pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Pembrolizumab (Keytruda) for Metastatic Urothelial Carcinoma (first line)

October 3, 2019

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List of Abbreviations

AE	Adverse event
APT	All-patients-treated
BICR	BICR
CGP	Clinical Guidance Panel
CI	Confidence interval
CPS	Combined positive score
CR	Complete response
DCR	Disease control rate
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
EGP	Economic Guidance Panel
EORTC QLQ-C30	European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire
EQ-5D-3L	European Quality of Life Five Dimensions Questionnaire 3 Levels
HR	Hazard ratio
HRQoL	Health related quality of life
IPD	individual patient data
IRR	Independent Radiology Review
KPS	Karnofsky Performance Score
MUC	Metastatic urothelial carcinoma
NMA	Network meta-analysis
ORR	Objective response rate
NR	Not reached
OS	Overall survival
PAG	Provincial Advisory Group
pCODR	pan-Canadian Oncology Drug Review
PD-L1	Programmed death-ligand 1
pERC	pan-Canadian Oncology Drug Review Expert Review Committee
PFS	Progression-free survival
PR	Partial response
RCT	randomized controlled trial
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SD	Stable disease
STC	Stimulated treatment comparison
WDAE	Withdrawals due to adverse events

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 locally advanced or 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 locally advanced or metastatic urothelial carcinoma conducted by 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 Sections 6 and 7. A background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input on pembrolizumab (Keytruda) for locally advanced or metastatic urothelial carcinoma, a summary of submitted Provincial Advisory Group Input on pembrolizumab (Keytruda) for locally advanced or metastatic urothelial carcinoma, and a summary of submitted Registered Clinician Input on pembrolizumab (Keytruda) for locally advanced or 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 monotherapy in patients with locally advanced or metastatic urothelial carcinoma (MUC) who are not eligible for cisplatin-containing chemotherapy and whose tumours express programmed death-ligand 1 (PD-L1) [Combined Positive Score (CPS) ≥10] as determined by a validated test, or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status.

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. Pembrolizumab has been issued a Health Canada marketing authorization with conditions, pending the results of trials to verify its clinical benefit. The Health Canada indication reflects the requested patient population for reimbursement: pembrolizumab is indicated as monotherapy for the treatment of adults with locally advanced unresectable or metastatic urothelial carcinoma, who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 [Combined Positive Score (CPS) ≥10] as determined by a validated test, or in adults who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status.

The recommended dose of pembrolizumab is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression, unacceptable toxicity or up to 24 months in patients without disease progression.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

The pCODR systematic review included one single-arm, open-label, phase II trial (KEYNOTE-052) that assessed the safety and efficacy of pembrolizumab as a first-line therapy in 374 cisplatin-ineligible patients with locally advanced and unresectable or metastatic urothelial cancer (MUC).[1]

It is important to highlight that the pCODR requested reimbursement criteria are for two subgroups within the KEYNOTE-052 trial: (1) patients with PD-L1 CPS ≥ 10 who are cisplatin ineligible, and (2) patients who are ineligible to receive any platinum chemotherapy, irrespective of the PD-L1 status. This pCODR review will present the results for the overall trial population as well for the two subgroups specified in the funding request.

Patients were eligible for enrollment if they met the following criteria: 18 years of age or older; histologically or cytologically confirmed locally advanced and unresectable or MUC of the renal pelvis, ureter, bladder, or urethra; were ineligible for cisplatin-based therapy (defined as meeting at least one of the following criteria: Eastern Cooperative Oncology Group [ECOG] performance status 2, creatinine clearance 30–60 mL/min, grade ≥2 audiometric hearing loss, grade ≥2 peripheral neuropathy, or New York Heart Association Class III heart failure); had not previously received systemic chemotherapy for advanced disease (perioperative, platinum-based chemotherapy with disease recurrence >12 months since completion was allowed); had centrally confirmed and measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1); had an ECOG performance status of 0 to 2; had adequate organ function.[2]

All patients who were enrolled in the trial were treated with a 200 mg dose of pembrolizumab every three weeks (Q3W). Patients were treated with pembrolizumab until RECIST-confirmed disease progression, intolerable toxic effects, doctor or patient decision to withdraw, inter-current illness preventing further treatment, confirmed pregnancy, non-compliance with trial procedures, loss to follow up, or completion of 24 months of treatment.[2] Clinically stable patients with progressive disease who were deriving benefit from pembrolizumab could remain on treatment until subsequent progression at the investigator's discretion. Patients receiving pembrolizumab who attained a complete response and had been on treatment for at least 24 weeks could discontinue treatment. Patients who stopped study treatment after 24 months, for reasons other than progressive disease or intolerability, or participants who attained a complete response and stopped study treatment, were eligible for up to one year of retreatment upon experiencing progressive disease.[2]

The primary outcome in the trial was objective response rate (ORR) as assessed by an independent radiology review (IRR) using RECIST 1.1. Secondary outcomes included: duration of response (DOR) as assessed by an IRR using RECIST 1.1, overall survival (OS) and progression free survival (PFS) as assessed by an IRR using RECIST 1.1 and safety outcomes. Exploratory outcomes included health-related quality of life (HRQoL).[2]

Efficacy analyses were performed in all patients who had more than one dose of pembrolizumab.[2] Overall, the efficacy results are provided for all patients (N=370) and a subgroup of patients who had a PD-L1 CPS ≥1% (N=282) or a PD-L1 CPS ≥10% (N=80). In the trial, PD-L1 expression levels were measured in formalin-fixed, paraffin-embedded tissues using a PD-L1 clinical trial assay (PD-L1 IHC 22C3 pharmDx assay; Agilent Technologies, Carpinteria, CA, USA).[1] PD-L1 expression levels were scored using a CPS, which was defined as the percentage of cells (i.e., tumour cells, macrophages, or lymphocytes) that expressed PD-L1 in a tumour biopsy.[1] The Submitter also performed a post-hoc subgroup analysis in patients who are considered platinum ineligible (N = 145). Here, patients were considered platinum ineligible if they had an ECOG performance status of 2 and one or more of visceral metastasis, advanced age (≥ 80 years) or GFR < 60 mL/min.

Four data cut-offs were identified in the pCODR systematic review, which include: 01-Sep-2016, 09-Mar-2017, 30-Nov-2017 and 26-Sep-2018. For the purpose of this review, the results of the 30-Nov-2017 database lock were presented, which represents a median follow-up of 11.5 months and aligns with the data cut used for the analyses in the economic model, which was submitted to pCODR as part of this submission.[3] However, where available, data from the 01-Sep-2016 and the 26-Sep-2018 data cut-offs were also be presented, which represents a median follow-up ranging

from 5 months (interquartile range: 3.0 to 8.6) to a mean follow-up of 15.3 months (standard deviation: 12.1).[1,4]

The sample size was based on the primary efficacy estimation of PD-L1 strongly positive patients. With a sample size of 350 patients it was assumed that 33% of patients would have a strongly positive PD-L1 expression level and that there would be 100 patients in the biomarker discovery population (discovery population was used to assess the potential for a high PD-L1 expression cutpoint). Therefore, there would be an 88% chance to have at least 75 patients with a strongly positive PD-L1 expression level and a 99.9% chance to have at least 60 patients with a strongly positive PD-L1 expression level from the validation cohort (mutually exclusive from the biomarker discovery population; N = 250).[1,2] A protocol amendment on 11-Mar-2016 was made to reflect the transition of the pembrolizumab clinical trial programme away from hypothesis testing for the primary objectives towards an estimation for single-arm clinical trials.[1] Thus, hypothesis testing was not performed and the original sample size was not adjusted.

The majority of patients enrolled in the trial had a mean age of 73 years (standard deviation: 9.9), were male (77.3%), were white (88.6%) and had an ECOG performance stage of 1 (35.9%) or 2 (42.2%).[5] In addition, the main reasons for cisplatin ineligibility were renal dysfunction (49.2%) and ECOG performance status 2 (32.4%).[5]

Efficacy

Objective Response Rate

At the 01-Sep-2016 data cut-off, the ORR as assessed by IRR using RECIST 1.1 for all patients was 24% (95% CI: 20% to 29%; N = 89).[1] The ORR as assessed by IRR using RECIST 1.1 was 29.1% (95% CI: 24.3% to 33.8%) at the 30-Nov-2017 data cut-off (Table 1.1).[3] The ORR as assessed by IRR using RECIST 1.1 was 28.6% (95% CI: 24.1% to 33.5%) at the 26-Sep-2018 data cut-off.[4]

For patients with a PD-L1 CPS ≥ 1%, the ORR as assessed by IRR using RECIST 1.1 was 32.6% (95% CI: 27.2 to 38.4; N = 92) at the 01-Sep-2016 data cut-off.[6] Similar estimates were observed at the 30-Nov-2017 data cut-off (Table 1.1).[7] The ORR for patients with a PD-L1 CPS ≥ 1% was not reported at the 26-Sep-2018 data cut-off.

At the 01-Sep-2016 data cut-off, the ORR as assessed by IRR using RECIST 1.1 for patients with a PD-L1 CPS ≥ 10% was 38.2% (95% CI: 29.1 to 47.9; N = 42).[6] The ORR as assessed by IRR using RECIST 1.1 was 47.3% (95% CI: 37.7 to 57.0) for patients with a PD-L1 CPS ≥ 10% at the 30-Nov-2017 data cut-off (Table 1.1).[7] Similar estimates were observed at the 26-Sep-2018 data cut-off.[4]

At the 30-Nov-2017 data cut-off, the ORR as assessed by IRR using RECIST 1.1 for platinum ineligible patients was 26.2% (95% CI: 19.3 to 34.2) (Table 1.1).[9] The ORR as assessed by IRR using RECIST 1.1 for platinum ineligible patients was not reported at the 01-Sep-2016 and the 26-Sep-2018 data cut-offs.

In their feedback on the initial recommendation, the Submitter suggested that there is a strong suggestion that ORR acts as a surrogate outcome for OS in patients treated with PD-1 inhibitors. To support this position, the Submitter referred to two articles, which reported that patients treated with a PD-1 inhibitor (i.e., pembrolizumab or nivolumab) and who achieved a complete or partial response had a better OS as compared to patients with no tumour response [Fradet et al, 2018[44] and El-Khoudry et al, 2017[43]]. In response to the Submitter's feedback, the pCODR Methods Team noted that the analyses provided by the Submitter may not provide sufficient statistical evidence to validate ORR as a surrogate outcome for OS [Fradet et al. (2018) [44] and El-Khourdry et al. (2017)[43]]. For instance, Buyse (2011)[42] stated that a surrogate outcome must demonstrate an

"individual-level" and a "trial-level" association using a meta-analytic/correlation approach.[42] Here, the surrogate outcome must be tightly correlated with the true endpoint and the treatment effect on the surrogate outcome must be tightly correlated with the treatment effect on the true endpoint. The pCODR Methods Team also commented that there were several differences between the KEYNOTE-052 trials and the two trials that were reported in the analyses by Fradet et al (2018)[44] (KEYNOTE-045) and El-Khoudry et al. (2017)[43] (CheckMate-040). First, there were differences in the trial designs. The KEYNOTE-052 trial was a single-arm phase II study while the KEYNOTE-052 trial was a randomized phase III trial and the CheckMate-040 trial was a non-comparative phase 1/2 study. Second, there were differences in patient characteristics. In the KEYNOTE-052 trial, patients were not allowed to have had any prior systemic chemotherapy for advanced/unresectable (inoperable) or metastatic urothelial cancer and had to be cisplatin-ineligible at enrolment while patients in the KEYNOTE-045 trial had to have progressive or recurrent disease after a first-line platinum-containing regimen (i.e., cisplatin, carboplatin) with the majority of patients entering the trial after having received prior cisplatin-based chemotherapy. In contrast, the CheckMate-040 trial included patients with hepatocellular carcinoma. Additionally, patients in the KEYNOTE-045 trial had overall lower ECOG performance status than patients enrolled in the KEYNOTE-052 trial. Notably, 42.2% of patients in the KEYNOTE-052 trial had an ECOG performance status of 2 as compared to less than 2% of patients in the KEYNOTE-045 trial. Thus, the results of the KEYNOTE-045 and CheckMate-040 trials may not be generalizable to the patient population of the KEYNOTE-052 trial. Finally, the pCODR Methods Team noted that there may be other limitations to take into consideration. For instance, the subgroup analyses for OS performed by El-Khoudry et al. (2017)[43] were reported to be exploratory and the updated subgroup analyses of OS (data cut: Oct 26, 2017) reported by Fradet et al (2018)[44] did not appear to be pre-specified in the protocol[22], and therefore, it is unclear whether the analysis was adjusted for multiplicity or adequately powered. The pCODR Methods Team concluded that given the above considerations it is challenging to confirm the appropriateness of ORR as a surrogate outcome for OS in the target patient population of the present reimbursement request.

Duration of Response

At the 01-Sep-2016 and the 30-Nov-2017 data cut-offs, the median DOR as assessed by IRR using RECIST 1.1 was not reached. The median DOR as assessed by IRR using RECIST 1.1 was 30.1 (95% CI: 18.8 to NR) at the 26-Sep-2018 data cut-off.[4]

The median DOR as assessed by IRR using RECIST 1.1 was not reported for patients with a PD-L1 CPS ≥ 1% or a PD-L1 CPS ≥ 10% at the 01-Sep-2016 data cut-off and it was not reached at the 30-Nov-2017 data cut-offs.[7] The median DOR as assessed by IRR using RECIST 1.1 for patients with a PD-L1 CPS ≥ 1% was not reported at the 26-Sep-2018 data cut-off. The median DOR as assessed by IRR using RECIST 1.1 for patients with a PD-L1 CPS ≥ 10% was not reached (95% CI: 18.1 to NR) at the 26-Sep-2018 data cut-off.[4]

In their feedback on the initial recommendation, the Submitter noted that in the Initial Clinical Guidance Report an incorrect median DOR of 2.1 months for the platinum ineligible subgroup was considered by pERC. The Submitter clarified that the accurate median DOR for this patient subgroup was not reached (range: 2.8, 27.6+ months). The pCODR Methods Team acknowledged the error and has corrected the DOR for the platinum ineligible patient subgroup in the following:

The median DOR as assessed by IRR using RECIST 1.1 was not reached (range: 2.8 to 27.6+ months) for patients who were platinum ineligible at the 30-Nov-2017 data cut-off.[45]

Overall Survival

At the 01-Sep-2016 data cut-off, 35.1% of patients had died (N = 130) and the median OS was 10.9 months (95% CI: 9.7 to NR).[6] At the 30-Nov-2017 data cut-off, 66.8% of patients had died (N = 247) and the median OS was 11.5 months (95% CI: 10.0 to 13.3) (Table 1.1).[3] Similar results were observed at the 26-Sep-2018 data cut-off.[4]

At the 01-Sep-2016 data cut-off, 30.1% of patients with a PD-L1 CPS ≥ 1% had died (N = 85) and the median OS was 11.6 months (95% CI: 10.1 to NR).[6] For those with a PD-L1 CPS ≥ 10%, 22.5% patients had died (N = 18) and the median OS was NR (95% CI: 8.4 to NR).[6] At the 30-Nov-2017 data cut-off, 63.5% of patients with a PD-L1 CPS ≥ 1% had died (N = 179) and the median OS was 12.5 months (95% CI: 10.8 to 15.1) (Table 1.1).[7] For those with a PD-L1 CPS ≥ 10%, 51.8% patients had died (N = 57) and the median OS was 18.5 months (95% CI: 12.2 to NR).[7] The median OS was not reported for patients with a PD-L1 CPS ≥ 1% at the 26-Sep-2018 data cut-off. The median OS for patients with a PD-L1 CPS ≥ 10% was 18.5 months (95% CI: 12.2 to 28.5) at the 26-Sep-2018 data cut-off.[4]

At the 30-Nov-2017 data cut-off, 74.5% of the platinum ineligible patients had died (N = 108) and the median OS was 9.2 months (95% CI: 5.3 to 11.3) (Table 1.1).[8] It was not reported at the 01-Sep-2016 or 26-Sep-2018 data cut-off.

Progression-Free Survival

At the 01-Sep-2016 data cut-off, 67.0% of patients had progressed or died (N = 248) and the median PFS as assessed by IRR using RECIST 1.1 was 2.1 months (95% CI: 2.1 to 3.0).[6] Similar results were reported at the 30-Nov-2017 data cut-off (Table 1.1)[3] and the 26-Sep-2018 data cut-off.[4]

In a Checkpoint Response, the Submitter provide the number of patients who were treated beyond progression and the type of medications they received at the 30-Nov-2017 data cut-off.[7] Overall, there were 246 patients with disease progression and 41.9% of these patients were treated beyond progression. Among these patients, the majority were treated with either carboplatin (26.4%) or gemcitabine (33.3%). [7]

At the 01-Sep-2016 data cut-off, 62.8% of patients with a PD-L1 CPS ≥ 1% had progressed or died (N = 177) and the median PFS as assessed by IRR using RECIST 1.1 was 3.0 months (95% CI: 2.1 to 3.5).[6] For those with a PD-L1 CPS ≥ 10%, 46.3% patients had progressed or died (N = 37) and the median PFS as assessed by IRR using RECIST 1.1 was 4.9 months (95% CI: 3.5 to NR).[6] Similar results were reported at the 30-Nov-2017 data cut-off (Table 1.1).[3] The median PFS as assessed by IRR using RECIST 1.1 was not reported for patients with a PD-L1 CPS ≥ 1% or a PD-L1 CPS ≥ 10% at the 26-Sep-2018 data cut-off.

Overall, 82.8% of platinum ineligible patients had progressed or died (N = 120) and the median PFS as assessed by IRR using RECIST 1.1 was 2.1 months (95% CI: 2.0 to 2.8) at the 30-Nov-2017 data cut-off (Table 1.1).[8] It was not reported at the 01-Sep-2016 or 26-Sep-2018 data cut-off.

Quality of Life

Patient-reported outcomes (PROs) were exploratory outcomes in the trial and they were assessed using the European Organization for Research and Treatment of Cancer (EORTC) QoL Questionnaire C30 (QLQ-C30) and European Quality of Life Five Dimensions Questionnaire 3 Levels (EQ-5D-3L).[2] Patients were included in the PRO analysis if they received at least one dose of pembrolizumab and completed at least one PRO instrument.[5] The Submitter stated that Week 9 was selected to minimize loss of data due to death or disease progression while allowing comparisons in scores while patients were still on treatment.[5]

Overall, there were 367 patients included in the PRO analysis.[11] At Week 9, the majority of patients experienced an improvement of 10 or more points (29%) or stable global health status/QoL (43%).[5] Similar results were observed at Week 15.[5] It should be noted that scores after Week 9 should be interpreted with caution because of small sample sizes. The Submitter reported that both the EQ-5D-3L score and the EQ-5D VAS score were stable over time.[5] The minimally important differences (MID) for the EQ-5D-3L and the EQ-5D VAS scores were 0.08 and 7.[10]

Harms

There were 370 patients in the safety set, which consisted of patients who had received at least one dose of pembrolizumab.[1,2] For the purpose of this review, the results from all the patients enrolled in the KEYNOTE-052 trial will be presented. The Submitter stated that the safety profile among patients with a PD-L1 CPS ≥10% were similar to all patients enrolled in the KEYNOTE-052 trial.[12] Not safety information was available addressing exclusively platinum ineligible patients. Overall, 97.6% of patients had AEs and 62.7% had grade 3-5 AEs at the 30-Nov-2017 data cut-off.[10] Overall, 68% of patients experienced a TRAE of any grade and 20.3% experienced a grade 3-5 TRAE.[3] The most common types of AEs were fatigue (18%), pruritus (18%) and rash (12%).[3] At the 26-Sep-2018 data cut-off, 20.8% of patients experienced a grade 3-5 TRAE.[4]

At the 30-Nov-2017 data cut-off, 17.0% of patients discontinued the trial due to an adverse event (AE) while 11.6% discontinued due to a serious adverse event (SAE).[10] Vuky et al (2018) reported that 10% of patients discontinued due to a TRAE, and among these patients, 5% discontinued due to a serious TRAE.[3] At the 26-Sep-2018 data cut-off, 9.2% of patients discontinued due to a TRAE, and among these patients, 4.3% discontinued due to a serious TRAE.[4]

At the 30-Nov-2017 data cut-off, 50.5% of patients had a SAE and 11.1% of patients had a serious TRAE.[10]

Vuky et al (2018) reported that 29% of patients had an immune-mediated adverse event (IMAE) and the most common grade 3 or 4 IMAEs were colitis (2%), pneumonitis (1%) and adrenal insufficiency (1%) (Table 6.14).[3] At the 26-Sep-2018 data cut-off, 25.9% of patients had an IMAE and the most common grade 3 or 4 IMAEs were hepatitis (2.2%), colitis (1.9%) and severe skin reactions (1.9%).[4]

At the 30-Nov-2017 data cut-off, it was reported that there was one drug-related death due to a myositis.[3]

Limitations

Although the KEYNOTE-052 was a well-designed trial, it was a non-comparative, exploratory trial. For instance, the nonrandomized design of this trial makes it difficult to interpret the efficacy and safety of pembrolizumab because all cisplatin-ineligible patients with locally advanced and unresectable or MUC received the same treatment. Some other limitations should also be taken into consideration, more specifically:

- KEYNOTE-052 was a single-arm, non-randomized, open-label phase II trial. In open-label trials, the study investigator and the study participants are aware of their treatment status, which increases the risk of detection bias and performance bias. This has the potential to bias results and outcomes in favour of pembrolizumab if the assessor (investigator or patient) believes the study drug is likely to provide a benefit. In order to mitigate the impact of this bias, the investigators used a blinded independent review committee to evaluate primary and secondary outcomes using standardized criteria. However, subjective outcomes (i.e. adverse outcomes and HRQoL) may be biased due to the open-label design.

- A protocol amendment on 11-Mar-2016 was made to reflect the transition of the pembrolizumab clinical trial programme away from hypothesis testing for the primary objectives towards an estimation for single-arm clinical trials.[1] Thus, all hypotheses were removed since the objective of the trial was to estimate efficacy, and the success of the trial was determined by clinically meaningful ORRs and durability of the response.[2] Therefore, no hypothesis tests were performed and the original sample size was not adjusted. Thus, all efficacy analyses and subgroup analyses should be interpreted with caution because they are considered exploratory.

- The robustness of the preliminary overall survival and PFS results are limited due to short follow-up of the study populations and the lack of a randomized comparison treatment group in KEYNOTE-052. The overall survival data should also be considered exploratory given the small sample sizes and no power calculation for PFS and overall survival. In addition, patients were able to receive subsequent therapies once they progressed, and therefore, future estimates of OS may be confounded.

- In the absence of direct comparisons in the KEYNOTE-052 trial, the Submitter provided an unpublished network meta-analysis (NMA), which indirectly compared pembrolizumab to gemcitabine and carboplatin + gemcitabine. A summary and critical appraisal of the NMA is available in section 7 of this report.

Table 1.1: Highlights of key outcomes in the KEYNOTE-052 Trial at the 30-Nov-2017 data cut-off

	KEYNOTE-052	
Efficacy Outcomes	**Pembrolizumab (N= 370)**	
Data cut-off	30-Nov-2017	
Median Duration of Follow-up, months	11.5 months	
ORR[A]	**Number of patients with response**	**ORR % (95% CI)**
All patients	107	29.1 (24.3 - 33.8)
PD-L1 CPS ≥ 1	92	32.6 (27.2 - 38.4)
PD-L1 CPS ≥ 10	52	47.3 (37.7 - 57.0)
Platinum ineligible[B]	38	26.2 (19.3 – 34.2)
OS	**N (%)**	**Median OS months (95% CI)**
All patients	247(66.8)	11.5 (10.0 - 13.3)
PD-L1 CPS ≥ 1	179 (63.5)	12.5 (10.8 - 15.1)
PD-L1 CPS ≥ 10	57 (51.8)	18.5 (12.2 - NR)
Platinum ineligible[B]	108 (74.5)	9.2 (5.3 - 11.3)
PFS[A]	**N (%)**	**Median PFS months (95% CI)**
All patients	301 (81.4)	2.3 (2.1 - 3.4)
PD-L1 CPS ≥ 1	222 (78.7)	3.4 (2.2 - 3.8)
PD-L1 CPS ≥ 10	75 (68.2)	4.9 (3.8 - 10.8)
Platinum ineligible[B]	120 (82.8)	2.1 (2.0 - 2.8)

	KEYNOTE-052
Harms Outcomes, n (%)	**Pembrolizumab (N= 370)**
AE (any grade)	361 (97.6)
TRAE (any grade)	250 (67.6)
WDAE	37 (10)
SAE	187 (50.5)

Abbreviations: AE= adverse events; **CPS** = combined positive score; **DOR** = duration of response; **NR** = not reached; **ORR** = objective response rate; **OS** = overall survival; **PD-L1** = programmed death-ligand 1; **PFS** = progression-free survival; **SAE** = serious adverse events; **TRAE** = treatment-related adverse events; **WDAE**=withdrawals due to adverse events

Notes
A The outcome was measured using RECIST 1.1 and it was assessed by an independent radiology review.
B Patients were considered platinum ineligible if they had an ECOG performance status of 2 and one or more of visceral metastasis, advanced age (≥ 80 years) or GFR < 60 mL/min.

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

One patient input was provided to pCODR through a patient advocacy group submission from Bladder Cancer Canada (BCC) for pembrolizumab for locally advanced or metastatic urothelial carcinoma (UC).

From a patient's perspective, blood in urine was the most commonly reported symptom related to UC, followed by fatigue and urination problems. Almost all patients surveyed by BCC had experience with some form of chemotherapy that led to additional fatigue, nausea, constipation and other well-known side effects, some of which were difficult to tolerate. By comparison, pembrolizumab gave rise to milder side effects, an aspect that was strongly appreciated by patients. The net effect was a subjective improvement in disease control, symptoms, and general quality of life in patients switching to pembrolizumab therapy. These benefits were in line with patients' expectations for alternative treatment options, which focused on achieving disease control, extending life expectancy and maintaining quality of life. Most patients with experience using pembrolizumab recommended the drug to other potential UC patients.

Provincial Advisory Group (PAG) Input

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

Clinical factors:

- Clarity on eligible patient population

Economic factors:

- Additional resources needed to monitor infusion reaction
- Potential for drug wastage with 200 mg fixed dose and discontinuation of 50mg vial

Registered Clinician Input

Four separate registered clinician inputs were provided for pembrolizumab for the treatment of locally advanced or metastatic urothelial carcinoma (UC). Three of the four inputs were prepared by individual clinicians while the other was jointly submitted by three clinicians from CancerCareOntario.

Clinicians providing input indicated that advanced UC is an area of clear unmet need owing to suboptimal treatment options. Many patients have comorbidities that preclude the use of toxic chemotherapy. In contrast, pembrolizumab is less toxic and can provide significant and durable benefits. There is general agreement that pembrolizumab should be the preferred first-line treatment for the target population. Next in line would be chemotherapy should the patient become eligible. Contraindications for pembrolizumab are not as numerous as for chemotherapy, but autoimmune disorders should be considered and managed. Some clinicians mentioned that PD-L1 testing is not standard in all settings and should be made more broadly available.

Summary of Supplemental Questions

A critical appraisal was performed for the submitted network meta-analysis (NMA), which provides evidence on the efficacy of first-line pembrolizumab as compared to other anticancer agents in patients with advanced or unresectable or MUC who were ineligible for cisplatin-based chemotherapy.

Although the results of the NMA overall support the efficacy of pembrolizumab in cisplatin-ineligible patients with advanced or MUC, there are several limitations that should be considered. First, the use of unanchored comparisons used as head-to-head studies in the NMAs is a serious limitation of the NMA. The simulated treatment comparison (STC) methodology is not considered as strong as an NMA using data from RCTs due to the presence of unknown or unmeasured prognostic factors. These unknown factors may potentially confound the outcomes of interest because they will not be captured in the prediction models. It should be noted that the bias resulting from missing prognostic factors is very difficult to quantify, and as a result, it is unclear what impact the missing prognostic factors have on the results of the NMA. Second, not all of the trials included in the NMA reported baseline values for the factors that were included in the prediction models. Although these missing values were imputed using repeated bootstrap samples, this method may increase the uncertainty of the predicted outcomes for these trials. Third, the subgroup analysis assessing platinum-eligibility status should be interpreted with caution because the models only partially adjusted for known prognostic factors as a result of how platinum-eligibility status was defined. Fourth, the systematic review was last updated in September 2017 and there is a potential that more recent publication may not have been captured. Fifth, the submitted systematic review and ITC were completed by external consultancy groups hired by the submitter. As a result, the information provided in the reports should be viewed considering this potential conflict of interest and lack of peer-review. Due to the above limitations, the comparative efficacy estimates obtained are likely biased, and it is not possible to quantify or identify the direction of the bias. As a result, the estimates may over- or underestimate the true treatment effect associated with pembrolizumab.

Comparison with Other Literature

The pCODR CGP and Methods Team identified one clinical trial that was relevant to 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 1.2: Assessment of generalizability of evidence for pembrolizumab for MUC (first line)

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence
(KEYNOTE-052 trial)</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td rowspan="3">Population</td><td>Stage of disease</td><td>Patients were enrolled in the trial if they had histologically or cytologically-confirmed diagnosis of locally advanced and unresectable (inoperable) or metastatic urothelial cancer of the renal pelvis, ureter, bladder, or urethra.</td><td>Does stage limit the interpretation of the trial results with respect to the target population (e.g., Canadian clinical practice, patients without the factor, etc.)?</td><td>Interpretation of the trial results applies to locally advanced and unresectable or metastatic disease.

