analysis.[20]Extend the second interim and final analysis to account for the number of OS events in patients with a PD-L1 CPS ≥1%.[20]
- Amendment #13 (19-Sept-2016): Include a rationale for using CPS cut points.[20] Adjustments to account for multiplicity in second interim and final analysis.[20]
- Amendment #15 (15-Dec-2016): Include the DMC recommendation to allow patients on chemotherapy to crossover to pembrolizumab if they meet eligibility criteria.[25]

b) Populations

Table 6 outlines the baseline characteristics of the patients in KEYNOTE-045. Bellmunt et al (2017) reported that the patient characteristics were generally balanced between the pembrolizumab and chemotherapy groups.[1] However, the pCODR Methods Lead observed a ≥ 5% difference between treatment groups for several baseline characteristics, which include: current or former smoker (pembrolizumab: 61.3% vs. chemotherapy: 69.1%), tumour PD-L1 CPS ≥10% (pembrolizumab: 28.5% vs. chemotherapy: 33.8%), first line setting in most recent therapy (pembrolizumab: 67.8% vs. chemotherapy: 57.7%) and ECOG status of 0 (pembrolizumab: 44.1% vs. chemotherapy: 39.0%).[1,16] At Checkpoint, the Submitter provided an exploratory analysis where they adjusted the OS and PFS HRs by smoking status, tumour PD-L1 CPS, setting in most recent therapy and ECOG status. The re-analyses showed that the imbalance of these selected baseline characteristics had a minimal impact on the primary estimates of OS and PFS (p-value for interaction ≥ 0.05 for all).[25]

The percentage of patients with a PD-L1 CPS ≥10% was 28.5% in the pembrolizumab group and 33.8% in the chemotherapy group.[1] It was noted that the PD-L1 CPS status was not evaluable for 10 (3.7%) patients in the pembrolizumab group and 6 (2.2%) in the chemotherapy group.[16]

Details on race, ethnicity and geographic location baseline characteristics were documented in the NICE Report. The majority of patients were white (71.8%) while a smaller percentage were Asian

(22.5%).[3] Furthermore, more patients enrolled in the trial were from a non-East Asian region (80.4%) as compared to an East Asian region (19.6%).[3]

Table 6. Demographic and Disease Characteristics at Baseline

	Pembrolizumab Group (N=270)	Chemotherapy Group (N=272)
Age		
Median (range), yr	67.0 (29-88)	65.0 (26-84)
≥65 yr, no. (%)	165 (61.1)	147 (54.0)
Male sex, no. (%)	200 (74.1)	202 (74.3)
ECOG performance status,† no. (%)		
0	119 (44.1)	106 (39.0)
1	143 (53.0)	158 (58.1)
2	2 (0.7)	4 (1.5)
Smoking status,‡ no. (%)		
Current	29 (10.7)	38 (14.0)
Former	136 (50.4)	148 (54.4)
Never	104 (38.5)	83 (30.5)
Histology,§ no. (%)		
Pure transitional cell	186 (68.9)	197 (72.4)
Predominantly transitional cell	82 (30.4)	73 (26.8)
PD-L1 CPS,‖ no. (%)		
<10%	186 (68.9)	176 (64.7)
≥10%	74 (27.4)	90 (33.1)
Site of primary tumor,¶ no. (%)		

Upper tract (renal pelvis or ureter)	38 (14.1)	37 (13.6)
Lower tract (bladder or urethra)	232 (85.9)	234 (86.0)
Visceral disease, no. (%)	240 (88.9)	233 (85.7)
Liver metastases	91 (33.7)	95 (34.9)
Hemoglobin level,** no. (%)		
<10 g/dL (<100 g/L)	43 (15.9)	44 (16.2)
≥10 g/dL (≥100 g/L)	219 (81.1)	223 (82.0)
No. of risk factors,†† no. (%)		
0	54 (20.0)	44 (16.2)
1	96 (35.6)	97 (35.7)
2	66 (24.4)	80 (29.4)
3-4	45 (16.7)	45 (16.5)
Setting of most recent prior therapy,‡‡ no. (%)		
Neoadjuvant or adjuvant	31 (11.5)	53 (19.5)
First line	183 (67.8)	157 (57.7)
Second line	55 (20.4)	60 (22.1)
Time since completion or discontinuation of most recent prior therapy,§§ no. (%)		
<3 months	103 (38.1)	104 (38.2)
≥3 months	166 (61.5)	167 (61.4)
Prior platinum,§§ no. (%)		
Cisplatin	198 (73.3)	213 (78.3)
Carboplatin	70 (25.9)	56 (20.6)

Oxaliplatin or nedaplatin	1 (0.4)	2 (0.7)
Prior cystectomy or nephroureterectomy, no. (%)	61 (22.6)	51 (18.8)
Prior Bacillus Calmette–Guérin therapy, no. (%)	32 (11.9)	22 (8.1)

*The intention-to-treat population includes all patients who were randomly allocated to treatment. There were no significant differences between treatment groups.
†Eastern Cooperative Oncology Group (ECOG) performance status ranges from 0 to 5, with 0 indicating no symptoms and higher score indicating increasing disability. Six (2.2%) patients in the pembrolizumab group and 4 (1.5%) patients in the chemotherapy group had a missing ECOG performance status.
‡Smoking status was missing for 1 (0.4%) patient in the pembrolizumab group and 3 (1.1%) patients in the chemotherapy group.
§One (0.7%) patient in the pembrolizumab group had clear cell adenocarcinoma, and 1 (0.7%) patient had unknown histology. Two (0.7%) patients in the chemotherapy group had missing histology.
‖PD-L1 combined positive score (CPS) was defined as the percentage of tumor and infiltrating immune cells with PD-L1 expression out of the total number of tumor cells. PD-L1 CPS was not evaluable for 10 (3.7%) patients in the pembrolizumab group and 6 (2.2%) in the chemotherapy group.
¶Primary tumor site was missing for 1 (0.4%) patient in the chemotherapy group.
**Baseline hemoglobin level was missing for 8 (3.0%) patients in the pembrolizumab group and 5 (1.8%) patients in the chemotherapy group.
††Risk factors include the Bellmunt risk factors of ECOG performance status >0, hemoglobin level <10 g/dL (<100 g/L), and presence of liver metastases1 plus time since completion or discontinuation of <3 months. The number of risk factors was unknown for 9 (3.3%) patients in the pembrolizumab group and 6 (2.2%) patients in the chemotherapy group.
‡‡The setting of the most recent prior therapy was the third line for 1 (0.4%) patient in the chemotherapy group and was missing for 1 (0.4%) patient each in the pembrolizumab and chemotherapy groups.
§§The time since completion or discontinuation of most recent prior therapy and the specific prior platinum were missing for 1 (0.4%) patient in each treatment group.
Data source: From N Engl J Med, Bellmunt J, de WR, Vaughn DJ, Fradet Y, Lee JL, Fong L, et al. Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carcinoma. . 2017 Mar 16 376(11):1015-26. Copyright © (2017) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[16]

c) Interventions

Patients in KEYNOTE-045 were randomized to receive either pembrolizumab (N = 270) or chemotherapy (N = 272). The single agent systemic therapies used in the chemotherapy group were: docetaxel (N = 84 [30.9%]), paclitaxel (N = 84 [30.9%]) and vinflunine (N =87 [32.0%]). In Canada, docetaxel and paclitaxel have been approved for the treatment of MUC while vinflunine has not been approved for this indication as noted by Provincial Advisory Group Input in Section 4. The protocol stated that the overall proportion of patients who received vinflunine in the chemotherapy group was capped at 35%; however, this cap was never implemented. Furthermore, vinflunine was only provided to patients in countries where it had been approved for the treatment of MUC.[17]

Treatment Dosing Schedule[17]

The dosing schedule for the two treatment groups in KEYNOTE-045 are presented below:

- *Pembrolizumab*
  - 200 mg IV dose every three weeks at the first day of each cycle.
- *Chemotherapy*
  - *Paclitaxel:* 175 mg/m^2 IV dose every three weeks at the first day of each cycle.
  - *Docetaxel:* 75 mg/m^2 IV dose every three weeks at the first day of each cycle.
  - *Vinflunine:* 320 mg/m^2 IV dose every three weeks at the first day of each cycle.

Dose delays, reductions or modifications[17]

- *Pembrolizumab*
    - Pembrolizumab was withheld for drug-related toxicities and severe or life threatening adverse events.
    - Dosing interruptions were permitted in the case of surgical and/or medical events or events that were not study related.
- *Chemotherapy*
    - Treatment with paclitaxel, docetaxel or vinflunine was withheld for drug-related grade 4 hematologic toxicities and for non-hematologic toxicity ≥ grade 3.
    - Dose modifications were applied for all subsequent doses.