There is no data to support the use of pembrolizumab in patients with other stages than the one observed in the KEYNOTE-052 trial.</td></tr>
<tr><td>Performance Status</td><td>Patients were enrolled in the trial if they had an ECOG status of 0, 1 or 2.

Table 1: Baseline characteristics at screening of patients enrolled in the KEYNOTE-052 trial
<table>
<tr><th>ECOG Status</th><th>Pembrolizumab
N = 370</th></tr>
<tr><td>0</td><td>80 (22%)</td></tr>
<tr><td>1</td><td>133 (36%)</td></tr>
<tr><td>2</td><td>156 (42%)</td></tr>
<tr><td>3</td><td>1 (<1%)</td></tr>
</table>
Table 2: The effect of pembrolizumab on ORR stratified by ECOG performance status among patients from the KEYNOTE-052 trial
<table>
<tr><th>ECOG Status</th><th>Pembrolizumab
N = 370</th><th>ORR (95% CI)</th></tr>
<tr><td>0 or 1</td><td>49/179</td><td>27% (21-35)</td></tr>
<tr><td>2*</td><td>34/128</td><td>27% (19-35)</td></tr>
</table>
*One patient had an ECOG status of 3</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>Most patients included in the trial had ECOG equal or smaller than 2.

The benefit for patients with ECOG 3 cannot be concluded based on the small subgroup including one patient only. The CGP concluded that the trial results cannot be generalized to ECOG 3 patients.</td></tr>
<tr><td>Organ dysfunction</td><td>Patients were enrolled in the trial if they had adequate organ function.</td><td>Does the exclusion of patients with organ dysfunction limit the interpretation of the trial results with respect to the target population (e.g., Canadian clinical practice, patients without the factor, etc.)?</td><td>Given the favorable safety profile of pembrolizumab, and the frail nature of the trial population at baseline, the CGP suggested to leave it up to the discretion of the treating physician to apply some flexibility in terms of using pembrolizumab in patients with slightly lower lab parameters than those outlined in the trial. For example, the CGP would feel comfortable generalising</td></tr>
</table>

Domain	Factor	Evidence (KEYNOTE-052 trial)	Generalizability Question	CGP Assessment of Generalizability
				the results of the trial to patients with an absolute neutrophil count of ≥ 1000/ mcl, platelets level > 90,000/ mcL, and a hemoglobin > 8 g/dl.
	Creatine clearance	Patients were enrolled in the trial if they were ineligibility to receive cisplatin-based combination therapy, which was based on at least one of the following criteria: • ECOG Performance Status of 2 (the proportion of these subjects will be limited to approximately 50% of the total population) • Creatinine clearance (calculated or measured) <60 mL/min but ≥30 mL/min. Note: Subjects with a creatinine clearance (calculated or measured) <30 mL/min or on dialysis are excluded from the trial • CTCAE v.4, Grade ≥2 audiometric hearing loss (25dB in two consecutive wave ranges) • CTCAE v.4, Grade ≥2 peripheral neuropathy • New York Heart Association Class III heart failure	Are the results generalizable to patients with a creatine clearance of less than 30 or more than 60 mL/min?	Patients with creatine clearance of less than 30 or more than 60 mL/min were excluded from the KEYNOTE-052 trial, and results cannot be generalized to this population. In addition, the CGP noted that the cut off point of < 60 mL/ min is based on cisplatin being a relative contraindication in patients with a creatinine clearance under 60. However, the CGP mentioned that this cut off point is subject to re-evaluation in the future (e.g. moving down to < 50 mg/ min) as it is not based on robust evidence.
	Active autoimmune disease	Patients were excluded if they had an active autoimmune disease that has required systemic treatment in past 2 years (i.e., with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) was not considered a form of systemic treatment.	Does the exclusion of patients with active autoimmune disease limit the interpretation of the trial results with respect to the target population (e.g., Canadian clinical practice, patients without the factor, etc.)?	The CGP suggested to leave it up to the discretion of the treating physician if patients are considered as having active autoimmune disease. In general, needing more than 10 mg per day of corticosteroids would be regarded as having active autoimmune disease.
	Measurable disease	Patients were enrolled in the trial if they had measurable disease based on RECIST 1.1 as determined by central review. Tumor lesions situated in a previously irradiated area.	Are the results generalizable to patients without measurable disease?	The trial results are generalizable to patients without measurable disease.
	Histological diagnosis	The trial allowed patients with histologically or cytologically confirmed diagnosis of advanced/unresectable (inoperable) or MUC of	Does histological diagnosis limit the interpretation of the trial results (efficacy or	The trial results are generalizable to patients with urothelial cancer of predominantly transitional histology

Domain	Factor	Evidence (KEYNOTE-052 trial)	Generalizability Question	CGP Assessment of Generalizability
		the renal pelvis, ureter, bladder, or urethra (transitional cell and mixed transitional/non-transitional cell histologies). In a Checkpoint Response, the Submitter stated that the majority of patients had a predominant histology of urothelial (transitional cell) carcinoma (94%, N = 349).[7] For instance, 94% of patients who had a primary tumor site in the lower tract and 97% of patients who had a primary tumor site in the upper tract had a predominant histology of "urothelial carcinoma" (including variants), respectively.[7]	toxicity) with respect to the target population (e.g., Canadian clinical practice, patients without the factor, etc.)?	of any primary site. In addition, the CGP noted that non-transitional cell carcinomas are rare (5 – 19% of patients) and clinical trials targeting this small subgroup of patients are unlikely. The CGP noted that there is no biological rationale to assume that outcomes of pembrolizumab would be different between transitional and non-transitional cell carcinomas and there is precedent of pembrolizumab treatment in patients with squamous cell carcinoma of the lungs. Therefore, the CGP agreed that generalizing the trial results to patients with predominantly squamous cell carcinomas who are ineligible for cisplatin or platinum containing chemotherapy would be reasonable.
	CNS metastases	Patients were excluded from the trial if they had known active CNS metastases and/or carcinomatous meningitis.	Did the exclusion of patients with certain sites of metastatic disease limit the interpretation of the trial results with respect to the target population (e.g., Canadian clinical practice, patients without the factor, etc.)?	The result of the trial can be generalized to patients with stable or treated CNS metastases at baseline.
	Biomarkers	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.	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?	The CGP agreed that for patients with cisplatin ineligible disease, pembrolizumab should be restricted to those with PD-L1 ≥ 10% expression level. ORR for patients with lower PD-L1 expression level was not clearly superior to the responses seen with the current standard chemotherapy treatment (gemcitabine plus carboplatin). In addition, the CGP noted that this was in line with the updated FDA recommendations (for more details,

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence
(KEYNOTE-052 trial)</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td></td><td></td><td>Table 6: Baseline characteristics of patients enrolled in the KEYNOTE-052 trial
<table><tr><td>PD-L1 expression — no.(%)</td><td>Pembrolizumab N = 370</td></tr><tr><td>PD-L1 CPS < 1%</td><td>79 (21.4)</td></tr><tr><td>PD-L1 CPS ≥1% to < 10%</td><td>172 (46.5)</td></tr><tr><td>PD-L1 CPS ≥ 10%</td><td>110 (29.7)</td></tr><tr><td>Unknown</td><td>9 (2.4)</td></tr></table>
Table 7: The effect of pembrolizumab on ORR stratified by PD-L1 status among patients from the KEYNOTE-052 trial
<table><tr><td>PD-L1 CPS</td><td>Pembrolizumab</td><td>ORR (95% CI)</td></tr><tr><td>PD-L1 CPS <1</td><td>64 (81.0)</td><td>15.2 (8.1, 25.0)</td></tr><tr><td>PD-L1 CPS ≥1 to < 10</td><td>122 (70.9)</td><td>23.3 (17.2, 30.3)</td></tr><tr><td>PD-L1 CPS ≥1</td><td>179/282 (63.5)</td><td>32.6 (27.2, 38.4)</td></tr><tr><td>PD-L1 CPS ≥10</td><td>57/110 (51.8)</td><td>47.3 (37.7, 57.0)</td></tr></table></td><td></td><td>see CGP interpretation section 1.2.4.). Further, the CGP agreed that for patients with platinum-ineligible disease, pembrolizumab should be given regardless of the PD-L1 expression level. The CGP felt that this patient group has no other effective treatment options available.</td></tr>
<tr><td></td><td>Prior Therapies</td><td>Patients were excluded from the trial if they had received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent.</td><td>Does the exclusion of patients who received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent limit the interpretation of the trial results with respect to the target population (e.g., Canadian clinical practice, patients without the factor, etc.)?</td><td>The CGP noted that none of the patients in the trial had received prior therapy. The CGP agreed that there is currently insufficient evidence to guide a recommendation if patients who had received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent for their UC would quality to be treated with pembrolizumab in the first line metastatic setting. The CGP acknowledged that in the near future this will become a relevant clinical question as trials are underway which investigate the effect of an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent in the pre-metastatic setting.</td></tr>
</table>

Domain	Factor	Evidence (KEYNOTE-052 trial)	Generalizability Question	CGP Assessment of Generalizability
Intervention	Dose and Schedule	The recommended dose of KEYTRUDA® is 200 mg administered 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.	Are the results generalizable to a different dose or administration schedule (i.e., (i) 2mg/kg up to a flat dose cap of 200mg every 3 weeks; (ii) 400mg every 6 weeks, or (iii) 4mg/kg up to a flat dose cap of 400mg every 6 weeks?	The CGP agreed that the fixed dose used in the trial reflects the standard dose schedule used in Canada that has been approved by Health Canada. The CGP noted that there is currently insufficient evidence to guide the decision on a weight-based dose schedule or alternative fixed dosing schedule of 400 mg every 6 weeks schedule.
	Treatment intent	The intent of treatment in the trial was curative and/or palliative?	Are the results of the treatment generalizable to an alternative treatment intent? (i.e., if the trial is palliative in intent, could the therapy also be used in the adjuvant setting or vice versa?)	There is no other relevant treatment intent for locally advanced or metastatic urothelial cancer: treatment is symptomatic and palliative.
Comparator	Standard of Care	There was no comparator in the trial. Please refer to Section 7 for more details on the network meta-analysis, which compared pembrolizumab to carboplatin plus gemcitabine or gemcitabine monotherapy, and in patients with advanced or MUC in patients who are cisplatin or platinum ineligible.	If the comparator is non-standard, are the results of the trial applicable in the Canadian setting?	Due to the lack of randomized comparative data, there is no reliable estimate of the comparative efficacy of pembrolizumab to carboplatin plus gemcitabine or gemcitabine monotherapy. The results from this non-comparative phase II study compare favorable to currently available chemotherapies in patients with cisplatin ineligible disease and PD-L1 ≥ 10 expression level. Further these results compare favourable to currently available chemotherapy in patients with platinum-ineligible disease irrespective of PD-L1 expression level.

Domain	Factor	Evidence (KEYNOTE-052 trial)	Generalizability Question	CGP Assessment of Generalizability
Outcomes	Appropriateness of primary and Secondary Outcomes	KEYNOTE 052 measured the following clinical outcomes: Primary outcome: object response rate (ORR) using RECIST 1.1 as assess by an independent radiology review (IRR). Secondary outcomes: duration of response (DOR) using RECIST 1.1 as assess by an IRR, overall survival (OS) and progression free survival (PFS) using RECIST 1.1 as assess by an IRR and safety outcomes.	Were the primary and secondary outcomes appropriate for the trial design?	Response rate is a reasonable primary outcome for this study and the critical outcomes including PFS and OS were secondary endpoints. the CGP feels that the RR reflects the ability of therapy to inhibit the target (i.e., the PD-L1 ligand) and consequently would be associated with benefit. However, the CGP noted that RR is not an established surrogate for OS in this setting and that, in the current era in which multiple anti-PD-1, anti-PD-L1, or anti-PD-L2 agents for locally advanced or metastatic urothelial cancer are being investigated in phase III trials, the duration of disease control has become one of the main deciding factors in treatment selection.
Setting	PD-L1 testing	Patients were required to provide a tumour biopsy for biomarker analysis. PD-L1 expression levels were measured in formalin-fixed, paraffin-embedded tissues using a PD-L1 clinical trial assay (PD-L1 IHC 22C3 pharmDx assay; Agilent Technologies, Carpinteria, CA, USA). PD-L1 status was scored using a combined positive score (CPS). CPS was defined as the percentage of cells (i.e., tumour cells, macrophages, or lymphocytes) that expressed PD-L1 in a tumour biopsy, tumour cells, macrophages, or lymphocytes) that expressed PD-L1 in a tumour biopsy.	Are the results generalizable to a treatment setting that is not able to access laboratory monitoring (e.g., lab reporting of a CPS for PD-L1) as required to determine PD-L1 expression levels in the KEYNOTE-052 trial.	The CGP felt that results are not generalizable to a treatment setting that is not able to access PD-L1 testing for patients with locally advanced or metastatic urothelial carcinoma.

1.2.4 Interpretation

Burden of Illness and Need

In patients with metastatic urothelial carcinoma (UC) the standard of care in first line remains cisplatin-based combination chemotherapy.[18] Unfortunately, up to 50% of metastatic UC patients will be considered cisplatin - ineligible due to the presence of significant comorbidities.[19] Patients with at least one of the following criteria: Eastern Cooperative Oncology Group (ECOG) performance status of 2, creatinine clearance less than 60ml/min, grade $\geq$ 2 hearing loss, grade $\geq$ 2 neuropathy, and/or New York Heart Association Class III heart failure are classified as cisplatin-ineligible and are not offered cisplatin-based regimens.

Until recently there were no approved treatments for these patients, underscoring a significant unmet medical need. Non-cisplatin containing chemotherapy regimens, such as gemcitabine and carboplatin are often used, but these regimens are inferior to cisplatin-based regimens and have toxicities limiting their use.[20] Gemcitabine and carboplatin shows an objective response rate (ORR) of 30-45%, a median duration of response (DOR) of 5-8 months and a median overall survival (OS) of only 7-10 months. Gemcitabine and carboplatin is associated with a higher rate of hematologic toxicities such as febrile neutropenia as well as nausea and vomiting, renal toxicity, and neuropathy which can impact on overall tolerability. Other non-cisplatin containing regimens have been compared against gemcitabine and carboplatin but found to be inferior and more toxic.[21] Among patients with metastatic UC, there is an additional subgroup of patients, who are considered platinum-ineligible and are not candidates for either cisplatin or carboplatin-based regimens. These patients have no available treatment options, highlighting a critical unmet medical need.

In their feedback on the initial recommendation, the patient advocacy group, Bladder Cancer Canada (BCC), strongly urged pERC to recommend funding for the platinum-ineligible group of patients. BCC noted that the platinum-ineligible group of patients represents a very small percentage of the overall group of patients with metastatic UC, who currently have no other effective treatment options and whose survival is 6 to 12 months at best. In response to the patient group's feedback the pCODR Clinical Guidance Panel (CGP) estimated that in clinical practice approximately 50% of the cisplatin-ineligible patients could be considered platinum-ineligible as well.

Monoclonal antibodies targeting the programmed death receptor (PD-1) or its ligand (PDL-1) have shown durable antitumor activity and tolerability in metastatic UC patients progressing on or after first line platinum-based chemotherapy. In the second line setting, several PD1/PD-L1 inhibitors have now been granted accelerated (FDA) or conditional (Health Canada) approvals. The only drug however to have received full approval in the second line setting is the PD1 inhibitor Pembrolizumab. This is based on the Keynote 045 Phase III study, that showed Pembrolizumab improved overall survival compared to chemotherapy in the second line setting.[22]

Based on encouraging efficacy and tolerability of the PD1/PD-L1 inhibitors in metastatic UC and significant unmet need in the first-line cisplatin-ineligible setting, Pembrolizumab and Atezolizumab (a PD-L1 inhibitor) have both been evaluated in open label single arm trials (Keynote 052[1] and Cohort 1 of Imvigor 210[23]) respectively in the first line cisplatin-ineligible setting. Both of these trials have shown encouraging results, and based on the Keynote 052 trial, Pembrolizumab has been granted conditional Health Canada approval in the first-line, pending final results of the ongoing randomized Keynote 361 [NCT02853305][14] and ongoing MK-7902-011 trials [NCT03898180][17].

Effectiveness

The KEYNOTE 052 trial is an important trial that showed pembrolizumab has both efficacy and tolerability in patients who are cisplatin-ineligible. Keynote 052 enrolled 370 patients. The median age was 74, 14% had lymph node-only metastatic disease, and 21% had liver involvement. The most common reason for cisplatin-ineligibility was impaired renal function.

At a median follow-up of 5 months, independent central review confirmed an ORR of 28.6% (95% CI: 24.1%-33.5%) in all treated patients. Both complete responses (CR) and partial responses (PR) were observed. ORR ranged from 11% in CPS < 1% to 39% in CPS $\geq$ 10%. Median duration of response in responders was 1.4-17.8 months. At the time of data cutoff, responses were ongoing for at least 6 months in 52% of patients and for at least 12 months in 7% of patients. The majority of patients discontinued treatment due to disease progression. The median treatment duration was 3.4 months (0.03-19.94 mo). Durable responses were seen in all demographic and disease subgroups including patients with lymph node only metastases, prior BCG exposure and in those with prior perioperative chemotherapy.[1]

These results are important because this trial was done in a patient population without effective and well tolerated treatment options and rapidly progressive disease. The response rates seen with pembrolizumab combined with the duration of response and tolerability compared with chemotherapy strongly supports its role in cisplatin-unfit metastatic UC patients. Further trials will be needed to confirm these results.

Response rates, however, were lower in patients whose tumour had a PD-L1 CPS expression cutoff of <10%. This trend has also been seen in two ongoing randomized studies, Keynote 361[14] and Imvigor 210.[23] In both of these trials, there was markedly reduced survival in patients with PD-L1-low expression status who received either pembrolizumab or atezolizumab monotherapy compared with platinum-based chemotherapy. This has led the FDA to issue a black box warning and revise their recommendations for the first-line setting. Pembrolizumab is now recommended in two specific settings: a) for the treatment of metastatic UC patients who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 (cutoff >10%); and b) in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 expression status. The pCODR requested reimbursement criteria are in line with the FDA revised recommendation.

Safety

All patients receiving at least one dose were included in the safety analysis. Overall 17% experienced an immune-mediated adverse event (imAE), including 8% needing systemic steroids and 8% needing hormone replacement therapy for endocrine disorders. Five percent of patients received an oral prednisone dose equivalent to $\geq$ 40 mg daily for an imAE. One imAE was myositis leading to multiple organ failure despite corticosteroids. The most common grade 1-4 adverse events were fatigue, musculoskeletal pain, decreased appetite, constipation, rash and diarrhea. Overall the pattern of imAEs was consistent with the side effects seen with pembrolizumab in other cancer trials and no new safety signals emerged. Despite the clear limitation of this non-comparative phase II study, the CGP agrees that pembrolizumab has a favourable toxicity profile compared to standard chemotherapy. Combination chemotherapy with gemcitabine plus carboplatin, in this advanced disease setting, is associated with significant toxicities including neutropenia (46%), thrombocytopenia (19%) and anemia (18%) which can preclude its use or result in early discontinuation.[24] Although the nature of toxicities differs between immunotherapy and chemotherapy, the incidence of high-grade toxicity related to pembrolizumab compared favorably and only 5% of patients required high dose steroids on trial. These results are supported by patient-reported outcomes data collected in the KEYNOTE 052 trial suggesting that the toxicities of pembrolizumab were not detrimental to quality of life, with 29% of patient experiencing

improved quality of life. This favorable toxicity profile is highly relevant to cisplatin-ineligible patients. As well, more patients with platinum ineligible disease may be considered for first-line treatment where before they would have only received best supportive care. Further, the CGP acknowledged the patient advocacy group input stating that the majority of patients with pembrolizumab exposure reported that pembrolizumab had a positive impact on their health and well-being, with mild adverse events that were well tolerable.

Limitations and Generalizability

The CGP agree that while PFS is the most important initial endpoint in the evaluation of therapies for the palliation of advanced or metastatic UC, disease response is a meaningful endpoint for patients because it often results in improvement of symptoms and quality of life. The response rates observed in the Keynote 052 trial are durable and consistent across subgroups. Responses in this patient population are important because of the accompanying improvement in distressing disease symptoms (pain, hematuria, fatigue) and improvement in performance status. It is too early to evaluate the true duration of PFS or OS, but the present results—though from a non-comparative phase II trial - compare favourably to currently available therapies, such as gemcitabine plus carboplatin and single agent gemcitabine. Chemotherapy in this advanced disease setting is associated with significant toxicities like febrile neutropenia, nephrotoxicity, and neuropathy that can negatively impact quality of life including multiple hospital admissions due to toxicity, which is largely avoided when pembrolizumab is used. In addition, the schedule for Pembrolizumab, at every 3 weeks is a preferable regimen with less chair time.

Several questions have been raised regarding the applicability of these results to certain patient populations:

1. If recommended for reimbursement, PAG noted patients currently on first-line treatment (gemcitabine monotherapy or gemcitabine-carboplatin) who have not progressed, would need to be addressed on a time-limited basis. If appropriate to switch to pembrolizumab, PAG is seeking guidance on the appropriate timeframe.

   Response: In patients currently receiving first line treatment with gemcitabine-carboplatin, it would not be appropriate to switch to pembrolizumab. If a patient progresses on first line treatment with gemcitabine-carboplatin, they would be eligible for pembrolizumab second line, which is already approved in this setting for patients who have disease progression during or following platinum-containing chemotherapy. The only caveat will be whether patients who receive non-platinum containing regimens, can receive pembrolizumab (as it is current neither funded in first line, nor second line) but has the potential to improve outcomes in these patients based on the totality of current evidence.

2. Pembrolizumab is a high cost drug and requires monitoring and treating 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.

   Response: Immunotherapy is now commonly used across many cancers, and experience in managing side effects is growing. Only centers appropriately trained to give these drugs are using these drugs. I do not anticipate an issue. Standard monitoring for these drugs, as with other drugs needs to be implemented.

3. PAG noted some patients may interrupt treatment with pembrolizumab due to toxicity or other reasons. PAG is seeking guidance on the appropriateness of re-initiation with pembrolizumab after toxicity resolution or treatment interruption for other reasons and if this occurs, clarification on the total duration of therapy (i.e., two year of treatment or a total of 35 administrations).

   Response: Although patients enrolled in Keynote 052 received a maximum of 24 months of treatment there is no good evidence that pembrolizumab should be stopped if the patient has stable disease without toxicity. Additionally, depending on the severity of the toxicity, pembrolizumab can be re-initiated. The approach should be similar to other tumor sites in which pembrolizumab has been funded.

4. PAG is seeking guidance, for patients who receive pembrolizumab in this setting:
   - Confirmation that patients would not receive subsequent PD-1 or PD-L1 inhibitors

     Response: At this point we do not have data to support retreatment.

   - Re-treatment for patients who discontinue treatment for reasons other than progression.

     Response: Retreatment upon progression would be an option. It is not possible to indicate the time-interval and would depend on resolution of toxicities for example. The CGP also cautions that this response is based on expert clinical opinion as there is no data in this setting regarding retreatment with pembrolizumab.

   - Following completion of 24 months, appropriateness of re-treatment and the time interval between end of treatment and relapse.

     Response: There is current very little data to guide re-treatment management. This is currently being explored in other tumor sites and in many clinical studies re-treatment may be considered.

   - Second-line treatment options following progression (e.g., paclitaxel)

     Response: Post Treatment options post pembrolizumab in the first line could include gemcitabine, gemcitabine plus carboplatin, carboplatin, paclitaxel or docetaxel

5. In what clinical scenarios would pembrolizumab or chemotherapy be the preferred treatment for first-line METASTATIC UC where patients are not eligible for platinum-containing chemotherapy? Please comment on the preference considering patient preference, efficacy, safety, and administration.

   Response: In patients with rapidly progressive disease, chemotherapy may be preferred. In patients with a history of autoimmune disease, chemotherapy may be preferable. In patients with residual toxicity from prior chemo – e.g., neuropathy, immunotherapy may be preferable.

6. In clinical practice, what is the clinical utility of a Combined Positive Score for PD-L1 in this setting (i.e., patients not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 [(CPS) ≥10] or patients who are not eligible for any platinum

containing chemotherapy regardless of PD L1 status)?

> Response: PD-L1 positive score is important because in patients with cisplatin ineligible disease who are PD-L1 < 10 the benefit is more from chemotherapy than from pembrolizumab, and patients should receive chemotherapy. Currently PD-L1 score is not useful as a biomarker for pembrolizumab in patients who are ineligible for ANY plantinum containing chemotherapy.

1.3 Conclusions

The submitter's requested reimbursement criteria are for two subgroups within the KEYNOTE-052 trial: (1) subjects with PD-L1 CPS ≥ 10 who are cisplatin ineligible, and (2) subjects ineligible to receive any platinum chemotherapy, irrespective of the PD-L1 status.

(1) Cisplatin ineligible with PD-L1 ≥ 10 status subgroup:

The CGP concluded that there may be a clinically meaningful net clinical benefit to pembrolizumab compared with standard care chemotherapy (carboplatin plus gemcitabine) in patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 CPS ≥10. This conclusion is based on evidence from a pre-specified subgroup analysis from the non-comparative phase II KEYNOTE 052 clinical trial, which showed a clinically meaningful overall response rate, prolonged durability of responses and excellent early overall survival, with a toxicity profile that is better than that experienced with chemotherapy. Prolonged responses in this patient population are important because despite initial response to chemotherapy, durability is short. In addition, many patients are not able to tolerate ongoing chemotherapy due to side effects and treatment needs to be discontinued even in the face of a response. The CGP acknowledged that it is challenging to draw firm conclusions on the efficacy of pembrolizumab based on the data obtained from a pre-specified but exploratory subgroup analysis based on a non-comparative phase II study with primary tumour response endpoints. However, this subgroup of patients has limited treatment options and effective therapies with improved toxicity are urgently needed in this disease setting.

(2) Platinum-ineligible, irrespective of PD-L1 status subgroup:

The CGP concluded that there may be a clinically meaningful net clinical benefit to pembrolizumab compared with standard care, chemotherapy (gemcitabine monotherapy) or best supportive care in patients with locally advanced or metastatic urothelial carcinoma who are not eligible for platinum-containing chemotherapy irrespective of the PD-L1 status. This conclusion is based on evidence from a post-hoc analysis from the non-comparative phase II KEYNOTE 052 clinical trial, which showed a clinically meaningful overall response rate and prolonged durability of responses, with a toxicity profile that is better than that experienced with chemotherapy. Prolonged responses in this patient population are important because this patient population is often not well enough to receive any treatment with no hope of benefit, or only single agent gemcitabine with a dismal response rate of 10% or less. The CGP acknowledges that it is challenging to draw firm conclusions on the efficacy of pembrolizumab based on the data obtained from an exploratory post-hoc analysis based on a non-comparative phase II study with primary tumour response outcomes. However, this particular subgroup of patients has no effective treatment options and new therapies that show tumour response with improved toxicity are urgently needed in this disease setting.

In making these conclusions the CGP also considered:

- The lack of efficacious and well tolerated options for cisplatin-ineligible metastatic urothelial cancer patients and their poor overall prognosis.
- A network meta-analysis was developed and provided by the submitter in order to compare the efficacy and safety of first-line pembrolizumab to other anticancer agents in patients with locally advanced or metastatic UC who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 CPS ≥10, or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status. Although the results of the NMA overall favoured pembrolizumab in the two subgroups of interest, several limitations were identified inherent to the use of this data. Hence no firm conclusions can be drawn from these results. The CGP noted that two randomised phase III trials (KEYNOTE 361 and MK 7902 PN 011) may provide additional data on ORR, PFS and OS outcomes and toxicities for pembrolizumab compared to alternative treatment options in patients belonging to the two subgroups included in the reimbursement request. It was acknowledged that the MK 7902 PN 011 trial uses a comparator that is not currently standard of care.
- The CGP also considered the results generalizable to patients who did not have measurable disease, had stable CNS metastases and CBC parameters slightly lower than outlined in the Keynote 052 trial.
- The CGP felt these results could also apply to cisplatin- ineligible patients with predominantly squamous histology although the data are very limited.
- Finally, in patients who come off Pembrolizumab after 2 years without progression, there is currently no data to guide ongoing treatment.

2 BACKGROUND CLINICAL INFORMATION

This section was prepared by the pCODR Pembrolizumab for Advanced or Metastatic Urothelial Cancer Clinical Guidance Panel. It is not based on a systematic review of the relevant literature.

2.1 Description of the Condition

Urothelial carcinoma (also known as transitional cell carcinoma) is the most common type of bladder cancer. It is the 5th most common cancer in Canada with 8,900 cases diagnosed in 2017, with 2,400 deaths. Of these cases 6,700 were in men making it the 4th most common cancer amongst males.[25] 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 and indwelling catheters. In the developing world, schistosomiasis is the most common cause of urothelial cancer. Most patients (70%) will have non-muscle invasive disease, but up to 25% will have muscle invasive disease and despite cystectomy or bladder sparing trimodality treatment carry a high risk of recurrence. Five percent will already be metastatic at presentation.[26]

2.2 Accepted Clinical Practice

Patients presenting with or developing metastatic disease remain incurable. The standard of care for these patients remains cisplatin-combination chemotherapy.[27] However, approximately 30%–50% of patients are considered ineligible for cisplatin-based chemotherapy because of comorbidities.[19] Patients with at least one of the following criteria: Eastern Cooperative Oncology Group (ECOG) performance status of 2, creatinine clearance less than 60ml/min, grade $\geq$ 2 hearing loss, grade $\geq$ 2 neuropathy, and/or New York Heart Association Class III heart failure are classified as cisplatin-ineligible and are not offered cisplatin-based regimens.

In patients who are ineligible for cisplatin, there are no approved therapies. Non-cisplatin-based regimens like gemcitabine plus carboplatin or gemcitabine single agent are used but considered to be inferior to cisplatin. There is also a subset of metastatic UC patients who will not be a candidate for any platinum-based chemotherapy and will receive either gemcitabine or best supportive care only. Several small single-arm trials of the most common regimens, including gemcitabine plus carboplatin demonstrated objective response rates (ORRs) of approximately 30%–45% with median duration of response of approximately 5–8 months. Overall survival (OS) in these patients is poor, ranging from only 7 to 10 months.[20,21,24] Cytotoxic therapy is also quite poorly tolerated in these patients, with a high incidence of hematologic toxicities.[24] Thus, there is a significant unmet need for effective and tolerable treatments in cisplatin-ineligible patients with metastatic UC.

In recent years, a new class of drugs, known as the immune checkpoint inhibitors, which target the PD1/PDL1 pathway, have shown both encouraging tolerability and efficacy in metastatic UC patients progressing on or after platinum-based therapy. In particular, pembrolizumab, a PD1 inhibitor, has gained full Health Canada approval based on a randomized Phase III trial (Keynote 045) which compared Pembrolizumab to second line investigator's choice chemotherapy (docetaxel, paclitaxel and vinflunine) and showed a survival benefit.

The tolerability and efficacy of Pembrolizumab in second line, has provided the rationale to evaluate Pembrolizumab in the first line, cisplatin-ineligible metastatic UC population where there is significant unmet need. The Keynote 052 trial,[1] was a single arm open label trial that enrolled patients regardless of their PDL1 expression level, having a creatinine clearance of >30 and <60 ml/min, hearing loss >grade 2, peripheral neuropathy or ECOG PS of 2. The submitter has performed a post-hoc analyses on the platinum-ineligible subgroup. The platinum-ineligible criteria are acceptable in clinical practice.

With a median follow-up of 5 months, ICR-confirmed ORR was 28.6% (95% CI: 24.1%–33.5%) in all treated patients. Both CRs and PRs were observed and observed duration of response ranged from 1.4+ to 17.8+ months. Patients were allowed to remain on study beyond progression if clinically well.

2.3 Evidence-Based Considerations for a Funding Population

Patients with muscle invasive cancer will either present with or later develop metastatic disease. It is estimated that approximately 2,000 metastatic UC patients per year would be candidates for 1st-line platinum-based chemotherapy.[41] However, up to 50% (1000 patients) may not be cisplatin-eligible and could be candidates for pembrolizumab as 1st line therapy, depending on their PD-L1 status. To date, no tumor markers have been predictive of benefit from either chemotherapy or immunotherapy in this population although PD-L1 and tumor mutation burden are under investigation.

It is important to note that in the ongoing phase III clinical trial with pembrolizumab (KEYNOTE 361)[14] and the phase II trial with atezolizumab (IMvigor130),[23] the Data Monitoring Committee (DMC) for each study performed an early unplanned review. They found that patients in the monotherapy arms of both trials with PD-L1-low status had decreased survival compared with patients who received cisplatin- or carboplatin-based chemotherapy. As a result, it is now recommended that only cisplatin-ineligible patients whose tumors have PDL1 high status receive immunotherapy, unless they are deemed to be platinum-unfit.

PD-L1 testing is not currently in use in metastatic UC. However, as immunotherapy is moved earlier in the treatment paradigm where there are potentially active agents, knowing PD-L1 status will be of critical importance to ensure patients are treated appropriately. Establishing PD-L1 testing in metastatic UC in Canada will be a change in routine practice and will require establishing centres equipped to test.

2.4 Other Patient Populations in Whom the Drug May Be Used

Confirmatory clinical trials are underway comparing checkpoint inhibitor drugs alone and in combination with chemotherapy to chemotherapy alone in 1st-line metastatic UC (e.g., ongoing phase III trial Keynote 361 trial[14]). Other uncommon non-urothelial histologies of bladder cancer can occur, and pembrolizumab may be considered for their treatment in the first line platinum unfit population, but evidence of benefit is much more limited.

3 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

One patient input was provided to pCODR through a patient advocacy group submission from Bladder Cancer Canada (BCC) for pembrolizumab for locally advanced or metastatic urothelial carcinoma (UC).

Information was obtained via an online survey and one-to-one interviews with patients. The online survey was conducted between January 28 and February 23, 2019. Potential respondents were identified through messages to BCC's mailing list as well as partner organizations in Australia and the United Kingdom. Messages were also posted on Facebook and Twitter as well as the Inspire and Cancer Survivors Network online discussion boards. Overall, 32 patients and 5 caregivers completed the survey. Some caregivers answered on behalf of patients who were unable to complete the survey. Of the respondents, 34 were from Canada, one was from the US, one from Italy, and one chose not to answer. Thirty-two respondents were diagnosed with locally advanced or metastatic UC. Fifteen respondents had treatment experience with pembrolizumab. Eight online survey participants, all with experience using pembrolizumab, agreed to participate in a follow-up phone interview.

From a patient's perspective, blood in urine was the most commonly reported symptom related to UC, followed by fatigue and urination problems. Almost all patients surveyed by BCC had experience with some form of chemotherapy that led to additional fatigue, nausea, constipation and other well-known side effects, some of which were difficult to tolerate. By comparison, pembrolizumab gave rise to milder side effects, an aspect that was strongly appreciated by patients. The net effect was a subjective improvement in disease control, symptoms, and quality of life in patients switching to pembrolizumab therapy. These benefits were in line with patients' expectations for alternative treatment options, which focused on achieving disease control, extending life expectancy and maintaining quality of life. Most patients with experience using pembrolizumab recommended the drug to other potential UC patients.

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

3.1 Condition and Current Therapy Information

3.1.1 Experiences Patients have with Urothelial Carcinoma

Sixty-nine percent of patients received or were offered chemotherapy with cisplatin and 31% received or were offered chemotherapy with carboplatin. The BCC survey did not ask about patient's PD-L1 status because very few (if any) respondents would have this information.

Nine respondents were diagnosed in 2018, eight in 2017, four in 2016, three 2015, twelve earlier than 2015 and one declined to answer. Blood in urine was the most commonly reported cancer symptom (69%, n=36), followed by fatigue (36%), burning during urination and difficulty urinating (31% each). Some patients who were interviewed reported few or no cancer symptoms prior to treatment.

3.1.2 Patients' Experiences with Current Therapy for Urothelial Carcinoma

Information from 34 survey respondents about intravenous treatments for UC can be found in Table 3.1.

Table 3.1: Treatments Experienced (n=34)

Treatments Received	n
Gemcitabine	21
Cisplatin	19
Carboplatin	9
Durvalumab	2
Atezolizumab	2
Nivolumab	1

Fatigue was the most commonly reported side effect of these treatments (69%, n=36), followed by nausea (42%), constipation (42%), loss of appetite (39%), low blood cell counts (36%) and insomnia (28%). Fatigue and constipation were most commonly identified as the side effects of treatment most difficult to tolerate.

According to BCC, comments about current treatments generally focussed on their lack of efficacy or the side effects that accompanied them:

"The Cisplatin treatments did not reduce the tumors in my bladder and cancer progressed in my body. Before my Keytruda, I was on morphine to control the pain."

"The side effects from cisplatin and gemcitabine were absolutely horrible."

"Cisplatin and gemcitabine left me fatigued, nauseous, and generally unwell. And it didn't stop the cancer from spreading to my lymph nodes."

3.1.3 Impact of UC and Current Therapy on Caregivers

No information on the impact of UC on surveyed caregivers was provided by BCC.

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Expectations for & Experiences To Date with Pembrolizumab

Surveyed patients reported on the importance of various outcomes for treating their UC. On a scale of 1 (not important) to 5 (very important), patients gave an overall rating of 4.7 to controlling disease, extending life expectancy and maintaining quality of life. Reducing symptoms and managing side effects received lower scores. These results suggest that patient values prioritize health outcomes over immediate concerns such as managing side effects. The distribution of the rating is found in Table 3.1.

Table 3.1: Expected outcomes (%, n)

Importance of outcome	1 - not important	2	3	4	5 – very important	Average Total n
Controlling disease	0.00% 0	0.00% 0	0.00% 0	5.41% 2	94.59% 35	4.95 (37)
Reducing symptoms	5.56% 2	8.33% 3	19.44% 7	16.67% 6	50.00% 17	3.83 (36)
Maintaining quality of life	0.00% 0	0.00% 0	2.70% 1	21.62% 8	75.68% 28	4.73 (37)
Managing side effects	2.94% 1	5.88% 2	20.59% 7	11.76% 4	58.82% 20	4.29 (34)
Extending life expectancy	0.00% 0	2.70% 1	0.00% 0	2.70% 1	94.59% 35	4.89 (37)

Respondents also reported on whether they would be willing to tolerate new side effects from drugs that can control disease progression or prevent recurrence. On a scale of 1 (will not tolerate side effects) to 10 (will tolerate significant side effects), respondents gave an average score of 7.79, supporting the conclusion that patient values prioritize long-term health outcomes. Patient ratings regarding side effects associated with effective treatments are detailed in Table 3.3.

Table 3.3: Willingness to tolerate side effects associated with drugs that achieve disease control (%, n)

Rating	Responses	Rating	Responses
1	0.00% 0	6	5.88% 2
2	0.00% 0	7	11.76% 4
3	0.00% 0	8	14.71% 5
4	2.94% 1	9	11.76% 4
5	20.59% 7	10	32.35% 11

Fifteen respondents reported that they had experience with pembrolizumab. Of these, two thirds were previously treated with gemcitabine or cisplatin and 52% were treated with both. Note that it is unclear how many patients with experience with pembrolizumab match the pCODR requested reimbursement criteria. It was noted by BCC that it was not possible to elicit this information, as respondents would not know if they were 'ineligible' for treatments and very few (if any) respondents would have information on the patient's PD-L1 status.

Five were treated with pembrolizumab for 0–3 months, four were treated for 3–6 months, four for 6–12 months, and two were treated for more than one year. Eleven patients were still receiving pembrolizumab for their bladder cancer. Only two respondents reported difficulty accessing treatment—one had difficulty with travel distance and another reported difficulty accessing the clinical trial.

Patients rated changes to quality of life while on pembrolizumab compared to other therapies they had received. The scale ranged from 1 (much worse) to 5 (much better). The average scores for all categories of change were higher than 4. At least half of all respondents gave the highest score to each category suggesting that respondents believe that pembrolizumab has had a strong positive effect on their quality of life. Patient ratings regarding quality of life on treatment are detailed in Table 3.4.

Table 3.4: Changes to patient outcomes while on pembrolizumab (%, n)

Change to outcome	1 – much worse	2	3	4	5 – much better	Average Total n
Metastatic cancer symptoms	0.00% 0	0.00% 0	25.00% 3	8.33% 1	66.67% 8	4.42 12
Drug side effects	0.00% 0	00.00% 0	35.71% 5	14.29% 2	50.00% 7	4.14 14

Maintaining quality of life	00.00% 0	0.00% 0	21.43% 3	28.57% 4	50.00% 7	4.29 14
Controlling disease	00.00% 0	7.69% 1	30.77% 4	7.69% 1	53.85% 7	4.08 13

Selected comments from respondents were provided by BCC:

"I have regained energy and quality of life. The CT scans show no progression of the cancer." [Patient more than one year on pembrolizumab]

"When I started taking Pembrolizumab I was in palliative care getting morphine every two hours and cancer tumours were located throughout my body. After seven treatments with pembrolizumab all signs of cancer were gone. Pembrolizumab is truly a miracle drug! It gives the patient an absolutely wonderful quality of life." [Patient more than one year on pembrolizumab)

"With so few side effects and such minor pain, my quality of life is as if I weren't sick at all." [Patient 6–12 months on pembrolizumab].

Patient respondents also reported on the side effects experienced with pembrolizumab. Skin problems were the most commonly reported side effect (33%, n=15), followed by fatigue (27%), decreased appetite and diarrhea (20% each). BCC stated that no other side effect, had been reported by more than one patient.

Patients respondents rated the impact of the side effects associated with pembrolizumab (scale of 1–5, no impact—significant impact) on their lives. The greatest impact was on the patients' ability to work and travel. No category received an average rating higher than 2, indicating that patients generally feel that pembrolizumab does not significantly interfere with everyday activities. More details can be found in Table 3.5.

Table 3.5: Impact of side effects of pembrolizumab on patient lives (%, n)

Impact of side effects on the lives of patients	1 - no impact	2	3	4	5—significant impact	Not applicable to me	Average Total n
Ability to work	42.86% 6	7.14% 1	0.00% 0	7.14% 1	7.14% 1	35.71% 5	1.88 9
Ability to travel	50.00% 7	14.29% 2	21.43% 3	7.14% 1	0.00% 0	7.14% 1	1.85 13
Ability to drive	64.29% 9	7.14% 1	14.29% 2	7.14% 1	0.00% 0	7.14% 1	1.62 13
Ability to exercise	64.29% 9	7.14% 1	21.43% 3	0.00% 0	0.00% 0	7.14% 1	1.54 13
Ability to perform household chores	57.14% 8	7.14% 1	7.14% 1	14.29% 2	0.00% 0	14.29% 2	1.75 12
Ability to care for children	42.86% 6	7.14% 1	0.00% 0	0.00% 0	0.00% 0	50.00% 7	1.14 (7)
Ability to fulfill family obligations	71.43% 10	7.14% 1	7.14% 1	7.14% 1	0.00% 0	7.14% 1	1.46 (13)
Ability to spend time with family and friends	64.29% 9	0.00% 0	14.29% 2	14.29% 2	0.00% 0	7.14% 1	1.77 (13)

BCC provided additional comments from patients:

"Since starting this treatment, my quality of life has been quite normal." [Patient with 0–3 months experience]

"I did things today that I didn't think I would ever do again." [Patient with 3–6 months experience]

"I can do whatever anyone else can do." [Patient with 6–12 months experience]

"I have had virtually no side effects other than tiredness. I have been able to function normally and do all of my regular activities." [6–12 months]

In addition, respondents to the BCC survey indicated that pembrolizumab was easier to access than other therapies they had experienced. The low duration and frequency of treatments were cited by patients as a benefit during interviews:

"I like the frequency of them, every three weeks and also the duration of the treatments themselves, I'm generally in and out in an hour" [Patient with 3–6 months experience]

3.3 Additional Information

Twelve of 13 respondents indicated that they would recommend pembrolizumab to other bladder cancer patients. Comments provided by BCC include:

"I cannot overstate the lifesaving impact that Pembrolizumab has had for me and it should be the first line treatment now for bladder cancer patients. The current first-line treatment with cisplatin and gemcitabine is very detrimental to a person's overall health. It destroys your immune system and makes your quality of life awful. Pembrolizumab does wonderful things for your quality of life and there are practically no side effects." [Patient with more than one year experience]

"No negatives. Such minor side effects that they are barely worth mentioning. This drug is saving my life right now. I hope it continues to do so." [Patient with 6–12 months experience]

"The short length of time and the positive results along with the minimal side effects, in my opinion, makes it a wonder drug." [Patient with 0–3 months experience]

"Keytruda saved my life or at least extended it." [Patients with 6-12 months experience].

BCC highlighted the lack of treatment options and poor survival (death within months) for UC patients who are not eligible or cannot tolerate cisplatin-based chemotherapy. BCC stated that the overall patient benefits from pembrolizumab in improving disease symptoms and quality of life are significant compared to currently available first-line options, a notion that they suggest is supported by responses to their survey.

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 **seven of nine** provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation:

Clinical factors:

- Clarity on eligible patient population

Economic factors:

- Additional resources needed to monitor infusion reaction
- Potential for drug wastage with 200 mg fixed dose and discontinuation of 50mg vial

Please see below for more details.

Please see below for more details.

4.1 Currently Funded Treatments

PAG identified that treatment options for patients with locally advanced or metastatic urothelial carcinoma (MUC), who are not eligible for cisplatin-containing chemotherapy is gemcitabine-carboplatin or gemcitabine monotherapy. For patients not eligible for platinum-containing chemotherapy, gemcitabine monotherapy would be offered.

PAG noted that the KEYNOTE-052 trial being submitted for review is a phase 2 non-comparative trial and is seeking information on the comparison of pembrolizumab to gemcitabine-carboplatin as well as gemcitabine alone.

4.2 Eligible Patient Population

In the KEYNOTE-052 trial, patients were excluded if they had active central nervous system (CNS) metastases and/or carcinomatous meningitis; prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent; or active autoimmune disease. PAG is seeking guidance on whether these subgroups of patients would be eligible for pembrolizumab in this setting.

Pembrolizumab was also recently reviewed at pCODR for the treatment of patients with MUC who have disease progression during or following platinum-containing chemotherapy or within 12 months of completing neoadjuvant or adjuvant platinum-containing chemotherapy. PAG is seeking guidance on whether generalizability in this setting should align with the previous pembrolizumab indication for MUC (e.g., patients with urothelial cancer of predominantly transitional histology of any primary site, patients without formal measurable disease).

If recommended for reimbursement, PAG noted patients currently on first-line treatment (gemcitabine monotherapy or gemcitabine-carboplatin) who have not progressed, would need to be addressed on a time-limited basis. If appropriate to switch to pembrolizumab, PAG is seeking guidance on the appropriate timeframe.
PAG noted that the reimbursement request for pembrolizumab is for patients who not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 ≥10 as

determined by a validated test, or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status. Pembrolizumab for patients who are eligible for first-line cisplatin-containing chemotherapy or platinum-containing chemotherapy is out of scope of the current review.

4.3 Implementation Factors

The dose is 200mg for urothelial cancer in the funding request and the KEYNOTE-052 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 (i.e., 2mg/kg up to 200mg) given the high cost of fixed dose compared to weight-based dose for patients weighing less than 100kg. PAG also identified emerging data of dosing pembrolizumab at 400mg every 6 weeks, PAG is seeking guidance on the appropriateness of alternate dosing/schedule (i.e., 400mg or 4mg/kg up to a flat dose cap of 400mg every 6 weeks).

As pembrolizumab is currently used in a number of other indications, drug wastage could be minimized with vial sharing. However, vial sharing may not be feasible in smaller outpatient cancer centres. Furthermore, discontinuation of the 50 mg vial may result in wastage, particularly in low volume or rural institutions where vial sharing is not feasible and weight-based dosing is utilized. PAG identified that the continued availability of the 50 mg vial and introducing a 25 mg vial would be an enabler to implementation.

Pembrolizumab is a high cost drug and requires monitoring and treating 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.

PAG noted some patients may interrupt treatment with pembrolizumab due to toxicity or other reasons. PAG is seeking guidance on the appropriateness of re-initiation with pembrolizumab after toxicity resolution or treatment interruption for other reasons and if this occurs, clarification on the total duration of therapy (i.e., two year of treatment or a total of 35 administration).

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.

4.4 Sequencing and Priority of Treatments

PAG is seeking guidance, for patients who receive pembrolizumab in this setting,

- Confirmation that patients would not receive subsequent PD-1 or PD-L1 inhibitors
- Re-treatment for patients who discontinue treatment for reasons other than progression
- Following completion of 24 months, appropriateness of re-treatment and the time interval between end of treatment and relapse
- Second-line treatment options following progression (e.g., paclitaxel)

4.5 Companion Diagnostic Testing

PAG has indicated that PD-L1 testing is currently done in other disease sites, however, PD-L1 testing is not currently completed for patients with locally advanced or metastatic urothelial carcinoma. There would be an increase volume for PD-L1 testing and PAG would like this accounted for in the economic analysis.

PAG also noted that labs are not reporting a Combined Positive Score for PD-L1, this would be a barrier to implementation as updates to lab reporting would need to occur.

4.6 Additional Information

None.

5 SUMMARY OF REGISTERED CLINICIAN INPUT

Four separate registered clinician inputs were provided for pembrolizumab for the treatment of locally advanced or metastatic urothelial carcinoma (UC). Three of the four inputs were prepared by individual clinicians while the other was jointly submitted by three clinicians from CancerCareOntario. A summary of the inputs is provided below.

Clinicians providing input indicated that advanced UC is an area of clear unmet need owing to suboptimal treatment options. Many patients have comorbidities that preclude the use of toxic chemotherapy. In contrast, pembrolizumab is less toxic and can provide significant and durable benefits. There is general agreement that pembrolizumab should be the preferred first-line treatment for the target population. Next in line would be chemotherapy should the patient become eligible. Contraindications for pembrolizumab are not as numerous as for chemotherapy, but autoimmune disorders should be considered and managed. Some clinicians mentioned that PD-L1 testing is not standard in all settings and should be made more broadly available.

Please see below for a summary of specific input received from the registered clinicians.

5.1 Current Treatment(s) for Locally Advanced or Metastatic UC

The clinician inputs indicated that the treatment options for patients with locally advanced or metastatic UC, who are not eligible for cisplatin-containing chemotherapy are gemcitabine-carboplatin or gemcitabine monotherapy. For patients not eligible for platinum-containing chemotherapy, gemcitabine monotherapy would be offered. Clinicians noted that this is a common scenario and an area of unmet need because many patients with this disease are elderly and have comorbidities precluding the use of cisplatin. A minority of these patients may benefit from carboplatin/gemcitabine (i.e., ECOG PS 0–1 with comorbidities or ECOG 2 without comorbidities or other contraindications). Single agent gemcitabine is not known to improve quality of life and is associated with poor response rates; many patients are also ineligible for this chemotherapy. Supportive/palliative care alone is currently given to such patients.

5.2 Eligible Patient Population

The clinicians providing input agreed that the reimbursement request aligns with the need identified in clinical practice. They believe the eligibility criteria of the clinical trial can be applied in practice. For example, in the metastatic setting, most clinicians will not offer cisplatin to patients with a creatinine clearance of less than 60 ml/min, which is consistent with the study population. According to the clinician inputs, the patient population composed of an elderly, frail population that cannot tolerate chemotherapies which represents the clinical reality. One clinician indicated that 40–50% of patients with advanced UC are eligible for cisplatin-based therapy, the remainder receiving the carboplatin-based therapy, gemcitabine monotherapy, or supportive care only. Another clinician estimated that approximately 25% of their metastatic UC population would be eligible for pembrolizumab under the current criteria. Clinicians reiterated that there is a clear unmet need in cisplatin-ineligible patients as carboplatin-based regimens are inferior and just as toxic as cisplatin, and there is no treatment for chemotherapy-ineligible patients. Clinicians stressed that patient choice is also important.

5.3 Relevance to Clinical Practice

Clinicians providing input noted that pembrolizumab is currently used in the post-platinum setting for advanced UC, so there is experience with this treatment in the clinical community. All clinicians agreed that they would use the treatment as described in the reimbursement request. According to a clinician, use of pembrolizumab in this population would be safer than subjecting unfit patients to chemotherapy in order to gain access to second-line pembrolizumab. In addition to the much-improved toxicity profile, responses to pembrolizumab are excellent and can be durable. One clinician with experience with pembrolizumab in the second line reported that responses have been meaningful with rapid symptomatic relief and excellent tolerability. The clinician reported an improved therapeutic index relative to chemotherapies similar to that seen in lung cancer and melanoma. The clinician mentioned challenges in terms of patient education and monitoring of autoimmune effects, but clinics are becoming more adept at managing and containing such problems.

One clinician noted that a contraindication to receiving this treatment would be active autoimmune disease. Another clinician added that poor patient compliance with side effect monitoring and reporting would constitute a contraindication. Contraindications to carboplatin or gemcitabine include a poor performance status, hearing impairment, poor oral intake of fluids, bleeding risk, poor hematological tolerance, significant renal dysfunction and neuropathy. In these situations, pembrolizumab would be preferable.

5.4 Sequencing and Priority of Treatments with Pembrolizumab

According to the clinicians providing input, pembrolizumab would be given first line in the target population, potentially avoiding the need for further chemotherapy. One clinician added that although adjuvant chemotherapy may have been given in the past, this treatment should not be a factor in eligibility. The clinician did not think patients should be given pembrolizumab if they had received prior immunotherapy. Subsequent lines of therapy could include chemotherapy (gemcitabine with or without carboplatin) if the patient's ECOG PS improved.

In that regard, one clinician explained that there is a small but real possibility that patients who were chemotherapy-ineligible at the time of pembrolizumab therapy could become platinum-eligible later on if they progress or recur and their performance status, renal function, etc. have significantly improved due to positive disease response to the pembrolizumab treatment.

5.5 Companion Diagnostic Testing

Clinician input indicated that for patients eligible for platinum-containing treatment, but not cisplatin specifically, PD-L1 testing would be required. Clinicians from Ontario noted that this test is currently not funded as part of standard of care and would need to be funded with an appropriate (up to 14 days) turnaround time for this subset of patients, given the prognosis of advanced UC patients. While the test is not expensive, there was concern that pathology labs would not have the necessary resources to meet the expected increase in demand. Clinicians from another province (Alberta) stated that the test was fully funded and results were provided with an acceptable turnaround. One clinician remarked that genitourinary pathologists should become familiar with the companion diagnostic test.

5.6 Additional Information

None.

5.7 Implementation Questions

5.7.1 In regards to question 3.2 above, the eligibility criteria for the KEYNOTE-052 trial included a specific patient population compared to the broader funding request. In clinical practice, is there evidence to extend the use of pembrolizumab to (provided all other eligibility criteria are met):

5.7.1.1 Patients with active central nervous system (CNS) metastases and/or carcinomatous meningitis

Three clinician inputs answered "yes." While they acknowledged a lack of evidence, they noted the very poor prognosis without therapy in this population and the minimal budget impact due to the small number of patients. One clinician added that CNS metastases would need to be treated first (for example, with radiation), while another expected immunotherapy to better address CNS metastases than chemotherapy, as seen with other metastatic cancers.

The other clinician input did not think treatment of this population with pembrolizumab would be appropriate.

5.7.1.2 Prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent

One clinician supported the extension if immunotherapy was completed over one year previously either in the neoadjuvant setting or if a response/disease stability was obtained in the metastatic setting. A second clinician indicated that treatment should not be offered, while another noted the absence of supporting evidence. Clinicians from the joint submission did not reach a consensus — some noted the absence of evidence while others had no issue with extending pembrolizumab to this population.

5.7.1.3 Patients with active autoimmune disease

One clinician explained that recent retrospective studies have demonstrated that, despite common concerns, only about 20–30% of patients with past autoimmune diseases suffer exacerbations on PD-1 or PD-L1 targeted therapies. However, in the clinician's experience, much higher numbers have been seen and they would support excluding eligibility for patients with active autoimmune disease. On the other hand, HIV patients on effective antiretroviral therapy should be allowed access. Another clinician also did not believe treatment should be offered.

The joint clinicians felt that treatment should be given if the autoimmune disease is well controlled with no more than 10 mg/day of an equivalent dose of prednisone.

Another clinician felt that autoimmunity is a spectrum and that this should be an individual decision made by the clinician.

5.7.1.4 Align with patient population for the pembrolizumab pCODR review "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".

For example, patients with urothelial cancer of predominantly transitional histology of any primary site or patients without formal measurable disease.

One clinician input was supportive of including transitional histology elsewhere in the urinary tract. The clinician who provided this input believe that patients with metastatic disease should be eligible regardless of formal measurable status. The other clinicians agreed that this patient population would be suitable for pembrolizumab.

5.7.2 In regards to question 3.4 above, please consider what treatment options would be available to patients upon progression of pembrolizumab.

Clinician inputs mentioned that options for PD-L1 positive, cisplatin-ineligible patients, best supportive care in addition to next line chemotherapy (gemcitabine alone, carboplatin/gemcitabine, taxane-based therapy) would be options. The likelihood of being chemotherapy-eligible would be slightly less for the generally platinum-unfit who progressed on pembrolizumab. Chemotherapy would be reserved for patients with an ECOG PS that improved on first-line treatment or remained good enough to allow for it.

5.7.3 In what clinical scenarios would pembrolizumab or chemotherapy be the preferred treatment for first-line MUC where patients are not eligible for platinum-containing chemotherapy? Please comment on the preference considering patient preference, efficacy, safety, and administration.

According to clinicians, CPS ≥10 patients and patients not eligible for platinum-based chemotherapy would be prime candidates for pembrolizumab. Patients may choose it because of lower toxicity and ease of administration with fewer medical visits. By comparison, gemcitabine monotherapy offers marginal or no value aside from the occasional short-term stabilization of disease.

5.7.4 In clinical practice, what is the clinical utility of a Combined Positive Score for PD-L1 in this setting (i.e., patients not eligible for cisplatin-containing chemotherapy and whose tumours express PD L1 [(CPS) ≥10] or patients who are not eligible for any platinum containing chemotherapy regardless of PD L1 status)?

One clinician indicated that while CPS is not currently routinely checked as there is no first-line immunotherapy option, it would become part of reflex testing same as in other cancers. Clinician inputs indicated that the CPS appears to be a good tool to measure PD-L1 status as evidenced by the clinical trials that validated the stated cut-off of CPS ≥ 10 using the particular assay and antibody. Evidence related to ROC dynamics and clinical utility suggests that CPS is more reliable than the TPS score used in lung cancer. Clinicians agreed that platinum-eligible patients should be investigated to be PD-L1 (CPS) positive in order to expect the benefits stated in the drug application as evidenced in the KN-052 trial. One clinician suggested that some patients with low PD-L1 CPS may still derive benefit from pembrolizumab.