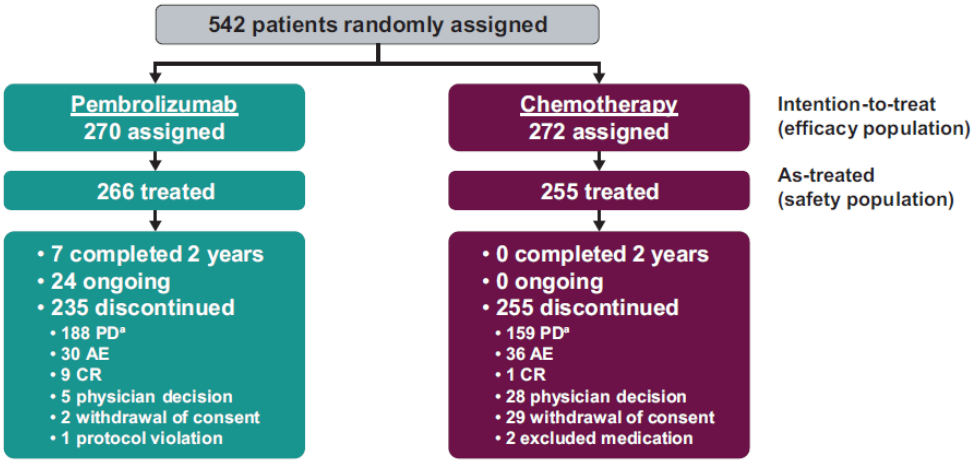
d) Patient Disposition

The patient disposition for KEYNOTE-045 is presented in Figure 3. In total, 748 patients were eligible for enrollment in the trial, and 542 were randomized to receive pembrolizumab (N = 270) or chemotherapy (N = 272). In the pembrolizumab group, 1.5% of patients did not receive their assigned treatment because of randomization in error based on failure to meet all eligibility criteria (0.7%; N = 2) and fatal adverse events (AEs) (0.7%; N = 2).[16] However, in the chemotherapy group, 6.3% of patients did not receive their intended therapy because they withdrew consent after randomization (88.2%; N=15), had worsening physical condition (5.9%; N=1) and had a decrease in platelet count that precluded treatment (5.9%; N=1).[16]

Three dates were considered for this review. The first cut-off occurred on 7-Sept-2016 at the second-interim analysis, where the DMC stopped the trial early.[1]The two latter data cut-offs represent a longer OS follow-up and were conducted on 18-Jan-2017 and 19-May-2017).[2,4] The patient disposition at the 19-May-2017 data cut-off will be presented.

At the 19-May-2017 data cut-off, 9.0% of patients (N = 24) were still receiving pembrolizumab while all patients had stopped receiving chemotherapy.[4] Furthermore, seven patients had completed two additional years of pembrolizumab therapy.[4] The most common reasons for discontinuation in the pembrolizumab group were progressive disease (N = 188) and adverse events (N= 30). In contrast, the most common reasons for discontinuation in the chemotherapy group were progressive disease (N = 159), adverse events (N= 36), patient withdrawal (N=29) and physician decision (N=28).[4]

Figure 3: Patient disposition for patients enrolled in the KEYNOTE-045 trial (19-May-2017 data cut-off)



AE, adverse event; CR, complete response; PD, progressive disease.
[a]Includes clinical progression.

Data Source: de Wit et al (2017) ESMO[4]

Twenty-two percent of patients in the chemotherapy group and 2.0% of patients in the pembrolizumab group received a subsequent cancer therapy.[3] The majority of patients in the chemotherapy arm were treated with pembrolizumab (10%) followed by atezolizumab (4%) and nivolumab (3%) while all patients in the pembrolizumab arm were treated with atezolizumab.[3] According to the protocol, there were no restrictions on the type of subsequent treatments or numbers of agents patients could receive.[17]

e) Limitations/Sources of Bias

- KEYNOTE-045 was an open-label RCT design. A double-blinded design would have been very difficult to implement due to the assignment of chemotherapy agents (i.e. paclitaxel, vinflunine or docetaxel). The assessment of OS will not be influenced by the open-label nature of the trial because it is an objective outcome.[6,7] In contrast, there is a greater risk of detection bias for subjective outcomes (i.e. disease progression, PROs and AEs) because patients and study investigators are aware of treatment assignment. However, the potential for this bias was mitigated by using an independent central review to assess key efficacy outcomes, such as PFS and ORR.

- In the chemotherapy arm, patients were randomized to docetaxel (30.9%), paclitaxel (30.9%) and vinflunine (32.0%).[1] Paclitaxel and docetaxel have been approved for the treatment of MUC in Canada while vinflunine has not been approved for this indication. Furthermore, Bellmunt et al (2017) performed a subgroup analysis of OS where they stratified the effect of pembrolizumab by Investigator's choice of paclitaxel, docetaxel or vinflunine.[1] The subgroup analysis demonstrated a consistent protective effect of pembrolizumab as compared to paclitaxel (HR: 0.76, 95% CI: 0.55 to 1.04), docetaxel (HR: 0.76, 95% CI: 0.55 to 1.05) and vinflunine (HR: 0.69, 95% CI: 0.51 to 0.94).[1] Although these results suggest that the effect of vinflunine may bias the overall results in favour of pembrolizumab, they should be interpreted with caution because of small sample sizes and the trial was not designed to compare individual chemotherapy agents to pembrolizumab. Thus, the OS estimates are unlikely to be biased.

- Among all of the patients who were assigned a therapy at randomization, 1.5% did not receive pembrolizumab and 6.3% did not receive chemotherapy.[1] Reasons for patients failing to receive their assigned therapy were randomization in error based on failure to meet all eligibility criteria (n=2) and fatal adverse events (n=2) in the pembrolizumab group and withdrawal of consent after randomization (n=15), worsening physical condition (n=1), and a decrease in platelet count that precluded treatment (n=1) in the chemotherapy group. To address the exclusion of these patients, the Submitter performed a post-hoc analysis on OS and PFS by removing the 21 patients who did not receive their intended treatments. The results of this re-analysis showed that the unbalanced exclusion did not impact the primary effect estimates of OS or PFS.

- There was a ≥ 5% difference between the treatment groups for several baseline characteristics, such as: smoking status, tumour PD-L1 CPS, setting in most recent therapy and ECOG performance status. These baseline characteristics represent potential confounders and an imbalance across these factors may bias effect estimates in either direction. Upon request, the Submitter provided a post-hoc analysis of OS and PFS adjusting for smoking status, tumour PD-L1 CPS, setting in most recent therapy and ECOG status. The p-value for interaction was not significant for any of the factors.

- Tumour PD-L1 expression was reported as a CPS. The rationale for using this measure was based on results from KEYNOTE-012, which was a Phase 1b multicenter, non-randomized, multi-cohort trial of pembrolizumab in UC patients with advanced solid tumors. The original intent of the trial was to use PD-L1 CPS ≥ 1% cut-off to define PD-L1 positivity.[20] However, validated results from another trial (i.e. KEYNOTE-052) showed that a CPS ≥ 10% cut-off appeared to be a better predictor of pembrolizumab response in UC patients. Based on these results, CPS ≥ 10% cut-off was pre-specified to assess pembrolizumab efficacy. Although PD-L1 CPS appears to be a well validated cut-

off, it may be difficult to compare these results with other studies that have assessed the effect of PD-L1 in MUC patients treated with immunotherapies. Other studies have measured PD-L1 tumour expression as a continuous outcome while CPS represents the percentage of PD-L1 expressing tumour cells and infiltrating immune cells relative to the total number of tumour cells.[1]

- OS may be confounded because patients could have received subsequent treatments (i.e., PD-1 therapies) after progression. To account for the potential effect of confounding, a sensitivity analysis was conducted using the Rank Preserving Structural Failure Time (RPSFT) model.[17] The results of the RPSFT model demonstrated a more modest, yet significant, OS effect estimate as compared to the primary analysis of OS.[25] Furthermore, the DMC allowed patients treated with chemotherapy to crossover and receive pembrolizumab.[3] However, this change was implemented after the trial was stopped early and it will not impact the primary analysis of OS but might influence future analyses.

- Although there was a significant treatment effect for OS, the Kaplan-Meier plots for the two treatment arms crossed each other (e.g. Figure 4) around months 2 and 3.[4] This may increase the uncertainty in the effect estimates as it suggests the hazard for death is not constant over time, which is an assumption required for the Cox proportional hazards model. One option for addressing this issue is by stratifying the estimated hazard ratio. Here, Cox regression models are fit at different time frames to obtain different hazard ratios. However, these methods reduce the sample size, and increase the likelihood of type 2 error. In response to a pCODR request, the Submitter provided a test of the proportional hazards assumption and an analysis of OS stratified by time.[25] Given this evidence, it is difficult to interpret the hazard ratio in the trial as an "average" of the curves over time (or the average of the different hazard ratios after stratifying by different time frames). Qualitatively, the overall analyses favour pembrolizumab over chemotherapy, but there is uncertainty associated with the actual magnitude of effect.