A clinician input maintained that inclusion of patients ineligible for any platinum chemotherapy regardless of PD-L1 status to potentially avail of pembrolizumab is of utmost importance in a clinical setting given the unmet need for this group of patients. Responses in unselected patients not eligible for any chemotherapy were still clinically meaningful at >20% and thus the CPS cut-off should not be used to deny patients therapy with pembrolizumab in that cohort.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the efficacy and safety of pembrolizumab monotherapy in patients with locally advanced or metastatic urothelial carcinoma (MUC) who are not eligible for cisplatin-containing chemotherapy and whose tumours express programmed death-ligand 1 (PD-L1) [Combined Positive Score (CPS) ≥10] as determined by a validated test, or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status.

Supplemental Questions and Comparison with Other Literature most relevant to the pCODR review and to the Provincial Advisory Group were identified while developing the review protocol and are outlined in section 7 and section 8.

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 table 6.1 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 6.1.: Review 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 MUC who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 [CPS ≥10] as determined by a validated test, or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status	Pembrolizumab	Gemcitabine monotherapy Carboplatin + gemcitabine	Primary • **OS** • **PFS** • **HRQoL** Secondary • **ORR** • DOR • DCR Safety • AEs • SAEs • WDAEs • Immune-related AEs • Dose adjustment, interruption and/or discontinuation • Time to next therapy
Abbreviations: AE=adverse events; **CPS** = combined positive score**; DCR**=disease control rate; **DOR=**duration of response; **HRQoL**=Health related quality of life; **MUC** = metastatic urothelial carcinoma; **ORR**=objective response rate; **PD-L1** = programmed				

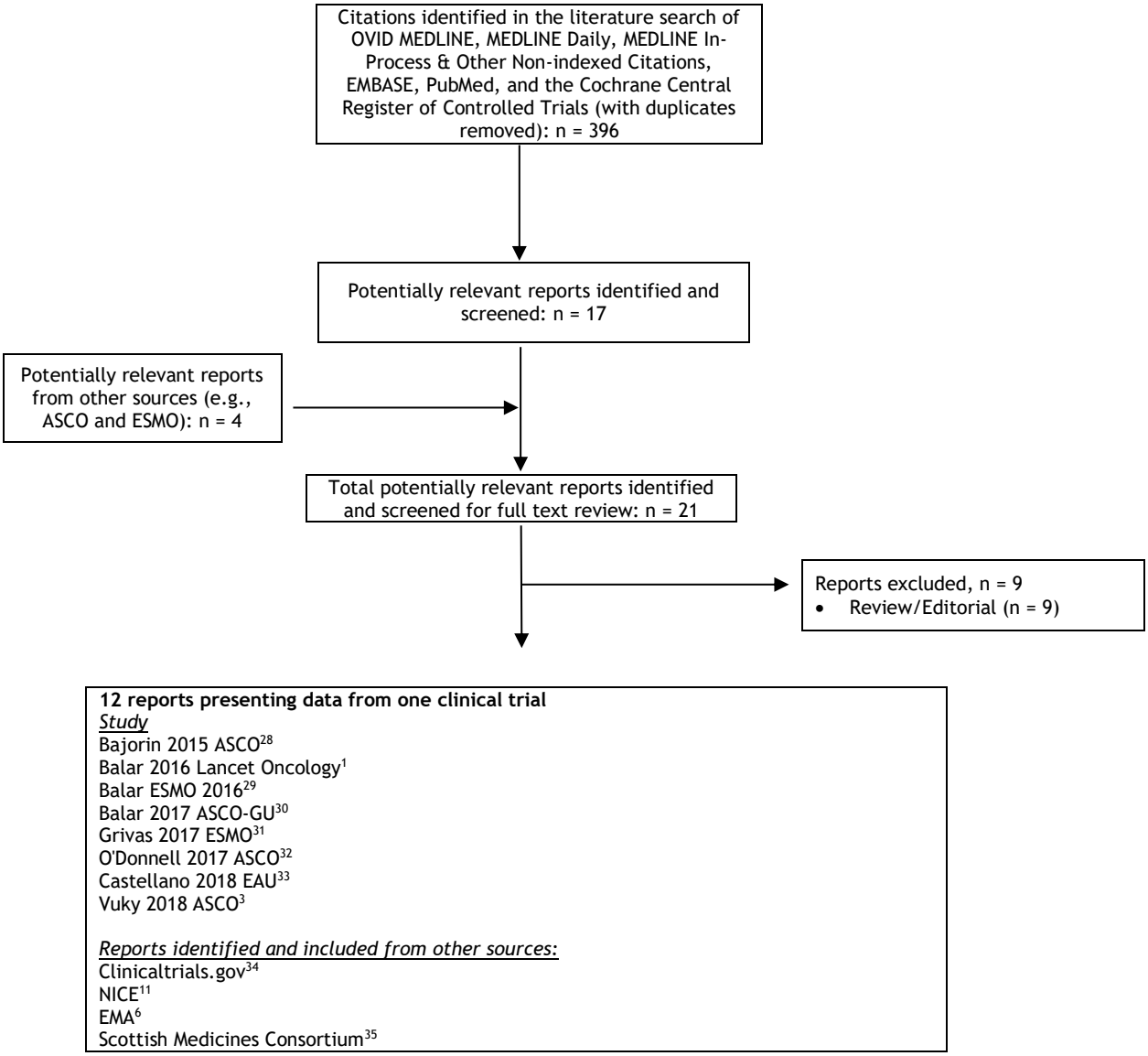
death-ligand 1; **PFS** = progression-free survival; **RCT**=randomized controlled trial; **SAE**=serious adverse events; **WDAE**=withdrawals due to adverse events
Notes: * Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions).

6.3 Results

6.3.1 Literature Search Results

Of the 396 potentially relevant reports identified, one study (KEYNOTE-052), reported in 12 citations, was included in the pCODR systematic review (Figure 6.1).[1-3,5-8,11,28-36] Nine reports were excluded because nine were reviews or editorials. Additional reports related to the KEYNOTE-052 trial were obtained from the Submitter.[2,5,7,8,36]

Figure 6.1. QUOROM Flow Diagram for Inclusion and Exclusion of studies



Note: Additional data related to the KEYNOTE-052 trial were also obtained through requests to the Submitter by pCODR [KEYNOTE-052 Protocol,[2] Clinical Rationale,[8] Indirect Treatment Comparison,[36] Clinical Study Report,[5] Checkpoint Responses,[7] Additional Information[8-10] and O'Donnell 2019 ASCO[4]]

6.3.2 Summary of Included Studies

The pCODR systematic review included one single-arm, open-label, phase II trial (KEYNOTE-052) that assessed the safety and efficacy of pembrolizumab as a first-line therapy in 374 cisplatin-ineligible patients with locally advanced and unresectable or metastatic urothelial cancer (MUC).[1]

It is important to highlight that the pCODR requested reimbursement criteria are for two subgroups within the KEYNOTE-052 trial: (1) patients with PD-L1 CPS ≥ 10% who are cisplatin ineligible and (2) patients who are ineligible to receive any platinum chemotherapy, irrespective of the PD-L1 status. This pCODR review will present the results for the overall trial population as well for the two subgroups specified in the funding request.

6.3.2.1 Detailed Trial Characteristics

The summary of the trial and select quality characteristics are presented in Table 6.2 and Table 6.3.

Table 6.2: Summary of KEYNOTE-052 trial

Trial Design	Inclusion Criteria	Intervention	Trial Outcomes
Study KEYNOTE-052 **Trial Characteristics** Ongoing, non-randomized, multi-site, open-label trial **Number Randomized** N= 374 **Number Treated** N= 370 **Number of centres and countries** 91 centres in 20 countries **Patient Enrolment Dates** 24-Feb-2015 to 8-Aug-2016 **Data cut-off** 01-Sep-2016 09-Mar-2017 30-Nov-2017 26-Sep-2018 **Primary completion data cut-off**	<u>Key Inclusion Criteria:</u> • Aged ≥ 18 years • Histologically or cytologically confirmed diagnosis of advanced/unresectable (inoperable) or MUC of the renal pelvis, ureter, bladder, or urethra (transitional cell and mixed transitional/non-transitional cell histologies) • Ineligibility to receive cisplatin-based combination therapy, based on at least one of the following criteria: ○ ECOG Performance Status of 2 (the proportion of these subjects will be limited to approximately 50% of the total population) ○ Creatinine clearance (calculated or measured) <60 mL/min but ≥30 mL/min. Note: Subjects with a creatinine clearance (calculated or measured) <30 mL/min or on dialysis are excluded from the trial ○ CTCAE v.4, Grade ≥2 audiometric hearing loss (25dB in two consecutive wave ranges) ○ CTCAE v.4, Grade ≥2 peripheral neuropathy ○ New York Heart Association (NYHA) Class III heart failure • Note: In the event that subjects are enrolled for the purposes of determining the biomarker cut-point prior to the start of the main body of this study, these subjects are not required to be cisplatin-ineligible and the above criteria does not apply.	<u>Intervention</u> Pembrolizumab 200 mg every 3 weeks	<u>Primary:</u> • ORR using RECIST 1.1 by IRR • ORR using RECIST 1.1 by IRR in PD-L1 positive patients • ORR using RECIST 1.1 by IRR in strongly PD-L1 positive patients <u>Secondary:</u> • DOR using RECIST 1.1 by IRR in all patients, PD-L1 positive patients and strongly PD-L1 positive patients • PFS using RECIST 1.1 by IRR in all patients, PD-L1 positive patients and strongly PD-L1 positive patients • OS using RECIST 1.1 by IRR in all patients, PD-L1 positive patients and strongly PD-L1 positive patients

Trial Design	Inclusion Criteria	Intervention	Trial Outcomes

19-Jun-2018
 	
Final Analysis Date
28-Sep-2020
 	
Funding
Merck
	• No prior systemic chemotherapy for advanced/unresectable (inoperable) or metastatic urothelial cancer.
	  ○ Adjuvant platinum-based chemotherapy, following radial cystectomy with recurrence >12 months from completion of therapy is permitted
	  ○ Neoadjuvant platinum-based chemotherapy, with recurrence >12 months since completion of therapy is permitted
	• Provided tissue for biomarker analysis from a newly obtained core or excisional biopsy of a tumor lesion not previously irradiated (mandatory). Adequacy of the biopsy specimen for PD-L1 biomarker analysis must be confirmed by the central laboratory.
	• Measureable disease based on RECIST 1.1 as assessed by central review.
	• ECOG performance status of 0, 1 or 2
	• Adequate organ function
	
	<u>Key Exclusion Criteria:</u>
	• Disease suitable for local therapy administered with curative intent.
	• Current or previous participation in a study of an investigational agent, with study therapy received or investigation device used within 4 weeks of the first dose of treatment.
	• Prior anticancer monoclonal antibody for direct anti-neoplastic treatment within 4 weeks prior to study Day 1 or not recovered (ie, ≤Grade 1 or at baseline) from AEs due to agents administered more than 4 weeks earlier.
	• Prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to Grade 1 or at baseline) from AEs due to a previously administered agent
	• Known additional malignancy progressing or requiring active treatment; active central nervous system metastases and/or carcinomatous meningitis; active autoimmune disease requiring systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs).
	• Prior therapy with an anti-PD-1, anti-PD-L1 agent, or with anagent directed to another co-inhibitory T-cell receptor (eg, CTLA-4,OX-40, CD137).
	• Known history of HIV
			<u>Tertiary:</u>
			• EORTC QLQ-C30 and EQ-5D-3L in all patients, PD-L1 positive patients and strongly PD-L1 positive patients

Abbreviations: **AE**=adverse events; **CNV** = central nervous system; **CPS** = combined positive score; **CTCAE** = Common Terminology Criteria for Adverse Events; **DCR**=disease control rate; **DOR**=duration of response; **ECOG** = Eastern Cooperative Oncology Group; **EORTC QLQ-C30**=European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire 3 Levels; **EQ-5D-3L** = European Quality of Life Five Dimensions Questionnaire; **HBV** = Hepatitis B; **HCV** = Hepatitis C; **HIV** = human immunodeficiency virus; **IRR** = Independent Radiology Review; **mAb** = monoclonal antibody; **MUC** = metastatic urothelial carcinoma; **NYHA** = New York Heart Association; **ORR**=objective response rate; **PD-L1** = programmed death-ligand 1; **PFS** = progression-free survival; **RECIST** = Response Evaluation Criteria in Solid Tumors; **SAE**=serious adverse events; **WDAE**=withdrawals due to adverse events

Table 6.3: Select quality characteristics of KEYNOTE-052 trial

Study	Treatment vs. Comparator	Primary outcome	Required sample size	Sample size	Randomization method	Allocation concealment	Blinding	ITT Analysis	Final analysis	Early termination	Ethics Approval
KEYNOTE-052	Pembrolizumab	ORR	350[A]	370	NA	NA	No[B]	No[C]	No[D]	No	Yes

Abbreviations: **ORR** = objective response rate; **NA** = not applicable

[A] The sample size was based on the primary efficacy estimation of patients with a PD-L1 CPS ≥10%. It was estimated that a sample size of 350 patients would be required. It was assumed that 33% of patients would have a PD-L1 CPS ≥10% and there would be 100 patients in the biomarker discovery population. Therefore, there would be an 88% chance to have at least 75 patients with a PD-L1 CPS ≥ 10% and an 99.9% chance to have at least 60 patients with PD-L1 CPS ≥ 10% in the validation cohort (N = 250).[1]

[B] It was reported that the study team was blinded to PD-L1 status throughout the study until the data cut-off for the primary outcome. The interim analyses were conducted by an unblinded statistician.[2]

[C] The primary analysis was conducted in all patients enrolled in the trial who received at least one dose of pembrolizumab.

[D] The study is ongoing and the study completion date is 28-Sep-2020.[3,4]

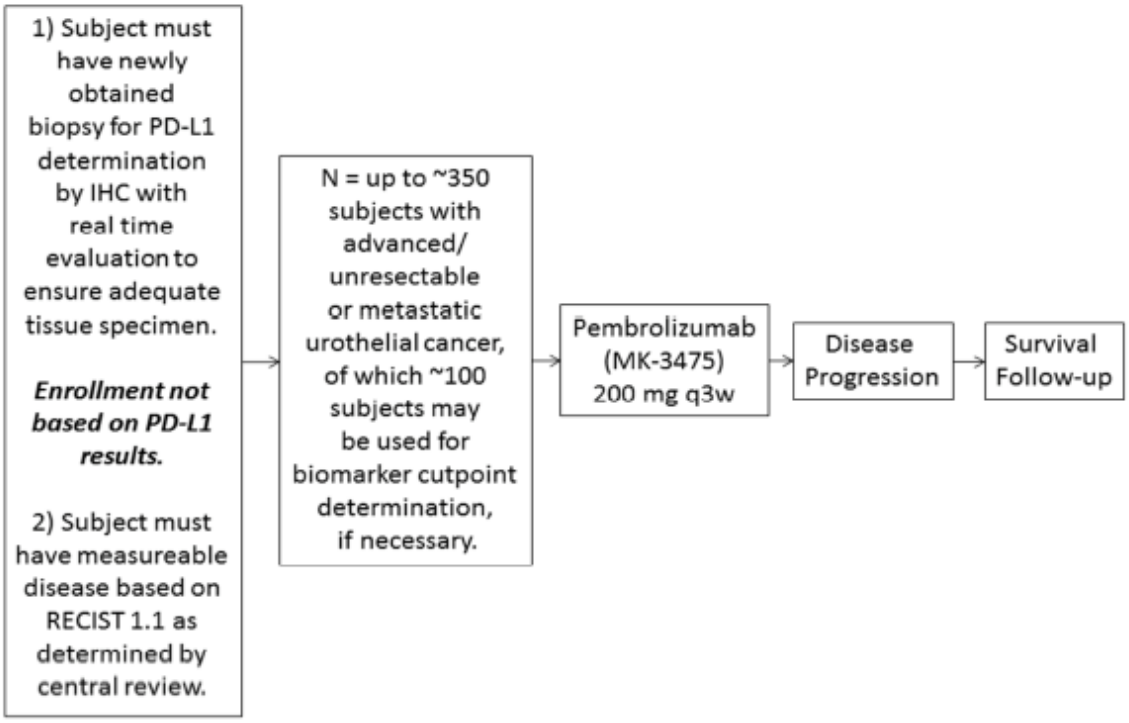
a) Trials

Trial Characteristics

KEYNOTE-052 was a multicentre, nonrandomized, open-label, phase II trial that assessed the safety and efficacy of pembrolizumab as a first-line therapy in cisplatin-ineligible patients with locally advanced and unresectable or MUC.[1] Patients were enrolled in the trial regardless of PD-L1 status. The trial was conducted in 20 countries, including Canada. The trial was sponsored by Merck.

Patients were included in the trial if they met the following criteria: 18 years of age or older; histologically or cytologically confirmed locally advanced and unresectable or MUC of the renal pelvis, ureter, bladder, or urethra; were ineligible for cisplatin-based therapy; had not previously received systemic chemotherapy for advanced disease; had centrally confirmed and measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1); had an ECOG performance status of 0 to 2; had adequate organ function.[2] Further details on the inclusion criteria and exclusion criteria are provided in Table 6.4.

Figure 6.2: Study design of the KEYNOTE-052 trial



Data Source: EMA Assessment Report[6]

Figure 6.2 represents the study design of the KEYNOTE-052 trial. It consisted of three phases: 1) the treatment phase, 2) the retreatment phase and 3) the follow-up phase. These phases will be described in further detail, more specifically:

Treatment Phase:[2]

- Prior to enrollment, patients were required to provide a tumour biopsy for a biomarker analysis.[1] However, enrollment was not dependent on PD-L1 measurements.[5]
    - PD-L1 expression levels were measured in formalin-fixed, paraffin-embedded tissues using a PD-L1 clinical trial assay (PD-L1 IHC 22C3 pharmDx assay; Agilent Technologies, Carpinteria, CA, USA).[1]
    - PD-L1 expression levels were scored using a CPS, which was defined as the percentage of cells (i.e., tumour cells, macrophages, or lymphocytes) that expressed PD-L1 in a tumour biopsy.[1]
    - Two PD-L1 CPS cut-offs were reported in the trial (i.e., 1% and a 10%).[1]

- Patients were randomized in an unblinded and unstratified fashion using a central computerized interactive voice and web response system.
- All patients who were enrolled in the trial were treated with 200 mg dose of pembrolizumab every three weeks (Q3W).
- Radiographic imaging was performed at 9 weeks after the first dose of the trial treatment on Day 1 of Cycle 1, and then every 6 weeks thereafter. Patients who remained on therapy for more than a year were evaluated every 12 weeks.
- All imaging was submitted to a central vendor for a blinded independent radiology review (IRR) using RECIST 1.1.

- Patients with initial radiological disease progression had repeated imaging occurring ≥ 4 weeks later to confirm disease progression.
    - If repeat imaging demonstrated stable disease (SD), partial response (PR) or complete (CR), then treatment was continued. If repeat imaging met the threshold for disease progression (i.e., ≥ 20% increase in tumor burden compared to nadir) but showed a reduction in tumour burden compared to the previous timepoint, then treatment was continued. If repeat imaging confirms disease progression without a reduction in tumour burden compared to the previous timepoint, then treatment was discontinued.
- The study investigator may have chosen to treat beyond RECIST 1.1 defined progression if patients continued deriving clinical benefit and they were clinically stable.
    - Clinically stable was defined by the following criteria:
        - Absence of signs and symptoms indicating disease progression,
        - No decline in ECOG performance status,
        - Absence of rapid progression of disease,
        - Absence of progressive tumour at critical anatomical sites requiring urgent alternative medical intervention,
        - Patients exhibiting toxicity from trial therapy.
- Patients could withdraw from treatment for any of the following reasons:
    - Patient or legal representative withdraws consent,
    - RECIST-confirmed radiologic disease progression,
    - Unacceptable AEs,
    - Incurrent illness that prevents further administration of treatment,
    - Investigator's decision to withdraw the patient,
    - Pregnancy,
    - Noncompliance with trial treatment or procedure requirements,
    - Lost to follow-up,
    - Completed 24 months of treatment with pembrolizumab.

Retreatment Phase:[2]

- Patients who had radiographic disease progression were eligible for an additional year of pembrolizumab therapy. Patients must have met the following criteria:
    - Either
        - Stopped initial treatment with pembrolizumab after attaining an investigator-determined confirmed CR according to RECIST 1.1
            - Was treated for at least 24 weeks with pembrolizumab before discontinuing therapy.
            - Received at least two treatments with pembrolizumab beyond the date when the initial CR was declared.
    - OR
        - Patient had SD, PR or CR and stopped pembrolizumab treatment after 24 months of trial treatment for reasons other than disease progression or intolerability.
    - AND
        - Experienced an investigator-determined confirmed radiographic disease progression after stopping their initial treatment with pembrolizumab.
        - Did not receive any anti-cancer treatment since the last dose of pembrolizumab.
        - Had an ECOG performance status of 0 or 1.
        - Adequate organ function.
- Patients received the same dose and frequency of pembrolizumab as in the treatment phase.

Follow-up Phase:[2]

- Safety follow-up was conducted approximately 30 days after the last dose of the trial treatment or before the initiation of a new anti-cancer treatment, whichever occurred first.
- 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 thereafter.
- Patients who stopped receiving pembrolizumab were followed for survival as well as post-treatment information.

Statistical Considerations

Efficacy and Safety Analyses: The primary efficacy and safety analyses were conducted in all patients. This population was defined as all those patients who were enrolled in the trial and received at least one dose of the study treatment.

The trial also included a biomarker discovery population. It included the first 100 patients who were enrolled in the trial and were deemed clinically evaluable.[2] Patients were classified as clinically evaluable if they received at least one dose of the study drug and they had scans completed at week 9 and 15, or they had discontinued due to radiographic or clinical progression or death before reaching week 15.[2] The biomarker discovery population was used to determine the PD-L1 strongly positive cut-point and were subsequently excluded from the efficacy analyses that were conducted in the PD-L1 strongly positive population; however, patients in the biomarker discovery population were included in the primary efficacy analyses.

The Submitter also performed a post-hoc subgroup analysis in patients who were platinum ineligible. Patients were classified as platinum ineligible if they had an ECOG performance status 2 and one or more of visceral metastasis, advanced age (≥ 80 years) or glomerular filtration rate (GFR) < 60 mL/min.[8]

Outcomes: The primary outcome in the trial was object response rate (ORR) using RECIST 1.1 criteria as assess by an independent radiology review (IRR). Secondary outcomes included: duration of response (DOR) using RECIST 1.1 criteria as assess by an IRR, overall survival (OS) and progression free survival (PFS) using RECIST 1.1 criteria as assess by an IRR and safety outcomes. Exploratory outcomes included health-related quality of life (HRQoL).

Sample Size: The sample size was based on the primary efficacy estimation of patients with a PD-L1 CPS ≥10%. It was estimated that a sample size of 350 patients would be required. It was assumed that 33% of patients would have a PD-L1 CPS ≥10% and there would be 100 patients in the biomarker discovery population. Therefore, there would be an 88% chance to have at least 75 patients with a PD-L1 CPS ≥10% and an 99.9% chance to have at least 60 patients with a PD-L1 CPS ≥10% in the validation cohort (N = 250).[1,2]

Hypothesis Testing and Multiplicity: On 11-Mar-2016, a protocol amendment removed all hypothesis testing.[2] This change was justified because the objective of the trial was to estimate efficacy, and the success of the trial was determined by clinically meaningful ORRs and durability of the response. Thus, hypothesis testing was not performed and the original sample size was not adjusted. Although the trial prespecified the PD-L1 subgroups, it is difficult to determine whether there are statistical differences across subgroups due to the lack of hypothesis testing, and therefore, these results should be interpreted with caution. In addition, as this was an estimation study no adjustments were made for multiplicity.

Database Locks: The pCODR literature search identified four data cut-offs (i.e., 01-Sep-2016; 09-Mar-2017, 30-Nov-2017 and 26-Sep-2018). In a Checkpoint Response, the Submitter reported that the 01-Sep-2016 database lock was used for the initial regulatory submission to the United States and European Union.[7] The 09-Mar-2017 data cut-off was created to provide an updated data analysis on the safety and efficacy of pembrolizumab and represents the secondary interim analysis.[7,11,35] The 30-Nov-2017 database lock was used to assess the long-term safety and efficacy of the data but it was not a final analysis and it was not used to support the United States and European Union submissions.[7] The Submitter also commented that data from the 09-Mar-2017 and 30-Nov-2017 database locks were submitted to Health Canada.[7] The Submitter also provided a poster representing the 26-Sep-2018 database lock, which presents a follow-up period of over 2 years since the last patient was enrolled in the KEYNOTE-052 trial.[4] The Submitter did not adjust for the multiple data cut-offs since the trial was considered exploratory and no hypothesis test were conducted.

Interim Analyses: Two interim analyses were planned for the KEYNOTE-052 trial. The first interim analysis was conducted to determine the PD-L1 strongly positive cut-point in the biomarker discovery population, which consisted of the first 100 patients enrolled in the trial.[2] The second planned analysis was conducted in order to determine if enrollment of PD-L1 negative (CPS <1%) patients should be stopped if ORR was low and ongoing enrollment was still required. This futility analysis was based on the number of evaluable PD-L1 negative patients in the biomarker discovery population, which could be up to the first 25 patients. However, if the number of PD-L1 negative patients in the biomarker discovery group was less than 20, then additional PD-L1 negative subjects could be included until the number reached at least 20.[2] The non-binding rule for futility required that the upper limit of the 95% confidence interval (CI) (2-sided) for the ORR be less than 20% (needed at least 1 response in N < 26 subjects and at least 2 responses in N = 26 to 40 subjects).

Protocol Amendments: Table 6.4 shows the two major protocol amendments that occurred on 08-Oct-2014 (Amendment 1) and 11-Mar-2016 (Amendment 2).

Table 6.4: Summary of the major protocol amendments that occurred in the KEYNOTE-052 trial on 08-Oct-2014 (Amendment 1) and 11-Mar-2016 (Amendment 2)

Amendment	Date	Changes
Amendment 1	08-Oct-2014	• The inclusion criteria were updated to state that subjects must be refractory to available or standard therapy for treatment of their bladder cancer in order to participate in the biomarker cut-point determination part of the trial if they do not meet cisplatin-ineligible criteria. • A trial objective was updated to state that safety and tolerability were to be evaluated in all subjects regardless of PD-L1 status. • The screening window for when the newly obtained (required) core or excisional biopsy for biomarker analysis were collected was increased to 56 days (8 weeks).
Amendment 2	11-Mar-2016	• Objectives were added to indicate that PD-L1 positive was prospectively defined as subjects with Combined Positive Score (CPS) ≥1%. • All hypotheses were removed since the objective of the trial was to estimate efficacy, and the success of the trial was determined by clinically meaningful ORRs and durability of the response. • The number of subjects to be used for the biomarker cut-point analysis was updated from ~150 subjects to ~100 subjects. • Modified RECIST was updated to exclude the 1.1 as a reference. • A clarification was made requiring that bone scans must have been submitted for review at baseline to the central imaging vendor even though bone scans were no part of determining RECIST measurability. • The 56 day screening window requirement for when the new core or excisional biopsy was removed from the protocol. • The requirement for sending all images to the central vendor was added. • The primary safety and efficacy will be conducted in the All-Patients-Treated (APT) population.