- Although pembrolizumab is an anti-PD-L1 inhibitor, PD-L1 expression was not a criterion for eligibility for the trial. However, patients were required to have adequate tissue for biomarker status testing. This may reduce the generalizability of the trial results because the results are not representative of those patients who did not have adequate tissue samples.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Efficacy Outcomes

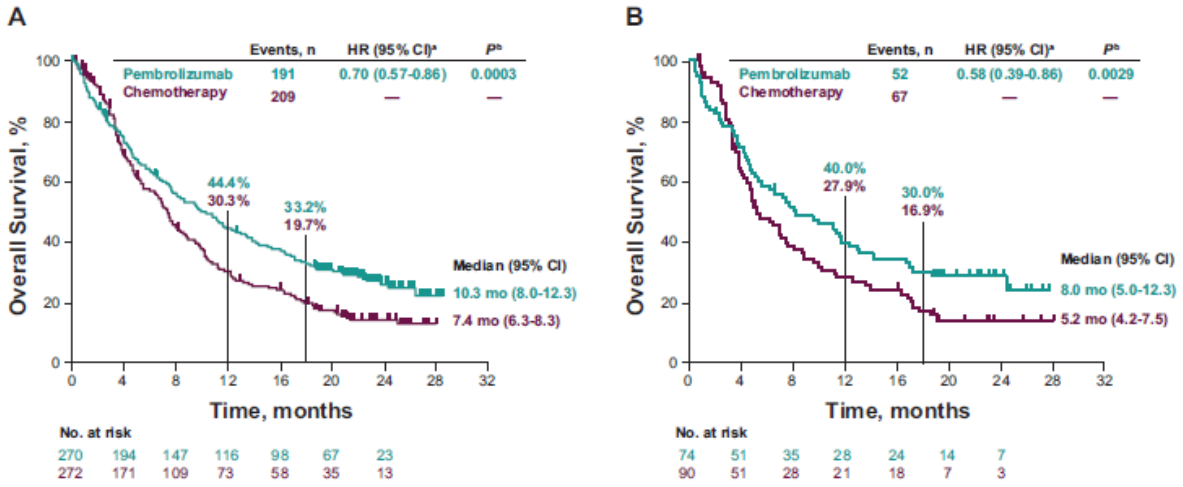
Efficacy analyses were performed in two patient populations: the ITT patient population (N = 542) and patients who had a tumour PD-L1 CPS of ≥10% (N = 164).[1] The PD-L1 CPS was expressed as a percentage of PD-L1 expressing tumour cells and infiltrating immune cells relative to the total number of tumour cells.[1]

Three data cut-offs will be presented in this pCODR review. The first data cut-off occurred on 7-Sept-2016 for the second-interim analysis and represents a median follow-up of 14.1 months (range: 9.9 to 22.1).[1] The second data cut-off was on 18-January-2017 and represents a median follow-up of 18.5 months (14.2 to 26.5).[2] The last data cut off was on 19-May-2017 and the median follow-up in the pembrolizumab and the chemotherapy arms were 22.5 months (range: 18.5 to 30.5) and 22.5 months (range: 18.2 to 29.3), respectively.[4]

Overall survival
One of the co-primary endpoints in KEYNOTE-045 was OS. It was defined as the time from randomization to death from any cause.[1]The OS curves were obtained using the Kaplain-Meier method and treatment differences were determined using a stratified log-rank test. Additionally, stratified Cox proportional hazard models with Efron's method of tie handling were used to calculate HRs with corresponding 95% confidence intervals (CIs).[17] HRs were stratified by randomization strata (i.e. ECOG status, presence of liver metastases, hemoglobin concentrations, and time since last dose of

chemotherapy). Upon confirmation of progressive disease, patients in the chemotherapy arm were allowed to receive a subsequent PD-1 agent.[17] In order to adjust for the potential confounding effect of subsequent therapies, the authors conducted a RPSFT model.[17]

Figure 4. OS Kaplain Meier curves for (A) all patients and (B) patients with a PD-L1 CPS ≥ 10% enrolled in the KEYNOTE-045 trial (19-May-2017 data cut off)



CPS, combined positive score; HR, hazard ratio; PD-L1, programmed death ligand 1.
[a]Based on a Cox regression model with treatment as a covariate stratified by Eastern Cooperative Oncology Group performance status (0/1 vs 2), liver metastases (yes vs no), hemoglobin (<10 vs ≥10 g/dL), and time from completion of chemotherapy (<3 vs ≥3 months).
[b]1-sided *P* value based on stratified log-rank test.

Data Source: de Wit (2017) ESMO[4]

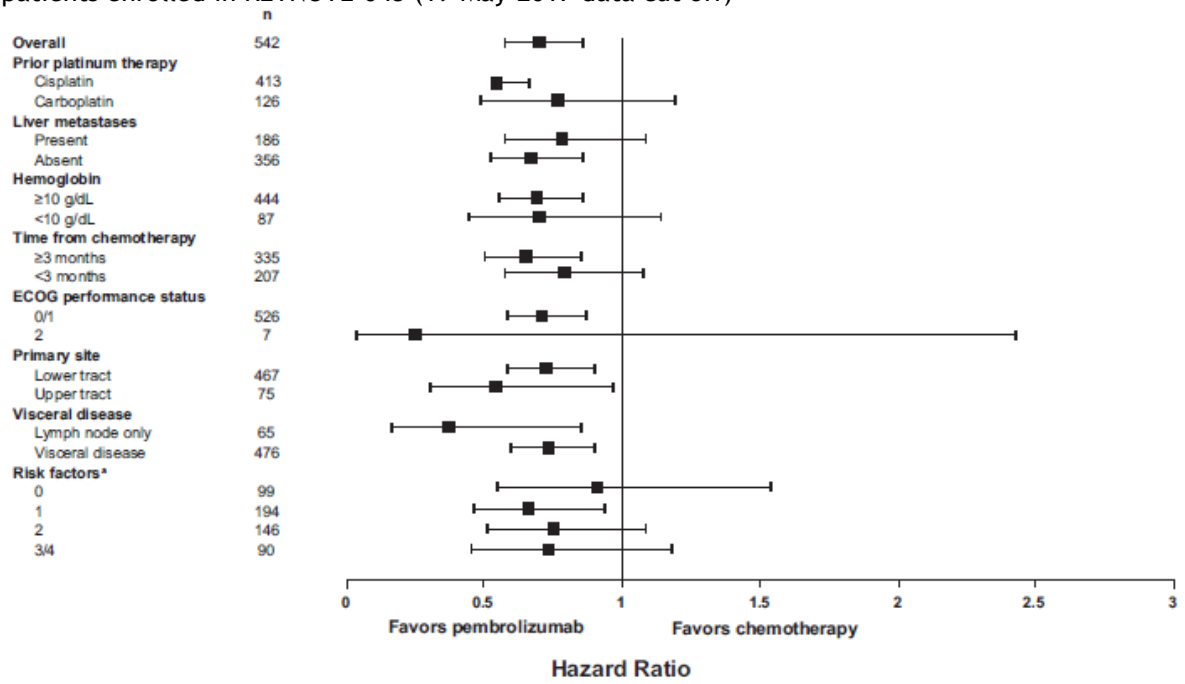
At the 7-Sept-2016 data cut-off, 57.4% of patients in the pembrolizumab group (N = 155) and 65.8% died in the chemotherapy group (N = 179) died.[3] The median OS for those treated with pembrolizumab was 10.3 months (95% CI: 8.0 to 11.8) while it was 7.4 months (95% CI: 6.1 to 8.3) in the chemotherapy arm.[1] Bellmunt et al (2017) reported that treatment with pembrolizumab was associated with a prolonged OS as compared to chemotherapy (HR: 0.73, 95% CI: 0.59 to 0.91; P=0.002).[1] Similar results were reported at the 18-Jan-2017 data cut-off.[2]

At the 19-May-2017 cut-off, 70.7% of patients assigned to pembrolizumab (N = 191) while 76.8% of patients assigned to chemotherapy died (N = 209) (Figure 4).[4] The median OS was 10.3 months (95% CI: 8.0 to 12.3) in the pembrolizumab group and 7.4 months (95% CI: 6.3 to 8.3) in the chemotherapy group. [4] Patients treated with pembrolizumab had a reduced risk of death as compared to those treated with chemotherapy (HR = 0.70, 95% CI: 0.57 to 0.86; P=0.0003).[4]

OS in patients who had a PD-L1 CPS ≥ 10% was also assessed in the KEYNOTE-045 trial (Figure 4). At the second interim analysis, patients with a PD-L1 CPS ≥ 10% who were treated with pembrolizumab had a reduced risk of death as compared to those treated with chemotherapy (HR: 0.57, 95% CI: 0.37 to 0.88; P = 0.005).[1] At the 19-May-2017 cut-off, 70.3% of patients in the pembrolizumab arm had died (N = 52/74) and the median OS was 8.0 months (95% CI: 5.0 to 12.3).[4] In contrast, 74.4% of patients in the chemotherapy arm had died (N = 67/90) and the median OS was 5.2 months (95% CI, 4.2 to 7.5]).[4] Patients with a PD-L1 CPS ≥ 10% who were treated with pembrolizumab had a reduced risk of death as compared to those treated with chemotherapy (HR: 0.58, 95% CI: 0.39 to 0.86; P = 0.0029).[4]

For the pre-specified subgroup analysis for OS, it was noted that pembrolizumab appeared to be associated with a protective effect against the risk of death as compared to chemotherapy across all subgroups (Figure 5).[4] However, these results should be interpreted with caution due to small sample sizes.