Data source: Clinical Study Report by Merck[5]

b) Populations

The baseline characteristics of the patients enrolled in the in the KEYNOTE-052 trial are presented in Table 6.5. The majority of patients had a mean age of 73 years (standard deviation: 9.9), were male (77.3%), were white (88.6%) and had an ECOG performance stage of 1 (35.9%) or 2 (42.2%).[5] In addition, the main reasons for cisplatin ineligibility were renal dysfunction (49.2%) and ECOG performance status 2 (32.4%).[5]

The Submitter stated that the baseline characteristics of patients with a PD-L1 CPS ≥ 10% were similar to all patients enrolled in the KEYNOTE-052 trial.[13]

In a Checkpoint Response, the Submitter stated that the majority of patients had a predominant histology of urothelial carcinoma (94%, N = 349).[7] For instance, 94% of patients who had a primary tumor site in the lower tract (N=282) and 97% of patients who had a primary tumor site in the upper tract had a predominant histology of "urothelial carcinoma" (including variants) (N=67), respectively.[7]

Table 6.5: Baseline characteristics for all patients enrolled in the KEYNOTE-052 trial

	Pembrolizumab	
	n	(%)
Subjects in population	370	
Gender		
Male	286	(77.3)
Female	84	(22.7)
Age (Years)		
< 65 Years	68	(18.4)
>= 65 Years	302	(81.6)
Mean	73.0	
SD	9.9	
Median	74.0	
Range	34 to 94	
Race		
American Indian Or Alaska Native	2	(0.5)
Asian	26	(7.0)
Black Or African American	8	(2.2)
Multiple	2	(0.5)
White	328	(88.6)
Missing	4	(1.1)
Ethnicity		
Hispanic Or Latino	22	(5.9)
Not Hispanic Or Latino	319	(86.2)
Not Reported	21	(5.7)
Unknown	8	(2.2)
Age Group 2		
< 65 Years	68	(18.4)
>= 65 to < 75 Years	123	(33.2)
>= 75 to < 85 Years	139	(37.6)
>= 85 Years	40	(10.8)
PD-L1 Status		
PD-L1 CPS < 1%	79	(21.4)
PD-L1 CPS >= 1% to < 10%	172	(46.5)
PD-L1 CPS >= 10%	110	(29.7)
Unknown	9	(2.4)
ECOG†		
[0] Normal Activity	80	(21.6)
[1] Symptoms, but ambulatory	133	(35.9)
[2] Ambulatory but unable to work	156	(42.2)
[3] Limited selfcare	1	(0.3)

	Pembrolizumab	
	n	(%)
Metastatic Staging		
M0	47	(12.7)
M1	323	(87.3)
Chemotherapy Naïve (Y/N)		
No	67	(18.1)
Yes	303	(81.9)
Baseline Hemoglobin		
>=10 g/dL	329	(88.9)
<10 g/dL	41	(11.1)
Liver Metastasis (Y/N)		
No	292	(78.9)
Yes	78	(21.1)
Prior Adjuvant or Neoadjuvant Platinum-based Chemotherapy		
No	334	(90.3)
Yes	36	(9.7)
Prior BCG Therapy		
No	316	(85.4)
Yes	54	(14.6)
Metastases Location		
Lymph Node Only	51	(13.8)
Visceral Disease	315	(85.1)
Not Reported	4	(1.1)
Primary Tumor Location		
Upper Tract	69	(18.6)
Lower Tract	300	(81.1)
Unknown	1	(0.3)
Reason for Cisplatin Ineligibility		
ECOG 2	120	(32.4)
Renal Dysfunction	182	(49.2)
ECOG 2 and Renal Dysfunction	35	(9.5)
Other Reasons‡	33	(8.9)

†ECOG performance status assessed during screening.
‡Including Class III Heart Failure, Grade ≥ 2 Peripheral Neuropathy, and Grade ≥ 2 Hearing Loss.
Missing: not reported or unknown
Renal dysfunction is defined as a baseline creatinine clearance < 60 mL/min.
M stage Database Cutoff Date: 14FEB2017
Database Cutoff Date: 01SEP2016

Source: [P052V01MK3475: analysis-adsl]

Data source: EMA Assessment Report[6]

c) Interventions

Treatment Dosing Schedule[2]

- 200 mg intravenous dose of pembrolizumab Q3W for a maximum of 35 doses on the first day of each three-week cycle.

Dose delays, reductions or modifications[2]

- Treatment with pembrolizumab was withheld or permanently discontinued based on the severity of the immune-related AEs. Patients who experienced severe immune-related AEs were treated with corticosteroids.
- Dose delays were permitted for medical or surgical events or for reasons not related to the study therapy. Patients were required to be placed back on their assigned therapy within three weeks of the scheduled interruption or unless otherwise specified by the study investigator.
- Dose escalations or dose reductions of pembrolizumab were not permitted in the trial.

Treatment duration

At the 30-Nov-2017 data cut-off, the median duration of treatment was 3.4 months (range: 0.03 to 27.89 months) among all patients enrolled in the trial.[3][05. Vuky_KN052_ASCO_2018 *DC Nov 30 2017]. The median number of administrations of pembrolizumab was 5.0 (range: 1.0 to 36.0).[10]

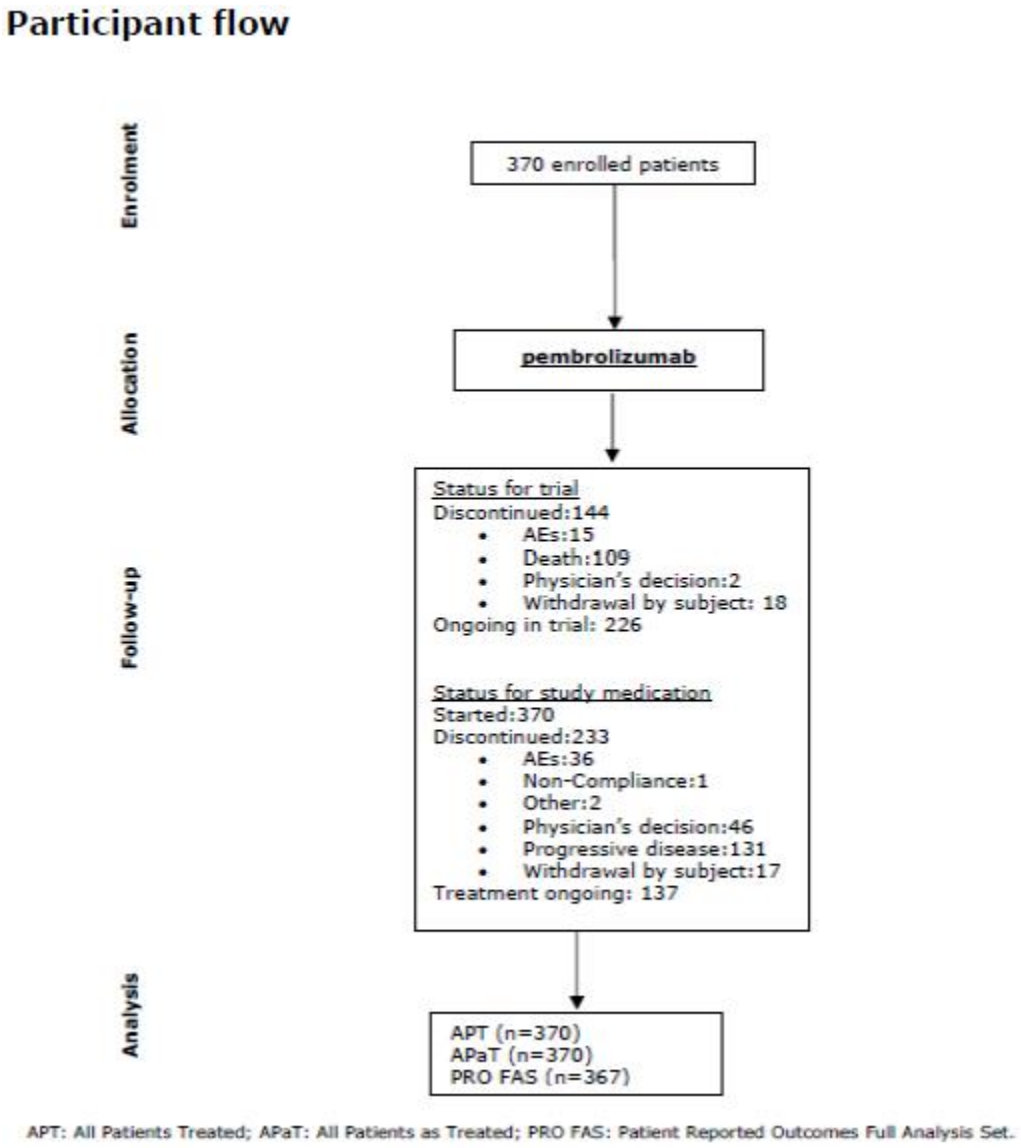
d) Patient Disposition

The patient disposition for the KEYNOTE-052 trial at the 01-Sep-2016 data cut-off is presented in Figure 6.3. Among the 374 patients enrolled in the trial, 1.1% of patients did not receive their assigned treatment because one patient had a screening failure, one withdrew, one had a protocol violation and one had a doctor's reason.[1]

At the 30-Nov-2017 data cut-off, 31.9% (N = 118) of patients were still participating in the trial and 10.5% were still receiving pembrolizumab (N=39).[8] Sixty-eight percent of patients discontinued pembrolizumab and the most common reasons for discontinuing treatment were progressive disease (47.0%; N = 174), AEs (17.3%), physician decision (13.5%) or the patient withdrew (4.6%).[8]

At the 29-Sep-2019 data cut-off, 88.4% (N = 327) patients discontinued from the trial and 11.6% (N = 43) of patients had completed the trial.[4] Moreover, at this data cut-off, 48.1% (N=178) of patients stopped study treatment within three month while 20.8% (N=77) remained on study treatment for more than 12 months.[4]

Figure 6.3: Disposition of patients enrolled in the KEYNOTE-052 trial at the 01-Sep-2016 data cut-off.



Data source: EMA Assessment Report[6]

541 Patients were screened. Of those 167 were not enrolled (did not meet eligibility criteria and one patient failed the screen without eligibility criteria.[1]

e) Limitations/Sources of Bias

Although the KEYNOTE-052 was a well-designed trial, it was a non-comparative, exploratory trial. For instance, the nonrandomized design of this trial makes it difficult to interpret the efficacy and safety of pembrolizumab because all cisplatin-ineligible patients with locally advanced and unresectable or MUC received the same treatment. Some other limitations should also be taken into consideration, more specifically:

- KEYNOTE-052 was a single-arm, non-randomized, open-label phase II trial. In open-label trials, the study investigator and the study participants are aware of their treatment status, which increases the risk of detection bias and performance bias. This has the potential to bias results and outcomes in favour of pembrolizumab if the assessor (investigator or patient) believes the study drug is likely to provide a benefit. However, in order to mitigate the impact of this bias, the investigators used a blinded independent review committee to evaluate responses using standardized criteria. However, subjective outcomes (i.e. adverse outcomes and HRQoL) may be biased due to the open-label design.

- A protocol amendment on 11-Mar-2016 was made to reflect the transition of the pembrolizumab clinical trial programme away from hypothesis testing for the primary objectives towards an estimation for single-arm clinical trials.[1] Thus, all hypotheses were removed since the objective of the trial was to estimate efficacy, and the success of the trial was determined by clinically meaningful ORRs and durability of the response.[2] Therefore, no hypothesis tests were performed and the original sample size was not adjusted. Thus, all efficacy analyses and subgroup analyses should be interpreted with caution because they are considered exploratory.

- The adequacy of the ORR as a primary endpoint in KEYNOTE-052 is unclear. Although ORR appears to be correlated with median overall survival, a statistical correlation does not necessarily equate to the prediction of a survival benefit from the response rate.

- The robustness of the preliminary overall survival and PFS results are limited due to short follow-up of the study populations and the lack of a randomized comparison treatment group in KEYNOTE-052. The overall survival data should also be considered exploratory given the small sample sizes and no power calculation for PFS and overall survival. In addition, patients were able to receive subsequent therapies once they progressed, and therefore, future estimates of OS may be confounded.

- For the safety evaluation, it is important to note that since the data come from single-arm studies, it is difficult to estimate the contribution of the underlying disease on adverse reactions.

- Patient reported outcomes (PROs) were collected as exploratory endpoints in the outcomes in the trial using the EORTC QLQ-C30 and EQ-5D-3L. The effect of pharmacological treatments on HRQoL is an important consideration when making treatment decisions. However, it should be noted that the HRQoL estimates were measured up to week 9, which may not represent an accurate picture of patients' experiences with pembrolizumab for a prolonged period of time. Additionally, the trial was non-randomized and the impact of pembrolizumab on patient's QoL in relation to other therapies is unknown.

- In the absence of direct comparisons in the KEYNOTE-052 trial, the Submitter provided an unpublished network meta-analysis (NMA), which indirectly compared pembrolizumab to gemcitabine and carboplatin + gemcitabine. A summary and critical appraisal of the NMA is available in section 7 of this report.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Efficacy Outcomes

Efficacy analyses were performed in all patients who had more than one dose of pembrolizumab.[2] Overall, the efficacy results are provided for all patients (N=370) and a subgroup of patients who had a PD-L1 CPS ≥1% (N=282) or a PD-L1 CPS ≥10% (N=80). In the trial, PD-L1 expression levels were scored using a CPS, which was defined as the percentage of cells (i.e., tumour cells, macrophages, or lymphocytes) that expressed PD-L1 in a tumour biopsy.[1] The Submitter also performed a post-hoc subgroup analysis in patients who are considered platinum ineligible (N = 145). Here, patients were considered platinum ineligible if they had an ECOG performance status of 2 and one or more of visceral metastasis, advanced age (≥ 80 years) or GFR < 60 mL/min.

Four data cut-offs were identified in the pCODR systematic review, which include: 01-Sep-2016, 09-Mar-2017, 30-Nov-2017 and 26-Sep-2018. For the purpose of this review, the results of the 30-Nov-2017 database lock will be presented, which represents a median follow-up of 11.5 months and aligns with the data cut used for the analyses in the economic model, which was submitted to pCODR as part of this submission.[3] However, where available, data from the 01-Sep-2016 and the 26-Sep-2018 data cut-offs will also be presented, which represents a median follow-up ranging from 5 months (interquartile range: 3.0 to 8.6) to a mean follow-up of 15.3 months (standard deviation: 12.1).[1,4]

Objective Response Rate

The primary outcome in the trial was ORR as assessed by IRR using RECIST 1.1.[2] It was defined as the proportion of patients who achieved a complete response (CR) or partial response (PR) using the RECIST 1.1 criteria.[2] The ORR was reported as a point estimate with corresponding 95% confidence intervals (CIs) using the exact binomial distribution for all patients and for those who were PD-L1 positive (e.g., PD-L1 CPS ≥ 1%) or PD-L1 strongly positive (e.g., PD-L1 CPS ≥ 10%).[2] The disease control rate was defined as the proportion of patients with a best overall response of CR, PR, or stable disease (SD).[2]

All patients

At the 01-Sep-2016 data cut-off, the ORR as assessed by IRR using RECIST 1.1 for all patients was 24% (95% CI: 20% to 29%; N = 89).[1]

Table 6.6 shows the results of ORR as assessed by IRR using RECIST 1.1 for all patients at the 30-Nov-2017 data cut-off. The ORR as assessed by IRR using RECIST 1.1 for all patients was 29% (95% CI: 24.3% to 33.8%).[3] Thirty-one patients (8%) did not have a post-baseline imaging assessment.[3] The DCR was 47% among all patients enrolled in the trial.[3]

The ORR as assessed by IRR using RECIST 1.1 was 28.6% (95% CI: 24.1% to 33.5%) at the 26-Sep-2018 data cut-off.[4]

Table 6.6: Best overall response rate as assessed by IRR using RECIST 1.1 for all patients enrolled in the KEYNOTE-052 trial at the 30-Nov-2017 data-cut off

Response	Response, n (%)	95% CI
Objective response	107 (29)	(24.3-33.8)
CR	30 (8)	(5.5-11.4)
PR	77 (21)	(16.8-25.3)
Stable disease	67 (18)	(14.3-22.4)
Progressive disease	156 (42)	(37.1-47.4)
No assessment[a]	31 (8)	(5.8-11.7)
NE[b]	9 (2)	(1.1-4.6)

BOR, best overall response; CR, complete response; NE, nonevaluable; PR, partial response.

[a]Patient had no postbaseline imaging.

[b]Patient had a postbaseline scan, and BOR was determined to be NE per RECIST v1.1.

Source: Vuky et al. 2018;[37] Merck, data on file

Table 6.7 presents the prespecified subgroup analysis for ORR as assessed by IRR using RECIST 1.1 in all patients enrolled in the KEYNOTE-052 trial at the 30-Nov-2017 data cut-off. Vuky et al (2018) showed that there was no difference in ORR stratified by age group, gender, ECOG performance status, prior chemotherapy experience, primary tumour location, and reason for cisplatin ineligibility.[3] However, the authors reported that the ORR as assessed by IRR using RECIST 1.1 appeared to be higher among patients with PD-L1 CPS ≥10 as compared to the all other patients.[3] Moreover, patients with metastases in the lymph node only had a higher ORR as compared to those with visceral metastases.[3] Although the subgroup analysis was prespecified, a protocol amendment on 11-Mar-2016 was made to reflect the transition of the pembrolizumab clinical trial programme away from hypothesis testing for the primary objectives towards an estimation for single-arm clinical trials.[1] Since no hypothesis tests were performed, it is difficult to determine whether there are statistical differences across subgroups, and therefore, these results should be interpreted with caution. Similar estimates were observed at the 01-Sep-2016 and 26-Sep-2018 data cutoff.[4]

Table 6.7: Subgroup analysis of ORR as assessed by IRR using RECIST 1.1 and OS stratified by prespecified factors for all the patients enrolled in the KENOTE-052 trial at the 30-Nov-2017 data cut-off.

Subgroups		Number of Events (%)	ORR (%) (95% CI)	Median OS (Months) (95% CI)
Age	<65	41 (60.3)	29.4 (19.0, 41.7)	15.7 (6.9, -)
	≥65	206 (68.2)	28.8 (23.8, 34.3)	11.0 (9.7, 12.8)
Age 2	<65	41 (60.3)	29.4 (19.0, 41.7)	15.7 (6.9, .)
	≥65 to <75	68 (55.3)	30.9 (22.9, 39.9)	16.7 (11.0, 27.1)
	≥75 to <85	104 (74.8)	27.3 (20.1, 35.5)	10.8 (8.4, 13.1)
	≥85	34 (85.0)	27.5 (14.6, 43.9)	6.7 (4.2, 10.6)
PD-L1 Subgroup	PD-L1 CPS < 1	64 (81.0)	15.2 (8.1, 25.0)	7.2 (4.9, 10.5)
	PD-L1 CPS ≥1	179 (63.5)	32.6 (27.2, 38.4)	12.5 (10.8,15.1)
	PD-L1 CPS ≥1 to < 10	122 (70.9)	23.3 (17.2, 30.3)	11.0 (8.5, 13.3)
	PD-L1 CPS < 10	186 (74.1)	20.7 (15.9, 26.3)	10.0 (7.8, 11.6)
	PD-L1 CPS ≥10	57 (51.8)	47.3 (37.7, 57.0)	18.5 (12.2, .)

Subgroups		Number of Events (%)	ORR (%) (95% CI)	Median OS (Months) (95% CI)
Gender	Female	58 (69.0)	28.6 (19.2, 39.5)	10.3 (6.3, 14.6)
	Male	189 (66.1)	29.0 (23.8, 34.7)	11.5 (10.0,13.9)
ECOG Status	0/1	134 (62.6)	30.4 (24.3, 37.0)	13.1 (11.0,16.8)
	2†	113 (72.4)	26.9 (20.1, 34.6)	9.7 (5.7, 11.6)
Prior Adjuvant/Neoadjuvant Platinum-based chemotherapy	Yes	24 (64.9)	29.7 (15.9, 47.0)	11.8 (6.3, 24.1)
	No	223 (67.0)	28.8 (24.0, 34.0)	11.0 (9.6, 13.5)
Met Location	Lymph node only	22 (43.1)	49.0 (34.8, 63.4)	. (12.4, .)
	Visceral disease	223 (70.8)	25.4 (20.7, 30.6)	10.8 (9.0, 11.8)
Primary tumour location	Upper tract	47 (68.1)	26.1 (16.3, 38.1)	10.8 (7.6, 17.0)
	Lower tract	200 (66.7)	29.7 (24.6, 35.2)	11.6 (10.0,13.5)
Reason for cisplatin ineligibility	ECOG 2	84 (70.0)	28.3 (20.5, 37.3)	10.5 (7.2, 12.4)
	Renal Dysfunction	121 (66.1)	27.9 (21.5, 35.0)	11.9 (9.7, 15.1)
	Other Reasons	16 (48.5)	33.3 (18.0, 51.8)	24.5 (9.7, .)

† Including 1 subject with ECOG = 3
Database Cutoff Date: 30NOV2017
Data source: Merck Checkpoint Response[7]

In their feedback on the initial recommendation, the Submitter suggested that there is a strong suggestion that ORR acts as a surrogate outcome for OS in patients treated with PD-1 inhibitors. To support this position, the Submitter referred to two articles, which reported that patients treated with a PD-1 inhibitor (i.e., pembrolizumab or nivolumab) and who achieved a complete or partial response had a better OS as compared to patients with no tumour response [Fradet et al, 2018[44] and El-Khoudry et al, 2017[43]]. In response to the Submitter's feedback, the pCODR Methods Team noted that the analyses provided by the Submitter may not provide sufficient statistical evidence to validate ORR as a surrogate outcome for OS [Fradet et al. (2018) [44] and El-Khourdry et al. (2017)[43]]. For instance, Buyse (2011)[42] stated that a surrogate outcome must demonstrate an "individual-level" and a "trial-level" association using a meta-analytic/correlation approach.[42] Here, the surrogate outcome must be tightly correlated with the true endpoint and the treatment effect on the surrogate outcome must be tightly correlated with the treatment effect on the true endpoint. The pCODR Methods Team also commented that there were several differences between the KEYNOTE-052 trials and the two trials that were reported in the analyses by Fradet et al (2018)[44] (KEYNOTE-045) and El-Khoudry et al. (2017)[43] (CheckMate-040). First, there were differences in the trial designs. The KEYNOTE-052 trial was a single-arm phase II study while the KEYNOTE-052 trial was a randomized phase III trial and the CheckMate-040 trial was a non-comparative phase 1/2 study. Second, there were differences in patient characteristics. In the KEYNOTE-052 trial, patients were not allowed to have had any prior systemic chemotherapy for advanced/unresectable (inoperable) or metastatic urothelial cancer and had to be cisplatin-ineligible at enrolment while patients in the KEYNOTE-045 trial had to have progressive or recurrent disease after a first-line platinum-containing regimen (i.e., cisplatin, carboplatin) with the majority of patients entering the trial after having received prior cisplatin-based chemotherapy. In contrast, the CheckMate-040 trial included patients with hepatocellular carcinoma. Additionally, patients in the KEYNOTE-045 trial had overall lower ECOG performance status than patients enrolled in the KEYNOTE-052 trial. Notably, 42.2% of patients in the KEYNOTE-052 trial had an ECOG performance status of 2 as compared to less than 2% of patients in the KEYNOTE-045 trial. Thus, the results of the KEYNOTE-045 and CheckMate-040 trials may not be generalizable to the patient population of the KEYNOTE-052 trial. Finally, the pCODR Methods Team noted that there may be other limitations to take into consideration. For instance, the

subgroup analyses for OS performed by El-Khoudry et al. (2017)[43] were reported to be exploratory and the updated subgroup analyses of OS (data cut: Oct 26, 2017) reported by Fradet et al (2018)[44] did not appear to be pre-specified in the protocol[22], and therefore, it is unclear whether the analysis was adjusted for multiplicity or adequately powered. The pCODR Methods Team concluded that given the above considerations it is challenging to confirm the appropriateness of ORR as a surrogate outcome for OS in the target patient population of the present reimbursement request.

PD-L1 expression level subgroups

PD-L1 CPS ≥ 1%

At the 01-Sep-2016 data cut-off, the ORR as assessed by IRR using RECIST 1.1 for patients with a PD-L1 CPS ≥ 1% was 32.6% (95% CI: 27.2 to 38.4; N = 92).[6]

Table 6.8 shows the results of ORR as assessed by IRR using RECIST 1.1 for patients with a PD-L1 CPS ≥ 1% at the 30-Nov-2017 data cut-off. The ORR as assessed by IRR using RECIST 1.1 was 32.6% (95% CI: 27.2% to 38.4%) for patients with a PD-L1 CPS ≥ 1%.[7] The DCR was 52.5% among those with a PD-L1 CPS ≥ 1%.[7]

The ORR for patients with a PD-L1 CPS ≥ 1% was not reported at the 26-Sep-2018 data cut-off.

Table 6.8: Best overall response rate as assessed by IRR using RECIST 1.1 for patients with a PD-L1 CPS ≥ 1% enrolled in the KEYNOTE-052 trial at the 30-Nov-2017 data-cut off

Response Evaluation	Number of patients	ORR (95% CI)	
Complete Response (CR)	27	9.6	(6.4, 13.6)
Partial Response (PR)	65	23.0	(18.3, 28.4)
Objective response rate (CR+PR)	92	32.6	(27.2, 38.4)
Stable disease (SD)	56	19.9	(15.4, 25.0)
Disease Control Rate (CR+PR+SD)	148	52.5	(46.5, 58.4)
Progressive Disease (PD)	109	38.7	(32.9, 44.6)
Non-evaluable	5	1.8	(0.6, 4.1)
No Assessment	20	7.1	(4.4, 10.7)

Database Cut-off Date: 30NOV2017
Data source: Merck Checkpoint Response[7]

PD-L1 CPS ≥ 10%

At the 01-Sep-2016 data cut-off, the ORR as assessed by IRR using RECIST 1.1 for patients with a PD-L1 CPS ≥ 10% was 38.2% (95% CI: 29.1 to 47.9; N = 42).[6]

Table 6.9 shows the results of ORR as assessed by IRR using RECIST 1.1 for patients with a PD-L1 CPS ≥ 10% at the 30-Nov-2017 data cut-off. The ORR as assessed by IRR using RECIST 1.1 was 47.3% (95% CI: 37.7 to 57.0) for patients with a PD-L1 CPS ≥ 10%.[7] The DCR was 67.3% among those with a PD-L1 CPS ≥ 10%.[7]

The ORR as assessed by IRR using RECIST 1.1 was 47.3% (95% CI: 37.7 to 57.0) at the 26-Sep-2018 data cut-off.[4]

Table 6.9: Best overall response rate as assessed by IRR using RECIST 1.1 for patients with a PD-L1 CPS ≥ 10% enrolled in the KEYNOTE-052 trial at the 30-Nov-2017 data-cut off

Response Evaluation	Number of patients	ORR (95% CI)	
Complete Response (CR)	21	19.1	(12.2, 27.7)
Partial Response (PR)	31	28.2	(20.0, 37.6)
Objective response rate (CR+PR)	52	47.3	(37.7, 57.0)
Stable disease (SD)	22	20.0	(13.0, 28.7)
Disease Control Rate (CR+PR+SD)	74	67.3	(57.7, 75.9)
Progressive Disease (PD)	30	27.3	(19.2, 36.6)
Non-evaluable	0	0.0	(0.0, 3.3)
No Assessment	6	5.5	(2.0, 11.5)

Database Cutoff Date: 30NOV2017
Data source: Merck Checkpoint Response[7]

Platinum ineligible subgroup

The ORR as assessed by IRR using RECIST 1.1 for platinum ineligible patients was not reported at the 01-Sep-2016 data cut-off.

At the 30-Nov-2017 data cut-off, the ORR as assessed by IRR using RECIST 1.1 was 26.2% (95% CI: 19.3 to 34.2) in this patient group and the CR was 4.8% while the PR was 21.4%.[8,9]

The ORR as assessed by IRR using RECIST 1.1 for platinum ineligible patients was not reported at the 26-Sep-2018 data cut-off.

Duration of Response

DOR as assessed by IRR using RECIST 1.1 was a secondary outcome in the trial. It was defined as the time from first RECIST 1.1 response to disease progression in patients who achieved a PR or CR.[5] In the protocol, it was stated that DOR would be descriptively summarized using Kaplan-Meier medians and quartiles.[2]

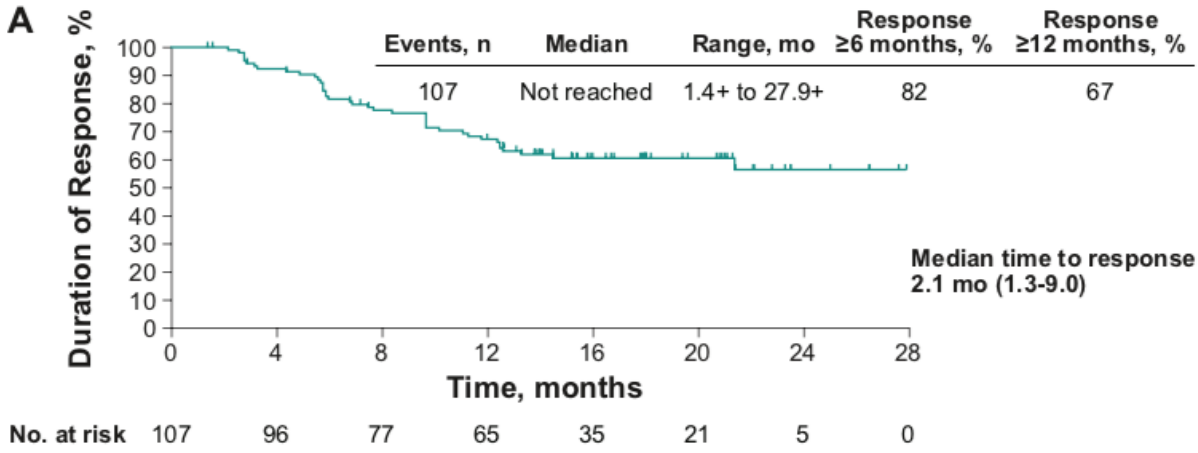
All Patients

At the 01-Sep-2016 data cut-off, the median DOR as assessed by IRR using RECIST 1.1 was not reached (Not reached [NR], range: 1.4+ to 19.6+).[6]

One hundred and seven patients experienced radiographic response to pembrolizumab and the median DOR as assessed by IRR using RECIST 1.1 was not reached (NR, range: 1.4+ to 27.9+) at the 30-Nov-2017 data cut-off (Figure 6.4).[3] The response rates at ≥ 6 and ≥ 12 months were 82.0% and 67.0%, respectively.[3]

The median DOR as assessed by IRR using RECIST 1.1 was 30.1 (95% CI: 18.8 to NR) at the 26-Sep-2018 data cut-off.[4] The response rates at ≥ 12 and ≥ 24 months were 67.0% and 52.0%, respectively.[4]

Figure 6.4: The Kaplain-Meier curves for duration of response as assessed by IRR using RECIST 1.1 among all patients enrolled in the KEYNOTE-052 trial at the 30-Nov-2017 data cut-off.



Data Source: Vuky et al (2018)[37]

PD-L1 expression level subgroups

At the 01-Sep-2016 data cut-off, the median DOR as assessed by IRR using RECIST 1.1 was not reported for patients with a PD-L1 CPS ≥ 1% or a PD-L1 CPS ≥ 10%.