Figure 5. Subgroup analysis of overall survival stratified by baseline and disease characteristics among all patients enrolled in KEYNOTE-045 (19-May-2017 data cut off)



ECOG, Eastern Cooperative Oncology Group.
[a]Includes Bellmunt risk factors of ECOG performance status >0, hemoglobin level <10 g/dL, and liver metastases[2] + time from prior chemotherapy <3 months.[3]

Data Source: de Wit et al (2017) ESMO[4]

It appears that the OS Kaplain-Meier curves cross at month 3 (Figure 4). At Checkpoint, the Methods Lead inquired whether the proportional hazard (PH) assumption was tested for OS. The PH assumption explores whether the ratio of the hazards in the two treatment groups remains constant over time even if the underlying hazards change over time.[25] The assumption can be assessed visually (i.e. log(-log(S(t)) plots) or statistically (i.e. test for PH using Schoenfeld Residuals). The Submitter provided the diagnostics of the OS curves and the test for PH. They stated that log(-log(S(t)) crossed and that the test for PH p-value was less than 0.05, which implies that there was a departure from proportionality.[25]

As a sensitivity analysis, an OS RPSFT model was used to explore the potential confounding effects of subsequent therapies in the chemotherapy arm.[17] A RPSFT model is preferred under these conditions because the ITT analysis will underestimate treatment effect.[26] RPSFT models reconstruct OS curves by accounting for the time when a patient received a subsequent therapy while assuming a consistent treatment effect of the intervention or control.[27] The RPSFT results demonstrated similar effect estimate as compared to the primary estimate of OS.[25]

Initially, Bellmunt et al (2017) performed a subgroup analysis of OS where they stratified the effect of pembrolizumab by Investigator's choice of paclitaxel, docetaxel or vinflunine.[1] The subgroup analysis demonstrated a consistent protective effect of pembrolizumab as compared to paclitaxel (HR: 0.76, 95% CI: 0.55 to 1.04), docetaxel (HR: 0.76, 95% CI: 0.55 to 1.05) and vinflunine (HR: 0.69, 95% CI: 0.51 to 0.94).[1] However, these results should be interpreted with caution because of small sample size. Given these results, the pCODR Methods Lead requested that the Submitter provide a post-hoc analysis of OS and PFS stratified by treatment with paclitaxel or docetaxel at the 18-Jan-2017 data cut-off. This analysis was requested because it aligns with the submitted economic model reviewed in the pCODR Economic Guidance Report and these two agents are approved for this indication in Canada. Overall, the baseline characteristics for those treated with paclitaxel and docetaxel was similar to patients who were treated with chemotherapy.[25] There was a modest, protective trend for the comparison between

pembrolizumab and paclitaxel or docetaxel on OS (Table 7); however, these results were not significant. These results should be interpreted with caution because of small sample sizes and the trial was not designed to compare individual chemotherapy agents to pembrolizumab.

Table 7. The association between pembrolizumab and paclitaxel or docetaxel on overall survival for all patients enrolled in the KEYNOTE-045 trial (18-Jan-2017 data cut off)

Study: P045[a]	Pembrolizumab			Control			Pembrolizumab vs. Control	
OS	N[b]	Patients with Event n (%)	Median Time[c] in Months [95 %-CI]	N[b]	Patients with Event n (%)	Median Time[c] in Months [95 %-CI]	Hazard Ratio[d] [95 %-CI]	p-Value for Interaction Test (I^2)
Choice of Investigator from paclitaxel or docetaxel								
Paclitaxel	94	60 (63.8)	10.3 [6.0; 13.9]	90	64 (71.1)	6.9 [4.8; 9.7]	0.83 [0.57; 1.21]	0.759 (0.00 %)
Docetaxel	94	56 (59.6)	10.1 [7.7; 14.4]	92	58 (63.0)	7.4 [5.5; 9.9]	0.77 [0.52; 1.12]	

a: Database Cutoff Date: 18JAN2017

b: Number of patients: intention-to-treat

c: From product-limit (Kaplan-Meier) method

d: Based on stratified Cox regression model with treatment as a covariate stratified by Eastern Cooperative Oncology Group (ECOG) Performance Scale (0/1 vs. 2), presence or absence of liver metastases, hemoglobin (>= 10 g/dL vs. <10 g/dL), and time from completion of most recent chemotherapy (<3 months or >=3 months).

CI: Confidence Interval.

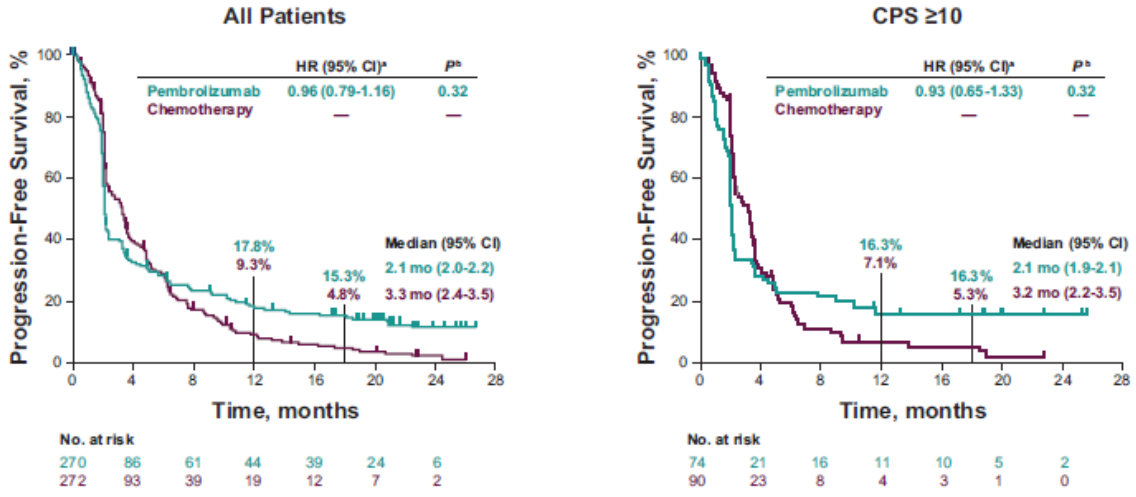
Data Source: Checkpoint Responses[25]

Progression-Free-Survival

The other co-primary end point in the trial was PFS. PFS was defined as the time from randomization to disease progression or death from any cause and it was assessed by BIRC using RECIST 1.1 criteria.[1] Patients who discontinued treatment following a documented disease progression were counted as having disease progression on the date of the documented PD assessment.[17] PFS curves were obtained using the Kaplan-Meier method and treatment differences were calculated using a stratified log-rank test.[17]Additionally, stratified Cox proportional hazard models with Efron's method of tie handling were used to obtain HRs and corresponding 95% CIs.[17]

At the 7-Sept-2015 cut-off, 80.7% of patients in the pembrolizumab group died or had disease progression and the median PFS was 2.1 months (95% CI: 2.0 to 2.2).[1,3] On the other hand, 80.5% patients in the chemotherapy arm died or had progressive disease and the median PFS was 3.3 months (95% CI: 2.3 to 3.5).[1] There were no treatment differences between pembrolizumab and chemotherapy on PFS (HR: 0.98, 95% CI: 0.81 to 1.19; P = 0.42).[1] Similar trends were observed for those with a PD-L1 CPS ≥ 10%.[1] Bajorin et al (2017) reported comparable results at the 18-Jan-2017 data cut-off.[2] Likewise, de Wit al (2017) stated that the treatment effect on PFS was attenuated in all patients (HR: 0.96, 95% CI: 0.79 to 1.16; P = 0.32) and those with a PD-L1 CPS ≥ 10% (HR: 0.93, 95% CI: 0.65 to 1.33; P = 0.32).[4]

Figure 6. PFS Kaplain Meier curves for (A) all patients and (B) patients with a PD-L1 CPS ≥ 10% enrolled in the KEYNOTE-045 trial (19-May-2017 data cut off)



CPS, combined positive score; HR, hazard ratio.
[a]Based on a Cox regression model with treatment as a covariate stratified by Eastern Cooperative Oncology Group performance status (0/1 vs 2), liver metastases (yes vs no), hemoglobin (<10 vs ≥10 g/dL), and time from completion of chemotherapy (<3 vs ≥3 months).
[b]1-sided *P* value based on stratified log-rank test.

Data Source: de Wit et al (2017) ESMO[4]

Patients in the pembrolizumab group were permitted to continue treatment beyond radiological progression provided that the patient was clinically stable. By 18-Jan-2017, 45.5% patients (N = 121/266) originally assigned to the pembrolizumab arm were treated beyond investigator assessed disease progression using RECIST 1.1 criteria.[25] Patients who were treated beyond progression received pembrolizumab for a median of 56 days (range: 1 to 643) and a median of 3 cycles (1 to 31).[25] It should be noted that as a result of a protocol amendment (14-Dec-2016) patients originally assigned to chemotherapy could crossover and receive pembrolizumab.[25] As of the 27-Sep-2017 date, nine patients treated with chemotherapy crossed over and received pembrolizumab.[25]

As previously mentioned, the pCODR Methods Lead also requested that the Submitter provide a post-hoc analysis of OS and PFS stratified by treatment with paclitaxel or docetaxel.[25] There were no significant differences between pembrolizumab and paclitaxel or docetaxel on the effect of PFS (P < 0.05 for all; Table 8).[25] These results should be interpreted with caution because of small sample sizes and the trial was not designed to compare individual chemotherapy agents to pembrolizumab.

Table 8. The association between pembrolizumab and paclitaxel or docetaxel on PFS for all patients enrolled in the KEYNOTE-045 trial (18-Jan-2017 data cut off)

Study: P045[a]	Pembrolizumab			Control			Pembrolizumab vs. Control	
Progression Free Survival	N[b]	Patients with Event n (%)	Median Time[c] in Months [95 %-CI]	N[b]	Patients with Event n (%)	Median Time[c] in Months [95 %-CI]	Hazard Ratio[d] [95 %-CI]	p-Value for Interaction Test (I^2)
Choice of Investigator from paclitaxel or docetaxel								
Paclitaxel	94	74 (78.7)	2.1 [2.0; 3.3]	90	78 (86.7)	3.1 [2.1; 3.4]	0.96 [0.68; 1.37]	0.857 (0.00 %)
Docetaxel	94	75 (79.8)	2.1 [1.9; 2.2]	92	71 (77.2)	3.4 [2.2; 4.4]	1.01 [0.71; 1.43]	
a: Database Cutoff Date: 18JAN2017 b: Number of patients: intention-to-treat c: From product-limit (Kaplan-Meier) method d: Based on stratified Cox regression model with treatment as a covariate stratified by Eastern Cooperative Oncology								

Group (ECOG) Performance Scale (0/1 vs. 2), presence or absence of liver metastases, hemoglobin (>= 10 g/dL vs. <10 g/dL), and time from completion of most recent chemotherapy (<3 months or >=3 months).
CI: Confidence Interval.

Data Source: Checkpoint Responses[25]

Objective Response Rate

ORR was a secondary outcome in the trial and it was defined as the proportion of patients who had a complete response (CR) or partial response (PR).[1] ORR was assessed by BIRC and response rates were based on RECIST 1.1 criteria.[17] In the protocol, it is stated that stratified Miettinen and Nurminen's method with strata weighted by sample size were used for the comparison of ORRs between treatment groups.[17] Point estimates of ORR and corresponding 95% CIs were stratified by the randomization strata. It was reported in the protocol that the ORR estimates were adjusted for type 1 error.[17]

At the 7-Sept-2017 cut-off data, the ORR was significantly higher in the pembrolizumab group (21.1%, 95% CI: 16.4 to 26.5) than in the chemotherapy group (11.4%; 95% CI: 7.9 to 15.8, p=0.001).[1] Similar results were also reported for patients with a PD-L1 CPS ≥ 10% (Table 9). At the later data cut-off of 18-May-2017, the ORR was 21.1% for those treated with pembrolizumab and 11.0% for those treated with chemotherapy.[4] For patients with a PD-L1 CPS ≥ 10%, the ORR was 11.0% in the pembrolizumab group and 6.7% in the chemotherapy group.[4]

Table 9: Response rates for all patients and patients with a PD-L1 CPS ≥ 10% enrolled in the KEYNOTE-045 trial (7-Sept-2017 data cut off)

Variable	Total Population		CPS ≥10% Population	
	Pembrolizumab Group (N=270)	Chemotherapy Group (N=272)	Pembrolizumab Group (N=74)	Chemotherapy Group (N=90)
Objective response†				
No. of patients	57	31	16	6
% (95% CI)	21.1 (16.4 to 26.5)	11.4 (7.9 to 15.8)	21.6 (12.9 to 32.7)	6.7 (2.5 to 13.9)
Time to response,‡ months				
Median (range)	2.1 (1.4 to 6.3)	2.1 (1.7 to 4.9)	2.1 (1.4 to 5.3)	2.1 (1.9 to 2.2)
Duration of response,‡§ months				
Median (range)	NR (1.6+ to 15.6+)	4.3 (1.4+ to 15.4+)	NR (1.6+ to 15.4+)	4.4 (1.5+ to 10.8+)
Response ≥6 months	41 (78)	7 (40)	14 (93)	1 (40)
Response ≥12 months	14 (68)	3 (35)	3 (76)	0
Best overall response, no. (%)				
Complete response	19 (7.0)	9 (3.3)	5 (6.8)	2 (2.2)
Partial response	38 (14.1)	22 (8.1)	11 (14.9)	4 (4.4)
Stable disease	47 (17.4)	91 (33.5)	9 (12.2)	35 (35.6)
Progressive disease	131 (48.5)	90 (33.1)	37 (50.0)	38 (31.1)
Nonevaluable or no assessment	35 (13.0)	60 (22.1)	12 (16.2)	24 (26.7)

*The intention-treat population includes all patients who were randomly allocated to treatment. PD-L1 combined positive score (CPS) was defined as the percentage of tumor and infiltrating immune cells with PD-L1 expression out of the total number of tumor cells. Response was assessed by Response Evaluation Criteria in Solid Tumors, version 1.1, but blinded, independent, central radiology review.
†Objective response included patients with confirmed complete or partial response. The estimated difference between the pembrolizumab and chemotherapy groups, assessed using the stratified Miettinen and Nurminen's method, was 9.6 percentage points (95% CI, 3.5 to 15.9) (P=0.0011) in the total population and 19.3 percentage points (95% CI, 8.6-31.7) in the CPS ≥10% population.
The one-sided superiority threshold for pembrolizumab in the total population was P=0.0170. No alpha was allocated to the comparison of response rate in the CPS ≥10% population.
‡Time to and duration of response were assessed in patients who experienced an objective response.
§Duration of response was calculated using the Kaplan-Meier method. Plus signs in the ranges indicate that the response was ongoing at the time of data cutoff.
Data source: From N Engl J Med, Bellmunt J, de WR, Vaughn DJ, Fradet Y, Lee JL, Fong L, et al. Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carcinoma. . 2017 Mar 16 376(11):1015-26. Copyright © (2017) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[16]

Duration of Response

DOR was a secondary outcome and it was defined as the time from first documented evidence of CR or PR until disease progression or death for patients who had a CR or PR.[17] DOR was assessed by BIRC using RECIST 1.1 criteria. At the 19-May-2017 data cut-off, the median DOR had not been met in pembrolizumab arm (not reached [NR], 95% CI: 1.6+ to 24.6+) while it was 4.4 months (95% CI: 1.4+ to 24.0+) in the chemotherapy arm.[4] Similar results were observed for patients with a PD-L1 CPS ≥ 10%.[4]