The median DOR as assessed by IRR using RECIST 1.1 was not reached for patients with a PD-L1 CPS ≥ 1% and ≥ 10% at the 30-Nov-2017 data cut-off.[1,7] The response rates at ≥ 6 and ≥ 12 months were 80.8% and 68.7% for those with a PD-L1 CPS ≥ 1% while the response rates at ≥ 6 and ≥ 12 months were 82.0% and 75.5% for those with a PD-L1 CPS ≥ 10%.[7]

The DOR as assessed by IRR using RECIST 1.1 for patients with a PD-L1 CPS ≥ 1% was not reported at the at the 26-Sep-2018 data cut-off. The DOR as assessed by IRR using RECIST 1.1 for patients with a PD-L1 CPS ≥ 10% was not reached (95% CI: 18.1 to NR) at the 26-Sep-2018 data cut-off.[4] The response rate at ≥ 24 months was 57.0%.[4]

Platinum ineligible subgroup

In their feedback on the initial recommendation, the Submitter noted that in the Initial Clinical Guidance Report an incorrect median DOR of 2.1 months for the platinum ineligible subgroup was considered by pERC. The Submitter clarified that the accurate median DOR for this patient subgroup was not reached (range: 2.8, 27.6+ months). The pCODR Methods Team acknowledged the error and has corrected the DOR for the platinum ineligible patient subgroup in the following:

The median DOR as assessed by IRR using RECIST 1.1 was not reached (range: 2.8 to 27.6+ months) for patients who were platinum ineligible at the 30-Nov-2017 data cut-off.[45]

Overall Survival

OS was a secondary endpoint in the trial and it was defined as time from treatment initiation to death from any cause.[1] The protocol stated that the Kaplan-Meier curves, median estimates and survival rates at 6 and 12 months with corresponding 95% CIs using the Greenwood formula would be reported for OS.[2]

All patients

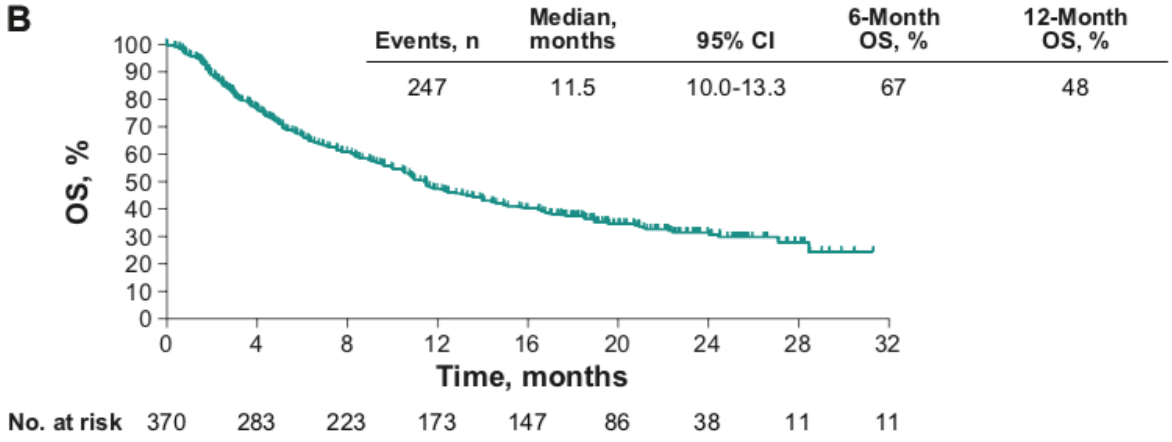
At the 01-Sep-2016 data cut-off, 35.1% of patients had died (N = 130) and the median OS was 10.9 months (95% CI: 9.7 to NR).[6]

At the 30-Nov-2017 data cut-off, 66.8% of patients had died (N = 247) and the median OS was 11.5 months (95% CI: 10.0 to 13.3) (Figure 6.5).[3] The 6 and 12-month OS rates were 67.0% and 48.0%, respectively.[3]

The median OS was 11.3 months (95% CI: 9.7 to 13.1) at the 26-Sep-2018 data cut-off.[4] The 12 and 24-month OS rates were 46.9% and 31.2%, respectively.[4]

Median OS was longer among patients with PD-L1 CPS ≥10% as compared to patients with a PD-L1 CPS ≤10% in the prespecified subgroup analysis (Table 6.11).[3,7] Additionally, patients who were younger than 65 years had a longer median OS relative to those who were older than 65 years and patients with an ECOG performance status of 0 or 1 had a longer median OS compared to those with an ECOG performance status of 2.[3,7]

Figure 6.5: The Kaplain-Meier curves for overall survival among all patients enrolled in the KEYNOTE-052 trial at the 30-Nov-2017 data cut-off.



Data Source: Vuky et al (2018)[37]

PD-L1 expression level subgroups

At the 01-Sep-2016 data cut-off, 30.1% of patients with a PD-L1 CPS ≥ 1% had died (N = 85) and the median OS was 11.6 months (95% CI: 10.1 to NR).[6] For those with a PD-L1 CPS ≥ 10%, 22.5% patients had died (N = 18) and the median OS was NR (95% CI: 8.4 to NR).[6]

At the 30-Nov-2017 data cut-off, 63.5% of patients with a PD-L1 CPS ≥ 1% had died (N = 179) and the median OS was 12.5 months (95% CI: 10.8 to 15.1).[7] For those with a PD-L1 CPS ≥ 10%, 51.8% patients had died (N = 57) and the median OS was 18.5 months (95% CI: 12.2 to NR).[7]

The median OS was not reported for patients with a PD-L1 CPS ≥ 1% at the 26-Sep-2018 data cut-off. The median OS for patients with a PD-L1 CPS ≥ 10% was 18.5 months (95% CI: 12.2 to 28.5) at the 26-Sep-2018 data cut-off.[4]

Platinum ineligible subgroup

OS for platinum ineligible patients was not reported at the 01-Sep-2016 data cut-off.

At the 30-Nov-2017 data cut-off, 74.5% of the platinum ineligible patients had died (N = 108) and the median OS was 9.2 months (95% CI: 5.3 to 11.3).[8]

OS for platinum ineligible patients was not reported at the 26-Sep-2018 data cut-off.

Progression-Free Survival

PFS as assessed by IRR using RECIST 1.1 was a secondary endpoint in the trial. PFS was defined as the time from treatment initiation to documented disease progression or to death from any cause, whichever occurred first.[1] The protocol stated that the Kaplan-Meier curves, median estimates and survival rates at 6 months and 12 months with corresponding 95% CIs (using the Greenwood formula) would be reported for PFS.[2]

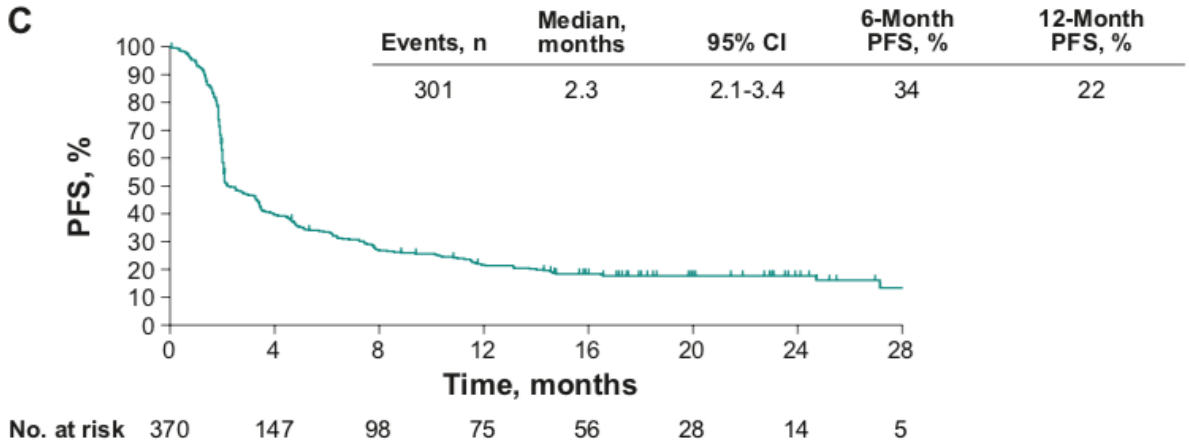
All patients

At the 01-Sep-2016 data cut-off, 67.0% of patients had progressed or died (N = 248) and the median PFS as assessed by IRR using RECIST 1.1 was 2.1 months (95% CI: 2.1 to 3.0).[6]

At the 30-Nov-2017 data cut-off, 81.4% of patients had progressed or died (N = 301) and the median PFS as assessed by IRR using RECIST 1.1 was 2.3 months (95% CI: 2.1 to 3.4) (Figure 6.6).[3] The 6 and 12-month PFS as assessed by IRR using RECIST 1.1 rates were 34.0% and 22.0%, respectively.[3]

The median PFS as assessed by IRR using RECIST 1.1 was 2.2 months (95% CI: 2.1 to 3.4) at the 26-Sep-2018 data cut-off.[4] The 6 and 12-month PFS as assessed by IRR using RECIST 1.1 rates were 33.4% and 22.0%, respectively.[4]

Figure 6.6: The Kaplain-Meier curves for progression-free survival as assessed by IRR using RECIST 1.1 among all patients enrolled in the KEYNOTE-052 trial at the 30-Nov-2017 data cut-off.



Data Source: Vuky et al (2018)[37]

In a Checkpoint Response, the Submitter provide the number of patients who were treated beyond progression and the type of medications they received at the 30-Nov-2017 data cut-off (Table 6.10).[7] Overall, there were 246 patients with disease progression and 41.9% of these patients were

treated beyond progression. Among these patients, the majority were treated with either carboplatin (26.4%) or gemcitabine (33.3%).[7]

Table 6.10: Summary of concomitant oncology medications for patients treated beyond disease progression for all patients enrolled in the KEYNOTE-052 trial at the 30-Nov-2017 data cut-off.

	Pembrolizumab[a] N=370	
	n	(%)
Number of Subjects with Disease Progression	246	
Subjects Treated Beyond Progression	103	(41.9)
[therapy unspecified]	1	(0.4)
anti-OX40 monoclonal antibody (unspecified)	1	(0.4)
atezolizumab	8	(3.3)
bortezomib	1	(0.4)
cabazitaxel	1	(0.4)
carboplatin	65	(26.4)
carboplatin (+) gemcitabine	1	(0.4)
cisplatin	24	(9.8)
docetaxel	3	(1.2)
doxorubicin	2	(0.8)
durvalumab	3	(1.2)
enfortumab vedotin	2	(0.8)
erdafitinib	2	(0.8)
everolimus	1	(0.4)
fibroblast growth factor receptor inhibitor (unspecified)	1	(0.4)
gemcitabine	82	(33.3)
gemcitabine hydrochloride	2	(0.8)
investigational drug (unspecified)	3	(1.2)
lenvatinib	1	(0.4)
methotrexate	2	(0.8)
paclitaxel	12	(4.9)
pazopanib	1	(0.4)
pemetrexed disodium	1	(0.4)
pertuzumab	1	(0.4)
trastuzumab	1	(0.4)
tremelimumab	3	(1.2)
vinblastine sulfate	2	(0.8)
vinflunine	1	(0.4)
vinorelbine tartrate	2	(0.8)
zoledronic acid	1	(0.4)

a: Database Cutoff Date: 30NOV2017

Percentages calculated using the total of the number of subjects with disease progression in the All Patients as Treated Population as denominator.

Data source: Merck Checkpoint Response[7]

PD-L1 expression level subgroups

Almost 63% of patients with a PD-L1 CPS ≥ 1% had progressed or died (62.8%; N = 177) and the median PFS as assessed by IRR using RECIST 1.1 was 3.0 months (95% CI: 2.1 to 3.5).[6] For those with a PD-L1 CPS ≥ 10%, 46.3% patients had progressed or died (N = 37) and the median PFS as assessed by IRR using RECIST 1.1 was 4.9 months (95% CI: 3.5 to NR).[6]

At the 30-Nov-2017 data cut-off, 78.7% of patients with a PD-L1 CPS ≥ 1% had progressed or died (N = 222) and the median PFS as assessed by IRR using RECIST 1.1 was 3.4 months (95% CI: 2.2 to 3.8).[7] For those with a PD-L1 CPS ≥ 10%, 68.2% of patients had progressed or died (N = 75) and the median PFS as assessed by IRR using RECIST 1.1 was 4.9 months (95% CI: 3.8 to 10.8).[7]

The median PFS as assessed by IRR using RECIST 1.1 was not reported for patients with a PD-L1 CPS ≥ 1% or a PD-L1 CPS ≥ 10% at the 26-Sep-2018 data cut-off.

Platinum ineligible subgroup

The median PFS as assessed by IRR using RECIST 1.1 was not reported for platinum ineligible patients at the 01-Sep-2016 data cut-off.

Overall, 82.8% of platinum ineligible patients had progressed or died (N = 120) and the median PFS as assessed by IRR using RECIST 1.1 was 2.1 months (95% CI: 2.0 to 2.8) at the 30-Nov-2017 data cut-off.[8]

The median PFS as assessed by IRR using RECIST 1.1 was not reported for platinum ineligible patients at the 26-Sep-2018 data cut-off.

Quality of Life

Patient-reported outcomes (PROs) were exploratory endpoints in the trial and they were assessed using the European Organization for Research and Treatment of Cancer (EORTC) QoL Questionnaire C30 (QLQ-C30) and European Quality of Life Five Dimensions Questionnaire 3 Levels (EQ-5D-3L).[2] Patients were included in the PRO analysis if they received at least 1 dose of pembrolizumab and completed at least one PRO instrument.[5] HRQoL was measured at baseline, cycles 1 to 4 and then every 2 cycles thereafter for up to a year or at the end of treatment, whichever comes first, and at the 30-day post-treatment discontinuation follow-up visit.[2]

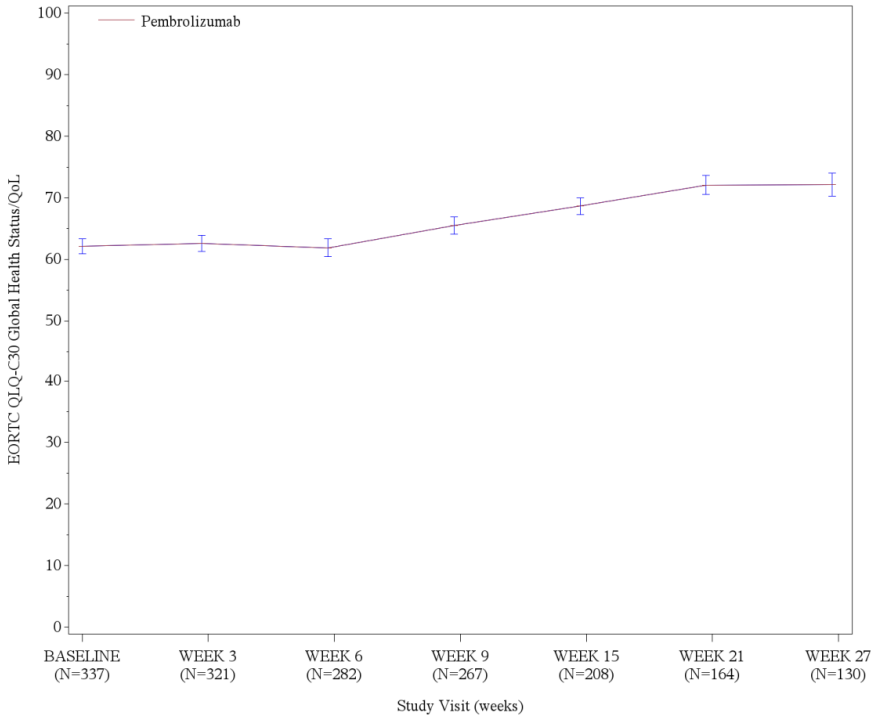
The completion and compliance rates were calculated for each visit from baseline to Week 57. The primary HRQoL endpoint was the change from baseline for the EORTC QLQ-C30 and the EQ-5D-3L to Week 9 using a constrained longitudinal data analysis model.[5] The Submitter stated that Week 9 was selected to minimize loss of data due to death or disease progression while allowing comparisons in scores while patients were still on treatment.[5]

Overall, there were 367 patients included in the PRO analysis.[11] The compliance rates for the EORTC QLQ-C30 and EQ-5D-3L questionnaires were above 90% at baseline and above 86% at Week 9.[6] In addition, completion rates remained above 70% at each time point after baseline until Week 9, where they dropped as patients discontinued the study due to disease progression, physician decision, AEs, or death.[6]

HRQoL was measured as the change from baseline to week 9 using the EORTC QLQ-C30 global health status/QoL score (defined as a ≥10-point decrease) (Figure 6.7). At Week 9, the majority of patients experienced an improvement of 10 or more points (29%) or stable global health status/QoL (43%).[5] Similar results were observed at Week 15.[5] It should be noted that scores after Week 9 should be interpreted with caution because of small sample sizes.

The Submitter reported that both the EQ-5D-3L score and the EQ-5D VAS score were stable over time. [5]

Figure 6.7: Summary of EORTC QLQ-C30 Global Health Status/QoL for all patients enrolled in the KEYNOTE-052 trial.



Source: Merck, data on file
Data cut-off: 30 November 2017
Note: Mean ± standard error (Full Analysis Set population)
Data Source: Clinical Study Report from Merck[5]

Harms Outcomes

There were 370 patients in the safety set, which consisted of patients who had received at least one dose of pembrolizumab.[1,2] For the purpose of this review, the results from all the patients enrolled in the KEYNOTE-052 trial will be presented. The Submitter stated that the safety profile among patients with a PD-L1 CPS ≥10% were similar to all patients enrolled in the KEYNOTE-052 trial.[12] No safety information was available specifically for the platinum ineligible patients only.

Dose modification, reductions, delays or discontinuation

Overall, 17.0% of patients discontinued the trial due to an adverse event (AE) while 11.6% discontinued due to a serious adverse event. (SAE).[10] Vuky et al (2018) reported that 10% of patients discontinued due to a treatment-related AE (TRAE), and among these patients, 5% discontinued due to a serious TRAE.[3] At the 26-Sep-2018 data cut-off, 9.2% of patients discontinued due to a TRAE, and among these patients, 4.3% discontinued due to a serious TRAE.[4]

All grades and grade 3 to 4 adverse events

Overall, 97.6% of patients had AEs and 62.7% and 20.3% had grade 3-5 AEs.[10] A summary of the TRAEs for patients in the KEYNOTE-052 trial safety set at the 30-Nov-2017 data cut-off are

presented in Table 6.11. Overall, 68% of patients experienced a TRAE of any grade and 20.3% experienced grade 3-5 TRAEs.[3] The most common types of AEs were fatigue (18%), pruritus (18%) and rash (12%).[3]

At the 26-Sep-2018 data cut-off, 67.3% of patients had a TRAE and 20.8% of patients experienced a grade 3-5 TRAE.[4]

Table 6.11: Summary of the treatment-related adverse events for patients in the KEYNOTE-052 trial safety set at the 30-Nov-2017 data cut-off.

Treatment-Related AEs	N (%)
Any AE	250 (67.6)
AEs ≥ 5%	
Fatigue	67 (18.1)
Pruritus	66 (17.8)
Rash	44 (11.9)
Decreased appetite	39 (10.5)
Hypothyroidism	37 (10.0)
Diarrhoea	34 (9.2)
Nausea	32 (8.6)

Data source: Vuky et al. 2018;[37]

Serious Adverse Events

At the 30-Nov-2017 data cut-off, 50.5% of patients had a SAE and 11.1% of patients had a serious TRAE.[10]

SAEs or serious TRAEs were not reported at the 26-Sep-2018 data cut-off.

Adverse Events of Special Interest

Balar et al (2017) defined immune-mediated adverse events (IMAE) as events that had potentially drug-related immunological causes and these events were reported irrespective of attribution by the investigator.[1,2] Vuky et al (2018) reported that 29% of patients had an IMAE and the most common grade 3 or 4 IMAEs were colitis (2%), pneumonitis (1%) and adrenal insufficiency (1%) (Table 6.12).[3] At the 26-Sep-2018 data cut-off, 25.9% of patients had an IMAE and the most common grade 3 or 4 IMAEs were hepatitis (2.2%), colitis (1.9%) and severe skin reactions (1.9%).[4]

Table 6.12: Immune-mediated adverse events and infusion-related reactions that occurred in ≥ two patients in the KEYNOTE-052 trial safety set at the 30-Nov-2017 data cut-off.

	All N (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)
Any	107 (29)	24 (9)	49 (13)	29 (8)	5 (1)
Hypothyroidism	42 (11)	9 (2)	33 (9)	0	0
Pneumonitis	15 (4)	4 (1)	6 (2)	5 (2)	0
Hyperthyroidism	11 (3)	8 (2)	3 (<1)	0	0
Colitis	10 (3)	2 (<1)	2 (1)	5 (2)	1 (<1)
Adrenal Insufficiency	6 (2)	0	1 (<1)	3 (<1)	2 (<1)
Hepatitis	3 (<1)	0	0	3 (<1)	0
Thyroiditis	3 (<1)	0	2 (<1)	1 (<1)	0
Type 1 diabetes mellitus	3 (<1)	0	1 (<1)	2 (<1)	0
Autoimmune hepatitis	2 (<1)	0	0	2 (<1)	0
Dermatitis bullous	2 (<1)	1 (<1)	1 (<1)	0	0
Diabetic ketoacidosis	2 (<1)	0	0	1 (<1)	1 (<1)
Myocarditis	2 (<1)	0	0	1 (<1)	1 (<1)
Pruritus	2 (<1)	0	0	2 (<1)	0
Rash	2 (<1)	0	0	2 (<1)	0
Tubulointerstitial nephritis	2 (<1)	0	0	2 (<1)	0

[a]Based on a list of terms specified by the sponsor and included by the investigator regardless of attribution to study treatment or immune relatedness; related terms included.

Data Source: Vuky et al. 2018;[37]

Deaths

At the 30-Nov-2017 data cut-off, it was reported that there was one drug-related death due to a myositis.[3]

6.4 Ongoing Trials

There is an ongoing randomized, international, open-label phase III trial (KEYNOTE-361 [NCT02853305]).[14] This trial will assess the efficacy and safety of pembrolizumab to pembrolizumab with chemotherapy or chemotherapy alone in cisplatin-eligible and cisplatin-ineligible patients with advanced or MUC. Patients who are randomized to the pembrolizumab with chemotherapy or chemotherapy alone arms will receive either cisplatin + gemcitabine or carboplatin + gemcitabine based on the investigator's choice.[14] An early unplanned data review by the Data Monitoring Committee (DMC) suggested reduced survival in patients with PD-L1 low status on pembrolizumab monotherapy compared to patients receiving platinum-based chemotherapy. As a result the European Medicines Agency (EMA) and FDA recommended that first-line pembrolizumab should be restricted to cisplatin-ineligible patients whose tumours have high PD-L1 expression, which was defined as a CPS of ≥10%.[15,16] In addition, the FDA allowed for use of pembrolizumab in patients who are ineligible for any platinum-containing therapy, regardless of the level of PD-L1 expression. However, unlike the KEYNOTE-052 trial, the Submitter stated that patients who were ineligible to receive platinum-based therapy were not included in the KEYNOTE-361 trial and there are no phase III trials with chemotherapy as a comparator in that sub-population.[8] However, there is an ongoing, international, double-blind, randomized phase III trial, that includes patients who are ineligible to receive platinum-based therapy with advanced or MUC. In the LEAP-011 trial, patients will be randomized to receive either pembrolizumab plus placebo or pembrolizumab plus lenvatinib.[17] For summary of the LEAP-011 trial see section 8.

Table 6.13: Summary of the KEYNOTE-361 trial[14]

Trial Design	Inclusion Criteria	Intervention	Trial Outcomes
Study KEYNOTE-361 Trial Characteristics Ongoing, multi-site, open-label, randomized-controlled trial Number Randomized N= 990 Patient Enrolment Dates 15-Sep-2016 Estimated Primary Completion 01-Jun-2019 Estimated Completion Date 31-May-2020 Funding Merck	Key Inclusion Criteria: • Aged ≥ 18 years • Histologically or cytologically confirmed diagnosis of advanced/unresectable (inoperable) or metastatic urothelial carcinoma of the renal pelvis, ureter [upper urinary tract], bladder, or urethra. Both transitional cell and mixed transitional/non-transitional cell histologies are allowed, but transitional cell carcinoma must be the predominant histology. • Received no prior systemic chemotherapy for advanced or metastatic urothelial carcinoma, with the following exceptions: ○ Neoadjuvant platinum-based chemotherapy with recurrence >12 months from completion of therapy is permitted. ○ Adjuvant platinum-based chemotherapy following radical cystectomy with recurrence >12 months from completion of therapy is permitted. • Provided tissue for biomarker analysis from an archival tissue sample or newly obtained core or excisional biopsy of a tumor lesion not previously irradiated from a muscle invasive urothelial carcinoma or a metastatic biopsy, originally from the original tumor. • ECOG Performance Status of 0, 1, or 2. • Demonstrates adequate organ function.	**Pembrolizumab** 200 mg every 3 weeks for a maximum of 35 doses **Pembrolizumab + Chemotherapy** 200 mg every 3 weeks for a maximum of 35 doses + Cisplatin 70 mg/m^2 IV every 3 weeks + gemcitabine 1,000 mg/m^2 on Day 1 and Day 8 of each 3-week cycle, OR Carboplatin AUC 5 every 3 weeks + gemcitabine 1,000 mg/m^2 IV on Day 1 and	Primary: • PFS using RECIST 1.1 by IRR • OS Secondary: • ORR using RECIST 1.1 • DOR using RECIST 1.1 • DCR using RECIST 1.1 Tertiary: • EORTC QLQ-C30 • Safety

Trial Design	Inclusion Criteria	Intervention	Trial Outcomes
	Key Exclusion Criteria: • Disease that is suitable for local therapy administered with curative intent. • Currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigation device within 4 weeks of the first dose of study drug. • Diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to randomization. • Has an active autoimmune disease that has required systemic treatment in the past 2 years. • Has had a prior anti-cancer mAb for direct anti-neoplastic treatment within 4 weeks prior to the first dose of study drug (6 weeks for nitrosoureas or mitomycin C) or who has not recovered (i.e., ≤ Grade 1 or at Baseline) from AEs due to mAbs administered more than 4 weeks earlier. • Has not recovered (i.e., AE ≤ Grade 1 or at Baseline) from AEs due to a previously administered agent. • Has a known additional malignancy that is progressing or requires active treatment within the past 5 years. ○ Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer. ○ A history of prostate cancer that was identified incidentally following cystoprostatectomy for bladder cancer is acceptable, provided that the following criteria are met: Stage T2N0M0 or lower; Gleason score ≤6; Prostate-specific Antigen level undetectable. • Has a history of (non-infectious) pneumonitis that required steroids or current pneumonitis. • Has a known history of active tuberculosis, HIV, HBV and HCV. • Has received prior therapy with an anti-PD-1, or anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another co-inhibitory T-cell receptor (e.g., [CTLA-4], OX-40, CD137)	Day 8 of each 3-week cycle. **Chemotherapy** Cisplatin 70 mg/m^2 IV every 3 weeks + gemcitabine 1,000 mg/m^2 on Day 1 and Day 8 of each 3-week cycle, OR Carboplatin AUC 5 every 3 weeks + gemcitabine 1,000 mg/m^2 IV on Day 1 and Day 8 of each 3-week cycle.	

Abbreviations: **AE**=adverse events; **CNV** = central nervous system; **CPS** = combined positive score; **CTCAE** = Common Terminology Criteria for Adverse Events; **DCR**=disease control rate; **DOR**=duration of response; **ECOG** = Eastern Cooperative Oncology Group; **HBV** = Hepatitis B; **HCV** = Hepatitis C; **HIV** = human immunodeficiency virus; **IRR** = Independent Radiology Review; **mAb** = monoclonal antibody; **MUC** = metastatic urothelial carcinoma; **NYHA** = New York Heart Association; **ORR**=objective response rate; **OS** = overall survival; **PFS** = progression-free survival; **RECIST** = Response Evaluation Criteria in Solid Tumors; **SAE**=serious adverse events; **WDAE**=withdrawals due to adverse events

7 SUPPLEMENTAL QUESTIONS

7.1 Critical appraisal of a network meta-analysis

7.1.1 Background

The pCODR-conducted literature search identified one open-label nonrandomized clinical trial that assessed the efficacy of pembrolizumab in cisplatin-ineligible patients with locally advanced and unresectable or MUC.[1] Thus, there is a lack of direct evidence comparing pembrolizumab to other active therapies. Given the absence of head-to-head trials, the Submitter provided a network meta-analysis (NMA), which provided an indirect comparison of pembrolizumab to gemcitabine and carboplatin + gemcitabine.[36]

The objective of this section is to summarize and critically appraise the submitted NMA.[36] This NMA provides evidence supporting the efficacy of pembrolizumab relative to other therapies in patients with locally advanced or MUC who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 CPS ≥10] as determined by a validated test, or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status.

7.1.2 Review of published NMA

Objectives of NMA

The objective of the NMA was to compare the efficacy of first-line pembrolizumab to other anticancer agents in patients with advanced or unresectable or MUC who were ineligible for cisplatin-based chemotherapy.[36]

7.1.3 Methods

Search and Study Selection

The Submitter conducted a systematic review to identify eligible RCTs, single-arm trials, retrospective studies and observational studies. Studies were eligible if they assessed the efficacy of first-line interventions on OS or PFS in advanced or unresectable or MUC patients who were ineligible for cisplatin-based chemotherapy.

The Submitter identified the following subgroups of interest, which include: patients with PD-L1 CPS ≥ 10%; platinum-ineligible patients (e.g., ECOG 2 and visceral metastasis or ECOG 2 and ≥ 80 years or ECOG 2 and GFR < 60 mL/min) and platinum-eligible patients (e.g., all other patients not included in the platinum-ineligible subgroup). The Submitter noted that the platinum-eligible and platinum-ineligible patient subgroups refer to those who are carboplatin-eligible or carboplatin ineligible.

The systematic review was originally conducted in 2015 and it was subsequently updated in October 2016 and September 2017. The following data sources were used for the systematic review: Medical Literature Analysis and Retrieval System Online (MEDLINE), Excerpta Medica database (EMBASE) and the Cochrane Central Register of Controlled Trials. In addition, conference proceedings were also searched for relevant studies. The Submitter stated that the NMA was performed using data from the KEYNOTE-052 trial at the 30-Nov-2017 cut-off.

Two reviewers independently screened titles and abstracts, as well as full text articles. If any discrepancies occurred, a third party was used to provide consensus.

The quality of all included studies were critically appraised using the Newcastle-Ottawa Quality Assessment Scale. The tool assesses the study group and selection, the comparability of groups within studies and the ascertainment of either the exposure or outcomes of interest. Study quality was ranked using a "star system". Here, a study can be given a maximum of one star for each numbered item within the "Selection" and "Exposure" categories and a maximum of two stars for "Comparability" category. The quality assessment was conducted by two independent reviewers, and, if any discrepancies occurred, a third party was used to provide consensus.

NMA Methodology

Indirect Treatment Comparison and the NMA

Since the Submitter conducted systematic review identified both RCTs and single arm trials, the Submitter used a simulated treatment comparison (STC). The STC acts to derive a targeted comparison of outcomes reflecting what may have been observed if two treatments had been studied together in the same trial.[38,39]

The Submitter used the KEYNOTE-052 trial as the basis (or index trial) for the STC. Here, the STC uses the individual patient data (IPD) from the KEYNOTE-052 trial and aggregate level data from previously published studies. Next, the Submitter identified a set of key prognostic factors that would be incorporated into the stimulation model. These factors were selected because they may affect the results of interest differentially for one intervention or another. These factors were determined using a literature scan and consultation with the Merck clinical team, and included: ECOG ≥2, poor renal function and presence of liver metastasis or visceral metastasis. In studies that did not report ECOG status, the Karnofsky Performance Score (KPS) was translated from the proportion of patients with KPS <80% into a proportion of patients with ECOG ≥2. The pCODR CGP confirmed that these factors were comprehensive.

The prediction model was then built based on the prognostic factors available in the IPD set. A prediction model was developed for all relevant outcomes using pembrolizumab (or the "index intervention") as a function of the relevant prognostic factors. This model predicts the selected outcomes with pembrolizumab for each "target" trial according to the distribution of prognostic factors reported in the "target" trial of interest. This creates a comparison of each intervention relative to the index intervention and these "predicted controlled trials" are incorporated into an evidence network using the index intervention as the common link.

Overall, the Submitter reported that the evidence networks created from the "predicted comparative studies" were sufficiently similar, and therefore, Bayesian NMAs were performed for OS and PFS. For time-to-event outcomes, it was assumed that proportional hazards assumption was met between treatments. Overall, these assumptions were met.

NMAs were developed separately for the overall target population (i.e., all patients treated [APT]) and potential effect modifiers (i.e., PD-L1 expression and platinum-eligibility status). For the PD-L1 expression subgroups, OS and PFS networks were conducted in patients with a PD-L1 CPS ≥ 10. The comparators for this patient group were carboplatin + gemcitabine and gemcitabine monotherapy. The prognostic factors included in the APT population and PD-L1 CPS ≥ 10 network analyses are presented in Table 7.1.

Table 7.1: Prognostic factors for the all patients treated and PD-L1 CPS ≥ 10 network analyses

Model	Prediction model
Model 1	ECOG ≥ 2 + liver metastasis + poor renal function + visceral metastasis
Model 2	ECOG ≥ 2 + liver metastasis + poor renal function + visceral metastasis + (liver metastasis X ECOG ≥ 2)
Model 3	ECOG ≥ 2 + liver metastasis + poor renal function + visceral metastasis + (visceral metastasis X ECOG ≥ 2)
Model 4	ECOG ≥ 2 + liver metastasis + poor renal function + visceral metastasis + (poor renal function X ECOG ≥ 2)

Data source: NMA Document prepared by Merck[36]

Subgroup analyses were also performed based on platinum-eligibility status. The platinum-ineligible subgroup included patients who had ECOG ≥ 2 and visceral metastases OR ECOG ≥ 2 and ≥ 80 years of age OR ECOG ≥ 2 and GFR < 60 mL/min. The platinum-ineligible NMA used gemcitabine monotherapy as a comparator as this regimen is only indicated for this patient group. On the other hand, the platinum-eligible subgroup was defined as those who did not have the criteria to define the platinum-ineligible subgroup. The platinum-eligible NMA used carboplatin + gemcitabine as a comparator as this regimen is only indicated for this patient group.

The Submitter constructed partially adjusted prediction models for the subgroup analyses conducted in the platinum-eligibility subgroups. The prognostic factors are presented in Table 7.2. The Submitter adopted these models because platinum-eligibility in the KEYNOTE-052 trial was defined using prognostic factors including ECOG status. Thus, it may not be possible to adjust for the effect of pembrolizumab in patients with only ECOG ≥ 2 (the platinum-ineligible subgroup) or ECOG <2 (the platinum-eligible subgroup) in order to be comparable to a population without these defining criteria. Therefore, these prognostic factors were excluded in all platinum-eligibility subgroup analyses. Partially adjusted prediction models are subject to bias because they exclude known prognostic factors.

Table 7.2: Prognostic factors for platinum-eligibility network analyses

Model*	Prediction model
Model 1	liver metastasis + poor renal function + visceral metastasis

* Within the overall target population (APT), patients included in platinum-ineligible subgroup are defined by the following characteristics: 1) ECOG 2 and visceral metastasis or, 2) ECOG 2 and ≥ 80 years, or 3) ECOG 2 and GFR < 60 mL/min; and the rest patients (who did not have these criteria) were included in the platinum-eligible subgroup.

Data source: NMA Document prepared by Merck[36]

Regression models were performed using a contrast-based normal likelihood for the log HR of each trial in the network. Normal non-informative prior distributions were used for all parameters (mean 0; variance of 10,000). The time-to-event outcomes were expressed as HRs with 95% credible intervals (CrIs). Although both fixed and random effects models were considered for the NMA, the Submitter used a fixed effects model because there were insufficient trials to achieve stable estimates of between-study heterogeneity.

7.1.4 Results

Included studies
The systematic review identified nine citations, which corresponded to two RCTs and six single-arm trials. The Submitter narrowed these search results to reflect a Canadian perspective, and therefore, six trials were included: Bamias 2006, Carles 2000, EORTC 30986, Linardou 2004, GETUG V01 and KEYNOTE-052. It was noted that two treatment arms (i.e., M-CAVI from the EORTC 30986 RCT and gemcitabine + oxaliplatin from the GETUG V01 RCT) were excluded from the NMA because they were not treatments of interest.

Trial characteristics

Details of the included studies are reported in Tables 7.3 and 7.4.

Table 7.3: Study characteristics of the studies included in the feasibility assessment
Data source: NMA Document prepared by Merck[36]

Trial ID	Interventions	Age	Performance score	Disease status	Creatinine Clearance	Cisplatin-ineligible description	Prior treatment (exclusion criterion)
Bamias 2007	Carboplatin + gemcitabine	--	--	Unresectable, recurrent or metastatic	--	One of the following: ECOG ≥ 2, impaired renal function (CrCl < 50 ml/min), pre-existing grade 2 neuropathy and any degree of hearing loss	No previous chemotherapy
Carles 2000	Carboplatin + gemcitabine	< 80	Karnofsky ≥ 50%	T4bN0M0 or Tx N1-3 M0-1 or relapsed	20-55 ml/min		No previous chemotherapy
EORTC 30986	Carboplatin + gemcitabine	--	--	Unresected lymph nodes (N+), distant metastases (M1, stage IV), or unresectable primary bladder cancer (T3-4)	--	WHO PS 2 and/or impaired reanl function (GFR 29-59 mL/min)	No previous cytotoxic or biologic systemic treatment
GETUG V01	Gemcitabine	>18	--	Locally advanced (T4 or regional lymph nodes) or metastatic disease	--	ECOG 2 and/or impaired renal function (GFR 29-69 mL/min)	No previous treatment with gemcitabine or oxaliplatin
KEYNOTE 052	Pembrolizumab	≥ 18	ECOG 0-2	Advancted/unresectable or metastatic	--	Cisplatin-ineligible	No prior systemic chemotherapy for metastatic disease
Linardou 2004	Carboplatin + gemcitabine	--	--	Inoperable or metastatic	--	One of the following: ECOG 3, GFR 30-49 mL/min, or > 75	No previous chemotherapy for advanced disease

Table 7.4: Patient characteristics of trials included in the feasibility assessment by treatment arm

Trial	Treatment	Year	N	Median Age (Range)	Performance Status Measure	ECOG: ≥1 (KPS ≤90%)	ECOG: 0 (KPS 100%)	ECOG: 1 (KPS 80-90%)	ECOG: 2 (KPS 60-70%)	Liver Met	Visceral Met
RCTs											
GETUG V01	Gemcitabine+oxaliplatin	2011	22	74 (48-85)	ECOG	1	0	0.55	0.45	0.21	0.59
	Gemcitabine	2011	22	77 (69-86)	ECOG	0.91	0.09	0.55	0.36	0.41	0.72
EORTC 30986	Carboplatin+gemcitabine	2012	119	70 (36-87)	WHO	0.46	0.17	0.39	0.45	0.17	0.46
	M-CAVI	2012	119	72 (34-86)	WHO	0.45	0.16	0.39	0.45	0.24	0.56
Single arm trials											
Bamias 2007	Carboplatin+gemcitabine	2007	34	76 (57-84)	ECOG	--	--	--	--	--	0.44
Carles 2000	Carboplatin+gemcitabine	2000	17	69 (54-78)	KPS	0.88	0.12	0.47	0.35	0.12	0.41
KEYNOTE 052	Pembrolizumab	2017	374	74 (34-94)	ECOG	0.42	0.22	0.36	0.42	0.21	0.85
Linardou 2004	Carboplatin+gemcitabine	2004	56	75 (54-86)	ECOG	0.86	0.14	0.39	0.23	0.18	0.43

Note: Treatments shaded in grey were not included in the final network meta-analyses.

Data source: NMA Document prepared by Merck[36]

				Renal failure					PD-L1 status		
Trial	Treatment	Year	N	Measure	GFR/CrCl	Value (mL/min)	Prop. Male	Prop PD-L1≥1%	Prop. IC0	Prop. IC1	Prop. IC2/3
RCTs											
GETUG V01	Gemcitabine+oxaliplatin	2011	22	Median	CrCl	48	0.91	--	--	--	--
	Gemcitabine	2011	22	Median	CrCl	43	0.73	--	--	--	--
EORTC 30986	Carboplatin+gemcitabine	2012	119	Median	GFR	50	0.76	--	--	--	--
	M-CAVI	2012	119	Median	GFR	48	0.81	--	--	--	--
Single arm trials											
Bamias 2007	Carboplatin+gemcitabine	2007	34	Median	CrCl	45	0.82	--	--	--	--
Carles 2000	Carboplatin+gemcitabine	2000	17	Median	CrCl	50	0.77	--	--	--	--
Linardou 2004	Carboplatin+gemcitabine	2004	56	Median	GFR	50	0.86	--	--	--	--
KEYNOTE 052	Pembrolizumab	2017	374	--	--	--	0.77	0.65	--	--	--

Note: Treatments shaded in grey were not included in the final network meta-analyses.

Data source: NMA Document prepared by Merck[36]

All patients in the included studies had advanced urothelial cancer. The included trials were comparable in terms of age (median age range: 69 to 77 years) and the proportion of males (range: 0.73 to 0.91). PD-L1 expression was only measured in the KEYNOTE-052 trial. The proportion of patients with ECOG ≥2 or KPS ≤80% ranged from: 0.41 (Carles 2000 and GETUG V01) to 0.68 (Bamias 2007) while those with liver metastasis or visceral metastasis ranged from 0.12 (Carles 2000) to 0.85 (KEYNOTE-052), respectively. Moreover, two trials reported median GFR while four reported median creatinine clearance (CrCl). GFR and CrCl ranged from 43 mL/min (GETUG V01 gemcitabine arm) to 50 mL/min in GFR and CrCl (Linardou 2004 and Carles 2000).

The direct estimates of OS and TTP/PFS from each trial included in the NMA are presented in Table 7.5.[7] Among all the included trials, the median OS ranged from 5.4 months (GETUG V01) to 11.5 months (KEYNOTE-052). The Submitter commented that TTP was used instead of PFS in cases where TTP was reported but not PFS. For PFS, the Bamias et al 2007 study reported a PFS Kaplan-Meier curve while the Linardou et al 2004 study reported a TTP Kaplan-Meier curve. The median PFS/TTP ranged from 2.3 months (KEYNOTE-052) to 5.8 months (EORTC 30986).

Table 7.5: Direct estimates of OS and TTP/PFS for all trials included in the NMA

Trial	Treatment	Median OS	Median TTP/PFS
Bamias 2007	Carboplatin + gemcitabine	9.8 mos. (95% CI: 4.7, 14.9)	4.4 mos. (95% CI: 1.03, 7.75)
Carles 2000	Carboplatin + gemcitabine	10 mos. (95% CI: NR)	--
EORTC 30986 (De Santis 2012)	Carboplatin + gemcitabine	9.3 mos.	5.8 mos.
Linardou 2004	Carboplatin + gemcitabine	7.2 mos. (95% CI: 5.9, 8.5)	4.8 mos. (95% CI: 3.5, 6.0)
GETUG V01 (Culine 2011)	Gemcitabine	5.4 mos. (95% CI: 3.3, 13.4)	3.8 mos. (95% CI: NR)
IMVigor 210 (Balar 2016)	Atezolizumab	14.8 mos. (95% CI: 10.1, NR)	--
KEYNOTE 052	Pembrolizumab	11.5 mos. (10.0, 13.3)	2.3 mos. (95% CI: 2.1, 3.4)

NR—not reported
Data source: Merck Checkpoint Response[7]

The risk of bias for all the included trials was assessed using the Newcastle-Ottawa quality assessment. The EORTC 30986 RCT (De Santis 2012) received 9 stars. Among the five single-arm studies, one study (GETUG V01) received nine stars, three studies (Bamias 2007, KEYNOTE-052, Linardou 2004) received 7 stars and one study (Carles 2000) received 6 stars due to a lack of

description of the length of follow-up. These trials were all judged to be high-quality cohort studies.[7]

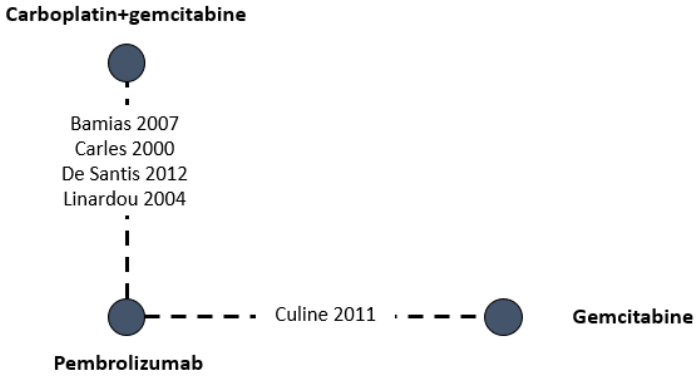
NMA

It should be noted that the results of the NMA are presented for the overall trial population of the KEYNOTE-052 trial and five subgroups (PD-L1 ≥10, platinum-ineligible, platinum-ineligible and PD-L1 ≥10, platinum-eligible, and platinum-eligible and PL-L1 ≥10). However, the economic evaluation submitted to pCODR only considers the following three patient populations: PD-L1 CPS ≥10%, platinum ineligible, and the overall trial population of the KEYNOTE 052 trial.

Overall Survival

Figure 7.1 show a graphical representation of the NMA for OS using a Canadian perspective. Here, the NMA includes comparators that are relevant in a Canadian context.

Figure 7.1: Network meta-analysis for overall survival using a Canadian perspective



Data source: NMA Document prepared by Merck[36]

APT population

Six trials were included in the APT network, which assessed the effects of three treatments on OS. Model 1 was the best fitting model because it had an AIC of 783.339 and it included the following prognostic factors as coefficients: ECOG ≥ 2, liver metastasis, poor renal function and visceral metastasis. The HRs generated for OS using Model 1 in the APT population are shown in Table 7.6.

Table 7.6: Constant HRs for OS in the APT population.

Study	Reference	Intervention	HR	logHR(SE)
Bamias 2007	Carboplatin + gemcitabine	Pembrolizumab	0.60	-0.51 (0.30)
Carles 2000	Carboplatin + gemcitabine	Pembrolizumab	0.86	-0.15 (0.49)
EORTC 30986	Carboplatin + gemcitabine	Pembrolizumab	0.59	-0.53 (0.15)
GETUG V01	Gemcitabine	Pembrolizumab	0.50	-0.69 (0.36)
Linardou 2004	Carboplatin + gemcitabine	Pembrolizumab	0.46	-0.78 (0.23)

Data source: NMA Document prepared by Merck[36]

Based on the fixed-effects NMA in the APT population, pembrolizumab was associated with a statistically significant longer OS as compared to carboplatin + gemcitabine (HR: 0.57, 95% CrI: 0.46 to 0.71) while there were no differences between pembrolizumab and gemcitabine on OS (HR: 0.50, 95% CrI: 0.25 to 1.00) (Table 7.7). Based on sensitivity analyses by the Submitter, it was noted that the constant HR results were deemed appropriate.

Table 7.7: Results of fixed-effects NMA for OS in the APT population. The results are presented as constant HRs between all competing interventions along with 95% credible intervals.

Carboplatin + gemcitabine	0.88 (0.42, 1.81)	**1.76** **(1.41, 2.20)**
1.14 (0.55, 2.37)	**Gemcitabine**	2.00 (1.00, 4.02)
0.57 **(0.46, 0.71)**	0.50 (0.25, 1.00)	**Pembrolizumab**
Note: Each cell represents the comparison (hazard ratio and 95% CrI) of the row treatment versus the column treatment. All bolded values are statistically meaningful at the 0.05 significance level. DIC: 5.02; Deviance: 3.02		

Data source: NMA Document prepared by Merck[36]

PD-L1 CPS ≥ 10 population

Five trials were included in the PD-L1 CPS ≥ 10 network, which assessed the effects of three therapies on OS. Model 3 was the best fitting model because it had an AIC of 138.507 and it included the following prognostic factors as coefficients: ECOG ≥ 2, liver metastasis, poor renal function, visceral metastasis and visceral metastasis x ECOG ≥ 2. The HRs generated for OS using Model 3 in the PD-L1 CPS ≥ 10 population are shown in Table 7.8.

Table 7.8: Constant HRs for OS in the PD-L1 CPS ≥ 10 population.

Study	Reference	Intervention	HR	logHR(SE)
Bamias 2007	Carboplatin + gemcitabine	Pembrolizumab	0.50	-0.69 (0.31)
Carles 2000	Carboplatin + gemcitabine	Pembrolizumab	0.62	-0.48 (0.53)
EORTC 30986	Carboplatin + gemcitabine	Pembrolizumab	0.45	-0.80 (0.16)
GETUG V01	Gemcitabine	Pembrolizumab	0.42	-0.87 (0.37)
Linardou 2004	Carboplatin + gemcitabine	Pembrolizumab	0.35	-1.05 (0.25)

Data source: NMA Document prepared by Merck[36]

Based on the fixed-effects NMA in the PD-L1 CPS ≥ 10 population, pembrolizumab was associated with a statistically significant longer OS as compared to carboplatin + gemcitabine (HR: 0.44, 95% CrI: 0.35 to 0.55) and gemcitabine monotherapy (HR: 0.42, 95% CrI: 0.20 to 0.87) (Table 7.9). Based on sensitivity analyses by the Submitter, it was noted that the constant HR results were deemed appropriate.

Table 7.9: Results of fixed-effects NMA for OS in the CPS ≥ 10 population. The results are presented as constant HRs between all competing interventions along with 95% credible intervals.

Carboplatin + gemcitabine	0.96 (0.45, 2.06)	**2.28** **(1.81, 2.87)**
1.04 (0.49, 2.24)	**Gemcitabine**	**2.38** **(1.15, 4.96)**
0.44 **(0.35, 0.55)**	**0.42** **(0.20, 0.87)**	**Pembrolizumab**
Note: Each cell represents the comparison (hazard ratio and 95% CrI) of the row treatment versus the column treatment. All bolded values are statistically meaningful at the 0.05 significance level. DIC: 4.85; Deviance: 2.84		

Data source: NMA Document prepared by Merck[36]

Platinum-ineligible population

One trial was included in the platinum-ineligible network, which assessed the effect of pembrolizumab relative to gemcitabine on OS. The prediction model for the platinum-ineligible subgroup incorporated three prognostic factors, such as: poor renal function, visceral metastases and liver metastases. ECOG ≥ 2 could not be included due to the definition of platinum-ineligible population. The HRs generated for OS in the platinum-ineligible population are shown in Table 7.10.

Table 7.10: Constant HRs for OS in the platinum-ineligible population.

Study	Reference	Intervention	HR	logHR(SE)
GETUG V01	Gemcitabine	Pembrolizumab	0.63	-0.46 (0.34)

Data source: NMA Document prepared by Merck[36]

Table 7.11: Results of fixed-effects NMA for OS in the platinum-ineligible patient population. The results presented as constant HRs between all competing interventions along with 95% credible intervals.

Gemcitabine	1.59 (0.81, 3.13)
0.63 (0.32, 1.24)	**Pembrolizumab**
Note: Each cell represents the comparison (hazard ratio and 95% CrI) of the row treatment versus the column treatment. All bolded values are statistically meaningful at the 0.05 significance level. DIC:1.48; Deviance: 0.48	

Based on the fixed-effects NMA in the platinum-ineligible population, there were no differences between pembrolizumab and gemcitabine on OS (HR: 0.63, 95% CrI: 0.32 to 1.24) (Table 7.11). The Submitter stated that the results in platinum-ineligible patients should not be compared to platinum-eligible patients as platinum-eligibility indicates a different standard of care chemotherapy regimens. In addition, results in this population should not be compared to the APT or PD-L1 CPS ≥ 10 populations because the prediction models incorporated different prognostic factors. Based on sensitivity analyses by the Submitter, it was noted that the constant HR results were deemed appropriate.

Platinum-ineligible and PD-L1 CPS ≥ 10 population

One trial was included in the platinum-ineligible and PD-L1 CPS ≥ 10 network, which assessed the effect of pembrolizumab relative to gemcitabine on OS. The prediction model for the platinum-ineligible and PD-L1 CPS ≥ 10 subgroup incorporated three prognostic factors, which includes: poor renal function, visceral metastases and liver metastases. ECOG ≥ 2 was not included due to the definition of platinum-ineligible population. The HRs generated for OS in the platinum-ineligible and PD-L1 CPS ≥ 10 population are shown in Table 7.12.

Table 7.12: Constant HRs for OS in the platinum-ineligible and PD-L1 CPS ≥ 10 population.

Study	Reference	Intervention	HR	logHR(SE)
GETUG V01	Gemcitabine	Pembrolizumab	0.49	-0.71 (0.36)

Data source: NMA Document prepared by Merck[36]

Table 7.13: Results of fixed-effects NMA for OS in the platinum-ineligible and PD-L1 CPS ≥ 10 population. The results are presented as constant HRs between all competing interventions along with 95% credible intervals.

Gemcitabine	**2.04 (1.00, 4.17)**
0.49 (0.24, 1.00)	**Pembrolizumab**

Note: Each cell represents the comparison (hazard ratio and 95% CrI) of the row treatment versus the column treatment.
All bolded values are statistically meaningful at the 0.05 significance level.
DIC: 1.45; Deviance: 0.45

Based on the fixed-effects NMA in the platinum-ineligible and PD-L1 CPS ≥ 10 population, pembrolizumab was associated with a statistically significant longer OS as compared to gemcitabine (HR: 0.49, 95% CrI: 0.24 to 1.00) (Table 7.13). The Submitter commented that the HRs in the platinum-ineligible and PD-L1 CPS ≥ 10 population were lower than the platinum-ineligible population. This may indicate that there is improved efficacy in PD-L1 expressing patients with respect to OS. It could also be inferred that pembrolizumab is more efficacious in PD-L1 expressing patients who are eligible for platinum-based therapy compared to both platinum-ineligible and platinum-ineligible and PD-L1 CPS ≥ 10 patients. Results in platinum-ineligible patients cannot be compared to platinum-eligible patients as platinum-eligibility indicates different standard of care chemotherapy regimens. In addition, results in this population should not be compared to the APT or PD-L1 CPS ≥ 10 populations because the prediction models incorporated different prognostic factors. Based on sensitivity analyses by the Submitter, it was noted that the constant HR results were deemed appropriate.

Platinum-eligible population

Four trials were included in the platinum-eligible network, which assessed the effect of pembrolizumab relative to carboplatin + gemcitabine on OS. The prediction model for the platinum-eligible subgroup incorporated three prognostic factors, which includes: poor renal function, visceral metastases and liver metastases but ECOG ≥ 2 was excluded because of the definition of the platinum-eligible population. The HRs generated for OS in the platinum-eligible population are shown in Table 7.14.

Table 7.14: Constant HRs for OS in the platinum-eligible population.

Study	Reference	Intervention	HR	logHR(SE)
Bamias 2007	Carboplatin + gemcitabine	Pembrolizumab	0.47	-0.76 (0.31)
Carles 2000	Carboplatin + gemcitabine	Pembrolizumab	0.73	-0.31 (0.51)
EORTC 30986	Carboplatin + gemcitabine	Pembrolizumab	0.52	-0.65 (0.15)
Linardou 2004	Carboplatin + gemcitabine	Pembrolizumab	0.39	-0.94 (0.23)

Data source: NMA Document prepared by Merck[36]

Based on the fixed-effects NMA in the platinum-eligible population, pembrolizumab was associated with a statistically significant longer OS as compared to carboplatin + gemcitabine (HR: 0.49, 95% CrI: 0.39 to 0.61). Results in this population should not be compared to the APT or PD-L1 CPS ≥ 10 populations because the prediction models incorporated different prognostic factors. Based on sensitivity analyses by the Submitter, it was noted that the constant HR results were deemed appropriate.

Platinum-eligible and PD-L1 CPS ≥ 10 population

Four trials were included in the platinum-eligible and PD-L1 CPS ≥ 10 network, which assessed the effect of pembrolizumab relative to carboplatin + gemcitabine on OS. The prediction model for the platinum-eligible and PD-L1 CPS ≥ 10 subgroup incorporated three prognostic factors, which includes: poor renal function, visceral metastases and liver metastases. ECOG ≥ 2 was not included in the model due to the definition of platinum-eligible population. The results of the HRs generated for OS in the platinum-eligible and PD-L1 CPS ≥ 10 population are shown in Table 7.15.

Table 7.15: Constant HRs for OS in the platinum-eligible and PD-L1 CPS ≥ 10 population.

Study	Reference	Intervention	HR	logHR(SE)
Bamias 2007	Carboplatin + gemcitabine	Pembrolizumab	0.32	-1.14 (0.35)
Carles 2000	Carboplatin + gemcitabine	Pembrolizumab	0.48	-0.73 (0.56)
EORTC 30986	Carboplatin + gemcitabine	Pembrolizumab	0.31	-1.17 (0.18)
Linardou 2004	Carboplatin + gemcitabine	Pembrolizumab	0.26	-1.35 (0.26)

Data source: NMA Document prepared by Merck[36]

Based on the fixed-effects NMA in the platinum-eligible and PD-L1 CPS ≥ 10 population, pembrolizumab was associated with a statistically significant longer OS as compared to carboplatin + gemcitabine (HR: 0.30, 95% CrI: 0.24 to 0.39). Results in this population should not be compared to the APT or PD-L1 CPS ≥ 10 populations because the prediction models incorporated different prognostic factors. Based on sensitivity analyses by the Submitter, it was noted that the constant HR results were deemed appropriate.

Progression Free Survival

Figure 7.2 show a graphical representation of the NMA for PFS using a Canadian perspective. There was insufficient evidence for gemcitabine monotherapy for PFS in the NMA.

Figure 7.2: NMA using a Canadian perspective for PFS

Data source: NMA Document prepared by Merck[36]

APT population

Two trials were included APT network, which assessed the effect of pembrolizumab relative to carboplatin + gemcitabine on PFS. Model 1 was the best fitting model because it had an AIC of 930.165 and it included the following prognostic factors as coefficients: ECOG ≥ 2 + liver metastasis + poor renal function + visceral metastasis. The HRs generated for PFS using Model 1 in the APT population are shown in Table 7.16.

Table 7.16: Constant HRs for PFS in the APT population.

Study	Reference	Intervention	HR	logHR(SE)
Bamias 2007	Carboplatin + gemcitabine	Pembrolizumab	1.29	0.26 (0.29)
Linardou 2004	Carboplatin + gemcitabine	Pembrolizumab	0.71	-0.34 (0.21)

Data source: NMA Document prepared by Merck[36]

Based on the fixed-effects NMA in the APT population, there were no significant differences between pembrolizumab and carboplatin + gemcitabine on PFS (HR: 0.88, 95% CrI: 0.62 to 1.23). Based on sensitivity analyses by the Submitter, it was noted that the constant HR results were deemed appropriate.