Quality of Life

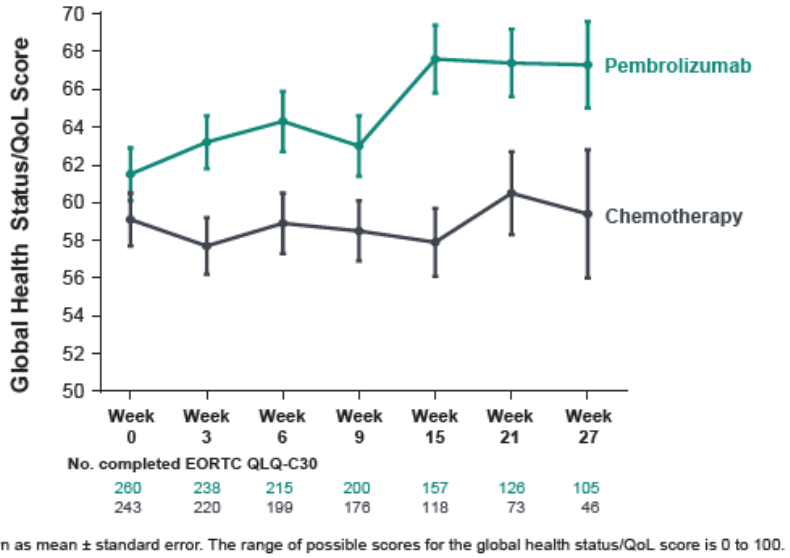
Patient-reported outcomes (PROs) were measured using the European Organization for Research and Treatment of Cancer (EORTC) QoL Questionnaire C30 (QLQ-C30) and European Quality of Life Five Dimensions Questionnaire (EQ-5D). Patients were included in the analysis if they received ≥ 1 dose of study treatment and completed ≥ 1 HRQoL questionnaire.[5]

PROs were measured at cycles 1, 2, 3, and 4 (i.e., at baseline and weeks 3, 6, and 9), then every 2 cycles (i.e., every 6 weeks) for up to 1 year or at end of treatment, whichever came first, and at the 30-day post-treatment discontinuation visit.[5] HRQoL was assessed at week 15. This pre-defined time point was chosen because the estimated median PFS and OS were projected to occur at 3-4 months and 7-8 months, respectively.[25] The Submitter stated that measuring HRQoL at week 15 would capture PROs with limited missing data but it may not be to representative of patients who were treated beyond week 15.[25]

Vaugh et al (2017) reported that the change from baseline was assessed using a mixed effects models and the missing data was assumed missing at random.[5] The score change from baseline was compared using a constrained longitudinal data analysis model stratified by randomization strata.[5] Furthermore, the authors noted that these results were not adjusted for type 1 error and should be interpreted with caution.[5]

HRQoL was measured as the change from baseline to week 15 using the EORTC QLQ-C30 global health status/QoL score (defined as a ≥10-point decrease).[5] In total, 95.9% of the trial population completed at least one EORTC QLQ-C30 questionnaire and received at least one study dose ($N_{pembrolizumab}$ = 266 and $N_{chemotherapy}$ = 254).[5] The baseline compliance and completion rates were high for both groups (pembrolizumab: 97.7% and chemotherapy: 95.7%). However, at week 15, both the compliance rates (pembrolizumab: 87.7% and chemotherapy: 88.1%) and completion rates (pembrolizumab: 59.0% and chemotherapy: 46.5%) decreased for both groups.[5]

Figure 7. EORTC QLQ-C30 global health status/QoL score by visit for all patients enrolled in the KEYNOTE-045 trial (7-Sept-2017 data cut off)



Data are shown as mean ± standard error. The range of possible scores for the global health status/QoL score is 0 to 100.

Data source: Vaugh et al (2017) ASCO[5]

At the 7-September-2016 data cut-off, the global health status/HRQoL score was similar for the pembrolizumab and chemotherapy arms at baseline. The results are presented in Table 10. Starting at week 3, the score was improved with pembrolizumab and a benefit was maintained through week 27 (Figure 7).[5] Patients in the pembrolizumab arm had better HRQoL at week 15 compared with patients in the chemotherapy group (least squares [LS] mean difference: 9.05 (4.61 to 13.48); nominal 2-sided P < 0.001). However, the MID was not met for the EORTC QLQ-C30 global health status /QoL Score (≥10-point decrease).[5]

Table 10. Change from baseline to week 15 in the EORTC QLQ-C30 global health status /QoL Score for all patients enrolled in KEYNOTE-045 (7-September-2016 data cut-off)

	Pembrolizumab	Chemotherapy
Baseline score, mean (SD)	n=260[a] 61.1 (23.1)	n=243[a] 59.1 (22.1)
Week 15 score, mean (SD)	n=157[a] 67.6 (22.6)	n=118[a] 57.9 (19.5)
Change from baseline to week 15, LS mean (95% CI)[c]	n=266[6] +0.75 (-2.34 to +3.83)	n=254[b] -8.30 (-11.76 to -4.83)
Difference in LS means (95% CI)	9.05 (4.61 to 13.48) P <0.001	

[a]Number of patients in each arm who completed the EORTC QLQ-C30 at that timepoint
[b]Number of patients in the total HRQoL analysis population
[c]Based on a constrained longitudinal a data analysis model with the global health status/QoL score as the response variable, treatment by study visit interaction, and stratification by the randomization stratification (ie. ECOG performance status 0/1 vs 2, presence vs absence of liver metastases, hemoglobin >= g/dL vs <10g/dL, and time from completion of most recent chemotherapy >3 months vs <3 months).

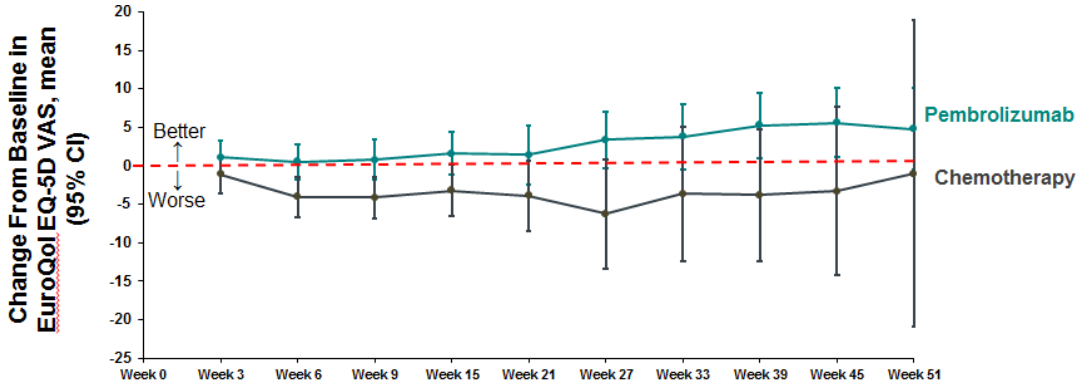
Data source: Vaugh et al (2017) ASCO[5]

The protocol stated that the EQ-5D visual analog scale (VAS) and EQ-5D utility index would also be measured along with the EORTC QLQ-C30 instrument. However, these results were not presented in the Vaugh et al (2017) ASCO poster[5] but they have been presented in NICE and were provided by the Submitter at Checkpoint.[3,25]

In total, 96.7% of the trial population completed at least one EQ-5D questionnaire and received at least one study dose ($N_{pembrolizumab}$ = 266 and $N_{chemotherapy}$ = 254).[3] The baseline compliance and completion rates were high for both groups (pembrolizumab: 97.7% and chemotherapy: 95.7%).[3] As observed

previously, the compliance rates (pembrolizumab: 87.7% and chemotherapy: 88.1%) decreased for both groups at week 15.[3]

Figure 8. Change from baseline in EuroQol EQ-5D VAS by visit for all patients enrolled in the KEYNOTE-045 trial (7-Sept-2017 data cut off)

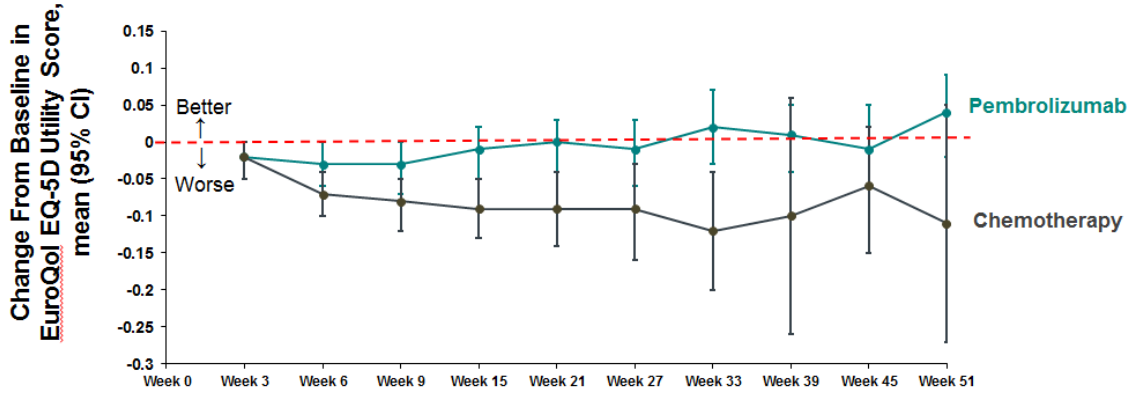


Pembrolizumab	260	232	210	195	153	124	104	83	75	61	54
Chemotherapy	242	208	190	167	111	67	43	26	12	11	7

Data source: Checkpoint Responses[25]

The EQ-5D VAS score was similar for the pembrolizumab and chemotherapy arms at baseline (Figure 8).[25] Similar to EORTC QLQ-C30, the EQ-5D score was improved with pembrolizumab at week 3 and a benefit was maintained through week 27.[25] Patients treated with pembrolizumab had an improved EQ-5D at week 15 as compared to those treated with chemotherapy (LS mean difference, 6.45 (95% CI: 2.75 to 10.16); nominal 2-sided P < 0.001). Although there was a statistically significant difference in the change from baseline to week 15, the MID (i.e. ≥7 points for the visual analogue scale score) was not reached.[25] The change from baseline in EQ-5D utility score using the European Algorithm was also assessed at week 15. The results are represented in Figure 9. At week 15, there was a significant difference in the change from baseline between pembrolizumab and chemotherapy (0.07 [95% CI: 0.03 to 0.12]; nominal 2-sided P = 0.002).[25] The MID for the EQ-5D utility score was not reached (MID: ≥0.08 points).

Figure 9. Change from baseline in EQ-5D utility score using the European Algorithm by visit for all patients enrolled in the KEYNOTE-045 trial (7-Sept-2017 data cut off)



Pembrolizumab	260	232	210	195	153	124	104	83	75	61	54
Chemotherapy	242	208	190	167	111	67	43	26	12	11	7

Data source: Checkpoint Responses[25]

Harms Outcomes

The safety set in KEYNOTE-045 consisted of patients who had received at least one dose of the study treatment. In total, there were 521 patients in the safety set, with 266 patients in the pembrolizumab group and 255 patients in the chemotherapy group.[1]

Study Exposure
At the 7-Sept-2016 data cut-off, the median duration of therapy for patients in the pembrolizumab group was 3.45 months (range: 0.03 to 20.04) and 1.54 months (range: 0.03 to 14.19) in the chemotherapy group.[3] Among those in the chemotherapy arm, the median duration of therapy was longer for patients treated with vinflunine (2.10 months [range: 0.03 to 12.02]) as compared to those treated with paclitaxel (1.45 months [range: 0.03 to 14.19]) or docetaxel (1.43 months [range: 0.03 to 10.48]).[3]

Deaths
At the 7-Sept-2016 cut-off, one patient died from treatment-related pneumonitis while three deaths were attributed to the study treatment by the investigator.[1] These deaths included urinary tract infection, malignant neoplasm progression and unspecified cause. On the other hand, in the chemotherapy group, four treatment-related deaths occurred, and included: sepsis (N = 2), septic shock (N =1) and unspecified cause (N =1).[1] No additional deaths were reported at the 19-May-2017 data cut-off.[4]

Adverse Events
Treatment-related AEs (TRAEs) occurred in 60.9% of the patients in the pembrolizumab group versus 90.2% of those in the chemotherapy group (Table 11).[1] Treatment-related grade 3 to 5 AEs were less frequent in the pembrolizumab group (15.0%) compared to chemotherapy (49.4%)[1]. The most common TRAEs of any grade in the pembrolizumab group were pruritus (19.5%), fatigue (13.9%), and nausea (10.9%). The most common TRAEs in the chemotherapy group were alopecia (37.6%), fatigue (27.8%), and anemia (24.7%). Similar trends were observed at the 19-May-2017 data cut-off.[4]

Table 11: Adverse events for all patients enrolled in the KEYNOTE-045 trial (7-Sept-2017 data cut off)

Table 2. Adverse Events in the As-Treated Population.*

Event	Pembrolizumab Group (N=266)		Chemotherapy Group (N=255)	
	Any Grade	Grade 3, 4, or 5	Any Grade	Grade 3, 4, or 5
	number of patients (percent)			
Treatment-related event†				
Any event	162 (60.9)	40 (15.0)	230 (90.2)	126 (49.4)
Event leading to discontinuation of treatment	15 (5.6)	12 (4.5)	28 (11.0)	16 (6.3)
Event leading to death	4 (1.5)	4 (1.5)	4 (1.6)	4 (1.6)
Event occurring in ≥10% of patients in either group‡				
Pruritus	52 (19.5)	0	7 (2.7)	1 (0.4)
Fatigue	37 (13.9)	3 (1.1)	71 (27.8)	11 (4.3)
Nausea	29 (10.9)	1 (0.4)	62 (24.3)	4 (1.6)
Diarrhea	24 (9.0)	3 (1.1)	33 (12.9)	2 (0.8)
Decreased appetite	23 (8.6)	0	41 (16.1)	3 (1.2)
Asthenia	15 (5.6)	1 (0.4)	36 (14.1)	7 (2.7)
Anemia	9 (3.4)	2 (0.8)	63 (24.7)	20 (7.8)
Constipation	6 (2.3)	0	52 (20.4)	8 (3.1)
Peripheral sensory neuropathy	2 (0.8)	0	28 (11.0)	5 (2.0)
Neutrophil count decreased	1 (0.4)	1 (0.4)	36 (14.1)	31 (12.2)
Peripheral neuropathy	1 (0.4)	0	27 (10.6)	2 (0.8)
Neutropenia	0	0	39 (15.3)	34 (13.3)
Alopecia	0	0	96 (37.6)	2 (0.8)
Event of interest§				
Any event	45 (16.9)	12 (4.5)	19 (7.5)	4 (1.6)
Hypothyroidism	17 (6.4)	0	3 (1.2)	0
Hyperthyroidism	10 (3.8)	0	1 (0.4)	0
Pneumonitis	11 (4.1)	6 (2.3)	1 (0.4)	0
Colitis	6 (2.3)	3 (1.1)	1 (0.4)	0
Infusion reaction	2 (0.8)	0	10 (3.9)	0
Nephritis	2 (0.8)	2 (0.8)	0	0
Severe skin reaction	2 (0.8)	1 (0.4)	3 (1.2)	3 (1.2)
Thyroiditis	2 (0.8)	0	0	0
Adrenal insufficiency	1 (0.4)	1 (0.4)	0	0
Myositis	0	0	1 (0.4)	1 (0.4)

* The as-treated population included all the patients who received at least one dose of study treatment.
† Events were attributed to treatment by the investigator and are listed as indicated by the investigator on the case-report form. Although decreased neutrophil count and neutropenia may reflect the same condition, they were listed by the investigators as two distinct events; this was also the case for peripheral sensory neuropathy and peripheral neuropathy and for fatigue and asthenia.
‡ Events are listed in descending order of frequency in the pembrolizumab group.
§ The events of interest are those with an immune-related cause and are considered regardless of attribution to study treatment by the investigator. They are listed in descending order of frequency in the pembrolizumab group. In addition to the specific preferred terms listed, related terms were also included.

Data source: From N Engl J Med, Bellmunt J, de WR, Vaughn DJ, Fradet Y, Lee JL, Fong L, et al. Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carcinoma. . 2017 Mar 16 376(11):1015-26. Copyright © (2017) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[1]

Serious Adverse Events
At the second interim analysis, more treatment-emergent SAE occurred in the chemotherapy group (22.4%) as compared to the pembrolizumab group (10.2%).[3]

Dose modification, reductions, delays or discontinuations
More patients in the chemotherapy arm (12.5%) had an adverse event that led to a dose discontinuation as compared to those in the pembrolizumab group (8.3%).[20] Similar results were observed at the 19-May-2017 data cut-off.[4]

Adverse Events of Special Interest
Adverse events of special interest were defined as immune-mediated events and/or infusion-related reactions that were related to pembrolizumab.[3] More IMAEs occurred in the pembrolizumab group as compared to the chemotherapy group (16.9% vs. 7.5%) (Table 11).[1] de Wit et al (2017) reported similar rates of IMAEs at the 19-May-2017 data cut-off.[4] For instance, the most common IMAEs that occurred were hypothyroidism (pembrolizumab: 6.4 % and chemotherapy: 1.2%), pneumonitis (pembrolizumab: 4.1 % and chemotherapy: 0.4%), hyperthyroidism (pembrolizumab: 3.8% and chemotherapy: 0.4%) and colitis (pembrolizumab: 2.3 % and chemotherapy: 0.4%). However, more severe skin reactions occurred in the chemotherapy group than the pembrolizumab arm (pembrolizumab: 0.8% and chemotherapy: 1.2%). The Submitter reported that among 266 patients in the pembrolizumab group, 10 discontinued due to IMAEs (nephritis n=1; pneumonitis n=9).[25]

6.4 Ongoing Trials

No ongoing trials were identified.

7 SUPPLEMENTAL QUESTIONS

No supplemental questions were identified.

8 COMPARISON WITH OTHER LITERATURE

No comparisons with other literature were identified.

9 ABOUT THIS DOCUMENT

This Clinical Guidance Report was prepared by the pCODR Genitourinary Clinical Guidance Panel and supported by the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding the clinical evidence available on Pembrolizumab (Keytruda) for Metastatic Urothelial Carcinoma. Issues regarding resource implications are beyond the scope of this report and are addressed by the relevant pCODR Economic Guidance Report. Details of the pCODR review process can be found on the CADTH website (www.cadth.ca/pcodr).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report was handled in accordance with the pCODR Disclosure of Information Guidelines

This Final Clinical Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Clinical Guidance Report supersedes the Initial Clinical Guidance Report. Note that no revision was made in between posting of the Initial and Final Clinical Guidance Reports.

The Genitourinary Clinical Guidance Panel is comprised of three medical oncologists. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package, which is available on the CADTH website (www.cadth.ca/pcodr). Final selection of the Clinical Guidance Panels was made by the pERC Chair in consultation with the pCODR Executive Director. The Panel and the pCODR Methods Team are editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

APPENDIX A: LITERATURE SEARCH STRATEGY AND DETAILED METHODOLOGY

1. Literature search via OVID platform

Database(s): **EBM Reviews - Cochrane Central Register of Controlled Trials** July 2017**, Embase** 1974 to 2017 August 07**, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)** 1946 to Present

Search Strategy:

#	Searches	Results
1	(pembrolizumab* or lambrolizumab* or keytruda* or MK-3475 or MK3475 or Merck3475 or Merck-3475 or Sch-900475 or Sch900475 or 1374853-91-4 or DPT0O3T46P).ti,ab,ot,kf,hw,rn,nm.	5378
2	Carcinoma, Transitional Cell/	27565
3	((transitional cell or urothelial) adj5 (cancer* or neoplasm* or tumor* or tumour* or malignan* or carcinoma* or adenocarcinoma*)).ti,ab,kf.	48167
4	urinary bladder neoplasms/ or Ureteral Neoplasms/ or Urethral Neoplasms/	67608
5	((bladder or vesical or urothelium or urinary or ureter* or urethra* or urachus) adj5 (cancer* or neoplasm* or tumor* or tumour* or malignan* or carcinoma*)).ti,ab,kf.	142127
6	or/2-5	173084
7	1 and 6	273
8	limit 7 to english language	249
9	8 use ppez	48
10	8 use cctr	21
11	9 or 10	69
12	*pembrolizumab/	1058
13	(pembrolizumab* or lambrolizumab* or keytruda* or MK-3475 or MK3475 or Merck3475 or Merck-3475 or Sch-900475 or Sch900475).ti,ab,kw.	3132
14	12 or 13	3255
15	transitional cell carcinoma/	40357
16	((transitional cell or urothelial) adj5 (cancer* or neoplasm* or tumor* or tumour* or malignan* or carcinoma* or adenocarcinoma*)).ti,ab,kw.	48593
17	exp bladder cancer/ or urinary tract cancer/ or exp ureter cancer/ or exp urethra cancer/ or exp urinary tract carcinoma/	135402

18	((bladder or vesical or urothelium or urinary or ureter* or urethra* or urachus) adj5 (cancer* or neoplasm* or tumor* or tumour* or malignan* or carcinoma*)).ti,ab,kw.	142631
19	or/15-18	189757
20	14 and 19	216
21	20 use oemezd	137
22	21 and conference abstract.pt.	55
23	limit 22 to yr="2012 -Current"	55
24	limit 23 to english language	55
25	21 not 22	82
26	11 or 25	151
27	limit 26 to english language	142
28	remove duplicates from 27	108
29	24 or 28	163

2. Literature search via PubMed

A limited PubMed search was performed to capture records not found in MEDLINE.

Search	Add to builder	Query	Items found
#15	Add	Search **(#13) AND #14**	4
#14	Add	Search **publisher[sb]**	523731
#13	Add	Search **(#9) AND #12**	51
#12	Add	Search **(#10) OR #11**	106221
#11	Add	Search **urinary bladder neoplasms[mh] OR Ureteral Neoplasms[mh] OR Urethral Neoplasms[mh] OR ((bladder[tiab] OR vesical[tiab] OR urothelium[tiab] OR urinary[tiab] OR ureter*[tiab] OR urethra*[tiab] OR urachus[tiab]) AND (cancer*[tiab] OR neoplasm*[tiab] OR tumor*[tiab] OR tumour*[tiab] OR malignan*[tiab] OR carcinoma*[tiab]))**	102086
#10	Add	Search **"Carcinoma, Transitional Cell"[Mesh] OR transitional cell carcinoma[tiab] OR urothelial carcinoma[tiab] OR urothelial cell carcinoma[tiab] OR ((transitional cell[tiab] OR urothelial[tiab]) AND (cancer*[tiab] OR neoplasm*[tiab] OR tumor*[tiab] OR tumour*[tiab] OR malignan*[tiab] OR carcinoma*[tiab]))**	27319
#9	Add	Search **pembrolizumab [Supplementary Concept] OR 1374853-91-4[rn] OR DPT0O3T46P[rn] OR pembrolizumab*[tiab] OR lambrolizumab*[tiab] OR keytruda*[tiab] OR MK-3475[tiab] OR MK3475[tiab] OR Merck-3475[tiab] OR Merck3475[tiab] OR Sch-900475[tiab] OR Sch900475[tiab]**	969

3. Cochrane Central Register of Controlled Trials (Central)

Searched via Ovid

4. **Grey Literature search via:**

Clinical trial registries:

U.S. NIH ClinicalTrials.gov
http://www.clinicaltrials.gov/

Canadian Partnership Against Cancer Corporation. Canadian Cancer Trials
http://www.canadiancancertrials.ca/

Search: pembrolizumab/Keytruda, urothelial carcinoma

Select international agencies including:

Food and Drug Administration (FDA):
http://www.fda.gov/

European Medicines Agency (EMA):
http://www.ema.europa.eu/

Search: pembrolizumab/Keytruda, urothelial carcinoma

Conference abstracts:

American Society of Clinical Oncology (ASCO)
http://www.asco.org/

European Society for Medical Oncology (ESMO)
http://oncologypro.esmo.org/

Search: pembrolizumab/Keytruda, urothelial carcinoma - last 5 years

Literature Search Methods

The literature search was performed by the pCODR Methods Team using the search strategy provided in Appendix A.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-) with in-process records & daily updates via Ovid; Embase (1974-) via Ovid; The Cochrane Central Register of Controlled Trials (July 2017) via Ovid; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Keytruda (pembrolizumab) and urothelial carcinoma.

No filters were applied to limit the retrieval by study type. The search was also limited to English-language documents, but not limited by publication year.

The search is considered up to date as of Nov 2, 2017.

Grey literature (literature that is not commercially published) was identified by searching the websites of regulatory agencies (Food and Drug Administration and European Medicines Agency), clinical trial registries (U.S. National Institutes of Health – clinicaltrials.gov and

Canadian Partnership Against Cancer Corporation - Canadian Cancer Trials), and relevant conference abstracts. Conference abstracts were retrieved through a search of the Embase database limited to the last five years. Abstracts from the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) were searched manually for conference years not available in Embase. Searches were supplemented by reviewing the bibliographies of key papers and through contacts with the Clinical Guidance Panel. In addition, the manufacturer of the drug was contacted for additional information as required by the pCODR Review Team.

Study Selection

One member of the pCODR Methods Team selected studies for inclusion in the review according to the predetermined protocol. All articles considered potentially relevant were acquired from library sources. Two members of the pCODR Methods Team independently made the final selection of studies to be included in the review and differences were resolved through discussion.

Included and excluded studies (with reasons for exclusion) are identified in section 6.3.1.

Quality Assessment

Assessment of study bias was performed by one member of the pCODR Methods Team with input provided by the Clinical Guidance Panel and other members of the pCODR Review Team. SIGN-50 Checklists were applied as a minimum standard. Additional limitations and sources of bias were identified by the pCODR Review Team.

Data Analysis

No additional data analyses were conducted as part of the pCODR review.

Writing of the Review Report

This report was written by the Methods Team, the Clinical Guidance Panel and the pCODR Secretariat:

- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental questions.
- The pCODR Clinical Guidance Panel wrote a summary of background clinical information and the interpretation of the systematic review. The Panel provided guidance and developed conclusions on the net clinical benefit of the drug.
- The pCODR Secretariat wrote summaries of the input provided by patient advocacy groups, by the Provincial Advisory Group (PAG), and by Registered Clinicians.

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