PD-L1 CPS ≥ 10 population

Two trials were included in the PD-L1 CPS ≥ 10 network, which assessed the effect of pembrolizumab relative to carboplatin + gemcitabine on PFS. Model 1 was the best fitting model because it had an AIC of 176.926 and it included the following prognostic factors as coefficients: ECOG ≥ 2, liver metastasis, poor renal function and visceral metastasis. The HRs generated for PFS using Model 1 in the CPS > 10 population are shown in Table 7.17.

Table 7.17: Constant HRs for PFS in the PD-L1 CPS ≥ 10 population.

Study	Reference	Intervention	HR	logHR(SE)
Bamias 2007	Carboplatin + gemcitabine	Pembrolizumab	0.92	-0.08 (0.30)
Linardou 2004	Carboplatin + gemcitabine	Pembrolizumab	0.48	-0.73 (0.22)

Data source: NMA Document prepared by Merck[36]

Based on the fixed-effects NMA in the PD-L1 CPS ≥ 10 population, pembrolizumab was associated with a statistically significant longer PFS as compared to carboplatin + gemcitabine (HR: 0.60, 95% CrI: 0.43 to 0.85). Based on sensitivity analyses by the Submitter, it was noted that the constant HR results were deemed appropriate.

Platinum-eligible population

Two trials were included in the platinum-eligible network, which assessed the effect of pembrolizumab relative to carboplatin + gemcitabine on PFS. The prediction model for the platinum-eligible subgroup incorporated three prognostic factors, which includes: poor renal function, visceral metastases and liver metastases. ECOG ≥ 2 was not included due to the definition of platinum-eligible population. The HRs generated for PFS in the platinum-eligible population are shown in Table 7.18.

Table 7.18: Constant HRs for PFS in the platinum-eligible population.

Study	Reference	Intervention	HR	logHR(SE)
Bamias 2007	Carboplatin + gemcitabine	Pembrolizumab	1.17	0.16 (0.30)
Linardou 2004	Carboplatin + gemcitabine	Pembrolizumab	0.71	-0.34 (0.21)

Data source: NMA Document prepared by Merck[36]

Based on the fixed-effects NMA in the platinum-eligible population, there were no differences between pembrolizumab and carboplatin + gemcitabine on PFS (HR: 0.85, 95% CrI: 0.60 to 1.17). Results in this population should not be compared to the APT or PD-L1 CPS ≥ 10 populations because the prediction models incorporated different prognostic factors. Based on sensitivity analyses by the Submitter, it was noted that the constant HR results were deemed appropriate.

Platinum-eligible and PD-L1 CPS ≥ 10 population

Two trials were included in the platinum-eligible and PD-L1 CPS ≥ 10 network, which assessed the effect of pembrolizumab relative to carboplatin + gemcitabine on PFS. The prediction model for the platinum-eligible and PD-L1 CPS ≥ 10 subgroup incorporated three prognostic factors, which includes: poor renal function, visceral metastases and liver metastases. ECOG ≥ 2 was not included due to the definition of platinum-eligible population. The HRs generated for PFS for the platinum-eligible and PD-L1 CPS ≥ 10 population are shown in Table 7.19.

Table 7.19: Constant HRs for PFS in the platinum-eligible and PD-L1 CPS ≥ 10 population.

Study	Reference	Intervention	HR	logHR(SE)
Bamias 2007	Carboplatin + gemcitabine	Pembrolizumab	0.94	-0.06 (0.29)
Linardou 2004	Carboplatin + gemcitabine	Pembrolizumab	0.53	-0.63 (0.22)

Data source: NMA Document prepared by Merck[36]

Based on the fixed-effects NMA in the platinum-eligible and PD-L1 CPS ≥ 10 population, pembrolizumab was associated with a statistically significant longer PFS as compared to carboplatin + gemcitabine (HR: 0.65, 95% CrI: 0.46 to 0.91). Results in this population should not be compared to the APT or PD-L1 CPS ≥ 10 populations because the prediction models incorporated different prognostic factors. Based on sensitivity analyses by the Submitter, it was noted that the constant HR results were deemed appropriate.

7.1.5 Critical Appraisal of the ITC

The quality of the NMA provided by the Submitter was assessed according to the recommendations made by the ISPOR Task Force on Indirect Treatment Comparisons.[40] Details of the critical appraisal are presented below.

Table 7.20: Adapted ISPOR Questionnaire to Assess the Credibility of an Indirect Treatment Comparison or Network Meta-Analysis adapted from Jansen et al (2014)[40]

ISPOR Questions	Details and Comments‡
1. Is the population relevant?	**Yes, in part.** Most of the study populations included in the NMA matched the indication under review, which was to evaluate the efficacy and safety of pembrolizumab in the treatment of patients with locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 [CPS ≥10] as determined by a validated test, or in patients who are not eligible for any platinum containing chemotherapy regardless of PD-L1 status. KEYNOTE-052 was the only trial to assess PD-L1 levels.
2. Are any critical interventions missing?	**Yes, in part**. The Submitter assessed all the relevant comparators for OS, which includes: carboplatin + gemcitabine and gemcitabine. However, there was insufficient evidence to assess all relevant comparators for PFS. For instance, due to a lack of information, the effect of pembrolizumab as compared

ISPOR Questions	Details and Comments‡
	to gemcitabine on PFS could not be assessed in the platinum ineligible or the PD-L1 CPS ≥ 10 subgroups.
3. Are any relevant outcomes missing?	**Yes, in part.** The following outcomes were identified as important during the pCODR protocol stage: OS, PFS, ORR, safety outcomes and HRQoL. However, given the lack of data, the Submitter was only able to assess OS and PFS. Similarly, PFS could not be assessed in patients who were platinum-ineligible due to a lack of trial data.
4. Is the context (e.g., settings and circumstances) applicable to your population?	**Yes**. The settings of all the included trials in the NMA were similar.
5. Did the researchers attempt to identify and include all relevant randomized controlled trials?	**Yes.** A summary of the systematic literature review process used in the NMA was reported. The information sources, search strategy and study selection criteria were clearly described.
6. Do the trials for the interventions of interest form one connected network of randomized controlled trials?	**No.** There were no closed loops in the NMA.
7. Is it apparent that poor quality studies were included thereby leading to bias?	**No.** The Submitter used the Newcastle Ottawa Scale to assess the quality of the included trials. Overall, the Submitter stated that there was a low risk of bias among the two RCTs and 4 single-arm trials.
8. Is it likely that bias was induced by selective reporting of outcomes in the studies?	**No.** There was no selective reporting of outcomes.
9. Are there systematic differences in treatment effect modifiers (i.e. baseline patient or study characteristics that impact the treatment effects) across the different treatment comparisons in the network?	**Yes**. The Submitter provided a qualitative assessment of the treatment modifiers.
10. If yes (i.e. there are such systematic differences in treatment effect modifiers), were these imbalances in effect modifiers across the different treatment comparisons identified prior to comparing individual study results?	**Yes, in part.** The Submitter performed subgroup analyses of PD-L1 status and platinum-eligibility status for PFS and OS. However, the Submitter reported that it is difficult to make comparisons between the platinum-eligible and platinum-ineligible patients and the APT or PD-L1 CPS ≥ 10 populations because the prediction models incorporated different prognostic factors.
11. Were statistical methods used that preserve within-study randomization? (No naïve comparisons)	**Yes, in part**. The Submitter conducted an STC and applied the relative treatment effects in an NMA, where pembrolizumab was the common comparator of each intervention.
12. If both direct and indirect comparisons are available for pairwise contrasts (i.e. closed loops), was agreement in treatment effects (i.e. consistency) evaluated or discussed?	**Not applicable.** There was no closed loop.
13. In the presence of consistency between direct and indirect comparisons, were both direct and indirect evidence included in the network meta-analysis?	**Not applicable.** There was no closed loop.
14. With inconsistency or an imbalance in the distribution of treatment effect modifiers across the different types of comparisons in the network of trials, did the researchers attempt to minimize this bias with the analysis?	**Yes, in part.** The Submitter performed subgroup analyses for PD-L1 expression and platinum-eligibility status on OS and PFS. However, there were differences in baseline characteristics among the included trials, such as differences in liver metastasis, visceral metastasis, ECOG/KPS, and renal function. The Submitter stated that these prognostic factors were included in the prediction models to simulate a control arm from the KEYNOTE-052 trial.
15. Was a valid rationale provided for the use of random effects or fixed effect models?	**Yes**. The Submitter stated that a fixed effects model was used for OS and PFS because there were too few studies to reliably estimate the between-study heterogeneity.

ISPOR Questions	Details and Comments‡
16. If a random effects model was used, were assumptions about heterogeneity explored or discussed?	**Not applicable.**
17. If there are indications of heterogeneity, were subgroup analyses or meta-regression analysis with pre-specified covariates performed?	**Yes, in part.** Subgroup analyses were performed; however, the Methods Team does recognize that assessment of heterogeneity may have been difficult due to a limited number of studies included in the NMA.
18. Is a graphical or tabular representation of the evidence network provided with information on the number of RCTs per direct comparison?	**Yes.** The NMA is presented in Figures 7.1 and 7.2.
19. Are the individual study results reported?	Yes. The individual study results were reported.
20. Are results of direct comparisons reported separately from results of the indirect comparisons or network meta-analysis?	**Yes.** The Submitter provided the baseline characteristics of the trials and the effect estimates of all outcomes used in the NMA.
21. Are all pairwise contrasts between interventions as obtained with the network meta-analysis reported along with measures of uncertainty?	**Yes**. The pairwise contrasts between interventions as obtained with NMA are reported along with measures of uncertainty.
22. Is a ranking of interventions provided given the reported treatment effects and its uncertainty by outcome?	**No.**
23. Is the impact of important patient characteristics on treatment effects reported?	**No.**
24. Are the conclusions fair and balanced?	**Yes, in part.** The Submitter concluded that the results of the NMA suggest that pembrolizumab is an efficacious treatment in cisplatin-ineligible patients with advanced or MUC, especially in patients with PD-L1 CPS ≥ 10. However, they noted that the NMA assessing the platinum-eligible and ineligible subgroups should be interpreted with caution because the models are only partially adjusted for known prognostic factors as a result of how platinum-eligibility status was defined. In addition, the prediction models were unable to adjust for the assumptions and potential differences across studies.
25. Were there any potential conflicts of interest?	**Not reported.**
26. If yes, were steps taken to address these?	**Not reported.**

7.1.6 Conclusion

The Submitter provided an NMA that compared pembrolizumab to carboplatin + gemcitabine and gemcitabine in cisplatin-ineligible patients with advanced or MUC. While the results of the NMA are presented for the overall trial population of the KEYNOTE-052 trial and five subgroups (PD-L1 ≥10, platinum-ineligible, platinum-ineligible and PD-L1 ≥10, platinum-eligible, and platinum-eligible and PL-L1 ≥10) this concluding section will focus on summarizing the results for the patient populations that were included in the economic evaluation that was provided to pCODR as part of this submission (i.e., PD-L1 ≥10, platinum ineligible, and the overall trial population of the KEYNOTE-052 trial).

The results of the overall trial population suggest that pembrolizumab was associated with a longer OS as compared with carboplatin + gemcitabine while there were no differences between pembrolizumab and carboplatin + gemcitabine on PFS. It was noted in the NMA that there was insufficient evidence to compare pembrolizumab to gemcitabine on the effect of PFS. On the other hand, among patients with a PD-L1 CPS ≥ 10, the results of the NMA suggest a higher OS rate

for pembrolizumab as compared with carboplatin + gemcitabine or gemcitabine as well as prolonged PFS as compared with carboplatin + gemcitabine. However, there was insufficient evidence to compare the effect of pembrolizumab to gemcitabine on PFS in this patient subgroup. Finally, there was no statistical differences between treatments for patients who were platinum-ineligible on OS.

Although the results of the NMA support the efficacy of pembrolizumab in cisplatin-ineligible patients with advanced or MUC, there are several limitations that should be considered. First, the use of unanchored comparisons used as head-to-head studies in the NMAs is a serious limitation of the NMA. The STC methodology does not account for the presence of unknown or unmeasured prognostic factors. These unknown factors may potentially confound the outcomes of interest because they will not be captured in the prediction models. It should be noted that the bias resulting from missing prognostic factors is very difficult to quantify, and as a result, it is unclear what impact the missing prognostic factors have on the results of the NMA. Second, not all of the trials included in the NMA reported baseline values for the factors that were included in the prediction models. Although these missing values were imputed using repeated bootstrap samples, this method may increase the uncertainty of the predicted outcomes for these trials. Third, the subgroup analysis assessing platinum-eligibility status should be interpreted with caution because the models only partially adjusted for known prognostic factors as a result of how platinum-eligibility status was defined. Fourth, the systematic review was last updated in September 2017 and there is a potential that more recent publications may not have been captured. Fifth, the submitted systematic review and ITC were completed by external consultancy groups hired by the submitter. As a result, the information provided in the reports should be viewed considering this potential conflict of interest and lack of peer-review. Due to the above limitations, the comparative efficacy estimates obtained are likely biased, and it is difficult to quantify or identify the direction of the bias. As a result, the estimates may over- or underestimate the true treatment effect associated with pembrolizumab.

8 COMPARISON WITH OTHER LITERATURE

Pembrolizumab has been issued a conditional Notice of Compliance (NOC/c) from Health Canada for the first-line setting. The NOC/c was conditional pending the final results of two ongoing phase III RCTs, which include: the KEYNOTE-361 and the LEAP-011 trials.[14,17] Further details on the KEYNOTE-361 trial are presented in Section 6.4. The LEAP-011 trial explores the efficacy and safety of pembrolizumab as compared to pembrolizumab with lenvatinib in patients with advanced/unresectable or MUC who are cisplatin-ineligible with a PD-L1 CPS ≥10 or who are ineligible for any platinum-containing chemotherapy regardless of CPS.[17] Although lenvatinib has not been approved for the indication under review, the patient population in the LEAP-011 trial closely resembles the funding request for pembrolizumab.

Table 8.1: Summary of the LEAP-011 trial[17]

Trial Design	Inclusion Criteria	Intervention	Trial Outcomes

Study
LEAP-011
 	
Trial Characteristics
Ongoing, multi-site, double-blind, randomized-controlled trial
 	
Number Randomized
N= 694
 	
Study Start Date
6-May-2019
 	
Estimated Primary Completion
30-Dec-2022
 	
Estimated Completion Date
30-Dec-2022
 	
Funding
Merck
	Key Inclusion Criteria:
	• A histologically or cytologically confirmed diagnosis of advanced/unresectable (inoperable) or MUC of the renal pelvis, ureter (upper urinary tract), bladder, or urethra.
	• ≥1 measurable target lesion per RECIST 1.1 as assessed by the local site investigator/ radiologist.
	• Provided an archival tumor tissue sample or newly obtained core or excisional biopsy of a tumor lesion not previously irradiated and adequate for PD-L1 evaluation.
	• Has received no prior systemic chemotherapy for advanced or MUC with the following exceptions:
	  • Neoadjuvant (prior to surgery) platinum-based chemotherapy for treatment of muscle-invasive bladder cancer with recurrence >12 months from completion of the therapy is permitted.
	  • Adjuvant (following surgery) platinum-based chemotherapy following radical cystectomy, with recurrence >12 months from completion of the therapy, is permitted.
	  • Meets criteria for either option a or option b (below):
	  • a. Has a tumor(s) with PD-L1 CPS ≥10 and is considered ineligible to receive cisplatin-based combination therapy, based on 1 of the following:
	  • ECOG performance status score of 2 within 7 days prior to randomization
	  • NCI CTCAE Version 4.0 Grade ≥2 audiometric hearing loss (25 dB in 2 consecutive frequency ranges)
	  • NCI CTCAE Version 4.0 Grade ≥2 peripheral neuropathy OR
	  • b. In the opinion of the investigator, is considered ineligible to receive any
		Pembrolizumab + Placebo
		200 mg every 3 weeks for a maximum of 35 doses and placebo
		
		Pembrolizumab + Lenvatinib
		200 mg every 3 weeks for a maximum of 35 doses
		+
		20 mg once daily until progressive disease or discontinuation. Lenvatinib may be continued past 35 cycles until a discontinuation criterion is met.
			Primary:
			• PFS using RECIST 1.1 by IRR
			• OS
			
			Secondary:
			• ORR using RECIST 1.1
			• DOR using RECIST 1.1
			• DCR using RECIST 1.1
			• EORTC QLQ-C30
			• Safety
			• WDAE

Trial Design	Inclusion Criteria	Intervention	Trial Outcomes
	platinum-based chemotherapy (i.e., ineligible for cisplatin and carboplatin) based on: • ECOG performance status of 2 within 7 days prior to randomization. and ≥1 of the following: • Documented visceral metastatic disease • NCI CTCAE Version 4.0 Grade ≥2 audiometric hearing loss • NCI CTCAE Version 4.0 Grade ≥2 peripheral neuropathy • Other reason for the participant's being unable to receive carboplatin safely. Additional criteria for platinum ineligibility will be considered and allowed on a case-by-case basis, following consultation with the Sponsor. Note: Participants considered ineligible for any platinum-based chemotherapy are eligible for this study regardless of their tumor PD-L1 status. • ECOG PS 0, 1, or 2 within 7 days prior to randomization and a life expectancy of ≥3 months. • Adequately controlled BP with or without antihypertensive medications, defined as BP ≤140/90 mm Hg at screening and no change in antihypertensive medications within 1 week prior to randomization. • Adequate organ function. <u>Key Exclusion Criteria:</u> • Disease that is suitable for local therapy administered with curative intent (e.g. chemotherapy and radiation for Stage 3 disease). • Tumor with any neuroendocrine or small cell component. • A history of a gastrointestinal condition or procedure (e.g. gastric bypass, malabsorption) that, in the opinion of the investigator, may affect oral drug absorption. • Had major surgery within 4 weeks prior to the first dose of study treatment • A pre-existing Grade ≥3 gastrointestinal or non-gastrointestinal fistula. • Radiographic evidence of major blood vessel invasion/infiltration, or has had clinically significant hemoptysis (≥0.5 teaspoon of bright red blood) or tumor bleeding within 2 weeks prior to the first dose of study treatment. • Has had significant cardiovascular impairment within 12 months of the first dose of study treatment, such as history of NYHA >Class II congestive heart failure, unstable angina,		

Trial Design	Inclusion Criteria	Intervention	Trial Outcomes
	myocardial infarction or cerebrovascular accident/stroke, cardiac revascularization procedure, or cardiac arrhythmia associated with hemodynamic instability. • Known intolerance or severe hypersensitivity (Grade ≥3) to pembrolizumab or lenvatinib or any of their excipients • Received lenvatinib as monotherapy or in combination with a PD-1/PD-L1 inhibitor or has previously been enrolled in a clinical study evaluating lenvatinib for bladder cancer, regardless of the treatment received. • Received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 inhibitor, indoleamine-pyrrole 2,3 dioxygenase inhibitor, or agent directed to another stimulatory or co-inhibitory T-cell receptor (e.g. cytotoxic T-lymphocyte-associated antigen 4, OX 40, CD137), or any other antibody or drug targeting T-cell costimulatory pathways in the adjuvant or advanced/metastatic setting. • Received prior radiotherapy to a metastatic site without the use of chemotherapy radiosensitization within 3 weeks of the first dose of study treatment, with the exception of palliative radiotherapy to bone lesions, which is allowed if completed 2 weeks before the start of study treatment. Participants must have recovered from all radiation-related toxicities, and must not require corticosteroids. • Received a live vaccine within 30 days prior to the first dose of study treatment. • In the investigator's judgment, has not recovered from toxicity or other complications from any major surgery prior to starting study treatment. • Is currently participating in or has participated in a study of an investigational agent or has used an investigational device within 4 weeks prior to the first dose of study treatment. Note: Participants who have entered the follow-up phase of an investigational study may participate as long as it has been 4 weeks after the last dose of the previous investigational agent. • History or presence of an abnormal electrocardiogram (ECG) that, in the investigator's opinion, is clinically meaningful. • A diagnosis of immunodeficiency or is receiving systemic steroid therapy (at a dose exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to randomization. • An active malignancy (except locally advanced or metastatic UC) within the past 36 months. Note: Participants with basal cell		

Trial Design	Inclusion Criteria	Intervention	Trial Outcomes
	carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ (e.g. breast carcinoma, cervical cancer in situ) who have undergone potentially curative therapy are not excluded. • A history of prostate cancer (T2NXMX or lower with Gleason score ≤7) treated with definitive intent (surgically or with radiation therapy) ≥1 year prior to study entry is acceptable, provided that the participant is considered prostate cancer-free. • CNS metastases, unless the participant has completed local therapy (e.g. whole brain radiation therapy, surgery, or radiosurgery) and has discontinued use of corticosteroids for this indication for ≥4 weeks before starting study treatment. Any signs (e.g. radiologic) or symptoms of CNS metastases must be stable for ≥4 weeks before starting study treatment. • An active autoimmune disease that has required systemic treatment in the past 2 years (i.e, with disease-modifying agents, corticosteroids, or immunosuppressive drugs). • Brief (<7 days) use of systemic corticosteroids is allowed when use is considered standard of care. • Participants with vitiligo, psoriasis, type 1 diabetes mellitus, hypothyroidism, or resolved childhood asthma/atopy will be an exception to this rule. • Participants requiring intermittent use of bronchodilators, inhaled steroids, or local steroid injections will not be excluded. • Participants with hypothyroidism that is stable with hormone replacement or Sjøgren's syndrome will not be excluded. • Has a history of (non-infectious) pneumonitis that required systemic steroids, or current pneumonitis. • Has an active infection requiring systemic therapy. • Has a known history of HIV; active HBV or has active HCV; tuberculosis. • Is receiving hemodialysis. • Had an allogeneic tissue/solid organ transplant.		

Abbreviations: **BP** = blood pressure; **CNV** = central nervous system; **CPS** = combined positive score; **CTCAE** = Common Terminology Criteria for Adverse Events; **DCR**=disease control rate; **DOR**=duration of response; **ECOG** = Eastern Cooperative Oncology Group; **HBV** = Hepatitis B; **HCV** = Hepatitis C; **HIV** = human immunodeficiency virus; **IRR** = Independent Radiology Review; **MUC** = metastatic urothelial carcinoma; **NCI** = National Cancer Institute; **NYHA** = New York Heart Association; **ORR**=objective response rate; **OS** = overall survival; **PD-1** = programmed cell death-1; **PD-L1** = Programmed Death-Ligand 1; **PFS** = progression-free survival; **RECIST** = Response Evaluation Criteria in Solid Tumors; **WDAE**=withdrawals due to adverse events

9 ABOUT THIS DOCUMENT

This Clinical Guidance Report was prepared by the pCODR 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 locally advanced or 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 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 January 2019, Embase 1974 to 2019 February 26, Ovid MEDLINE(R) ALL 1946 to February 26, 2019

#	Searches	Results
1	(Keytruda* or Pembrolizumab* or Lambrolizumab* or HSDB 8257 or HSDB8257 or Merck 3475 or Merck3475 or MK 3475 or MK3475 or Sch 900475 or Sch900475 or DPT0O3T46P).ti,ab,ot,kf,kw,hw,nm,rn.	11907
2	exp Carcinoma, Transitional Cell/	42962
3	Urologic Neoplasms/ or exp Urinary bladder neoplasms/ or exp Ureteral neoplasms/ or exp Urethral neoplasms/	144827
4	((urologic* or urothel* or urinary tract or bladder or uretra* or urethra* or ureter* or transitional cell* or transitional epithel* or renal pelvis or uroepitheli* or uro-epitheli* or urogenital* or uro-genital*) adj4 (tumor* or tumour* or cancer* or carcinoma* or malignan* or metasta* or adenocarcinoma* or adeno-carcinoma*)).ti,ab,kf,kw.	164063
5	1 and (2 or 3 or 4)	1058
6	5 use medall	164
7	5 use cctr	59
8	*pembrolizumab/ or (Keytruda* or Pembrolizumab* or Lambrolizumab* or HSDB 8257 or HSDB8257 or Merck 3475 or Merck3475 or MK 3475 or MK3475 or Sch 900475 or Sch900475).ti,ab,kw,dq.	7880
9	Transitional Cell Carcinoma/	42962
10	Urinary tract carcinoma/ or Bladder carcinoma/ or Ureter carcinoma/ or Urethra carcinoma/	18045
11	((urologic* or urothel* or urinary tract or bladder or uretra* or urethra* or ureter* or transitional cell* or transitional epithel* or renal pelvis or uroepitheli* or uro-epitheli* or urogenital* or uro-genital*) adj4 (tumor* or tumour* or cancer* or carcinoma* or malignan* or metasta* or adenocarcinoma* or adeno-carcinoma*)).ti,ab,kw,dq.	163805
12	8 and (9 or 10 or 11)	601
13	12 use oemezd	400
14	13 not conference abstract.pt.	209
15	6 or 7 or 14	432
16	remove duplicates from 15	291
17	13 and conference abstract.pt.	191
18	limit 17 to yr="2014 -Current"	191
19	16 or 18	482

20	limit 19 to english language	440

2. Literature search via PubMed

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

Search	Query	Items found
#10	Search #9 AND publisher[sb] Filters: English	16
#9	Search #3 AND #8 Filters: English	146
#8	Search #4 OR #5 OR (#6 AND #7) Filters: English	86683
#7	Search tumor[tiab] OR tumour[tiab] OR tumors[tiab] OR tumours[tiab] OR cancer*[tiab] OR carcinoma*[tiab] OR malignan*[tiab] OR metasta*[tiab] OR adenocarcinoma*[tiab] OR adeno-carcinoma*[tiab] Filters: English	2614550
#6	Search urologic*[tiab] OR urothel*[tiab] OR urinary tract[tiab] OR bladder[tiab] OR uretra*[tiab] OR urethra*[tiab] OR ureter*[tiab] OR transitional cell*[tiab] OR transitional epithel*[tiab] OR renal pelvis[tiab] OR uroepitheli*[tiab] OR uro-epitheli*[tiab] OR urogenital*[tiab] OR uro-genital*[tiab] Filters: English	250300
#5	Search Urinary bladder neoplasms[mh:noexp] or Ureteral neoplasms[mh] or Urethral neoplasms[mh] Filters: English	43940
#4	Search Carcinoma, transitional cell[mh] Filters: English	14824
#3	Search #1 OR #2 Filters: English	2155
#2	Search Keytruda*[tiab] OR Pembrolizumab*[tiab] OR Lambrolizumab*[tiab] OR HSDB 8257[tiab] OR HSDB8257[tiab] OR Merck 3475[tiab] OR Merck3475[tiab] OR MK 3475[tiab] OR MK3475[tiab] OR Sch 900475[tiab] OR Sch900475[tiab] OR DPT0O3T46P[rn] Filters: English	2155
#1	Search "pembrolizumab" [Supplementary Concept] Filters: English	783

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/

World Health Organization
http://apps.who.int/trialsearch/

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

Search: Keytruda/pembrolizumab, 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: Keytruda/pembrolizumab, urothelial carcinoma

Conference abstracts:

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

European Society for Medical Oncology (ESMO)
https://www.esmo.org/

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

Detailed Methodology

The literature search was performed by the pCODR Methods Team using the search strategy above.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-Feb 26, 2019) with in-process records & daily updates via Ovid; Embase (1974-Feb 26, 2019) via Ovid; The Cochrane Central Register of Controlled Trials (January 2019) 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 retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English-language documents, but not limited by publication year.

The search is considered up to date as of July 4, 2019.

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, World Health Organization International Clinical Trials Registry 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. One member 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.

REFERENCES

1. Balar AV, Castellano D, O'Donnell PH, et al. First-line pembrolizumab in cisplatin-ineligible patients with locally advanced and unresectable or metastatic urothelial cancer (KEYNOTE-052): a multicentre, single-arm, phase 2 study. *Lancet Oncol*. 2017;18(11):1483-1492.
2. Merck Sharp & Dohme Corp. NCT02335424: Study protocol and statistical analysis plan. *ClincalTrials.gov*. Bethesda (MD): U.S. National Library of Medicine; 2017: https://clinicaltrials.gov/ProvidedDocs/24/NCT02335424/Prot_SAP_000.pdf. Accessed 2019 Jun 19.
3. Vuky J, Balar AV, Castellano D, et al. Updated efficacy and safety of KEYNOTE-052: a single-arm phase 2 study investigating firstline pembrolizumab (pembro) in cisplatin ineligible advanced urothelial cancer (UC) [abstract]. *J Clin Oncol*. 2018;36(15 Suppl 1): Presented at: American Society of Clinical Oncology Annual Meeting; 2018 June; Chicago, IL. https://meetinglibrary.asco.org/record/160444/abstract. Accessed 2019 Jun 19.
4. O'Donnell PH, Balar A, Vuky J, et al. KEYNOTE-052: Phase 2 study evaluating first-line pembrolizumab (pembro) in cisplatin-ineligible advanced urothelial cancer (UC)— updated response and survival results [abstract]. *J Clin Oncol*. 2019;37(Suppl):abstr 4546. Presented at American Society of Clinical Oncology Annual Meeting; 2019 May-Jun; Chicago, IL. https://abstracts.asco.org/239/AbstView_239_264035.html. Accessed 2019 Jun 29.
5. Clinical Study Report #P052V02MK3475. In: pan-Canadian Oncology Drug Review manufacturer submission: Keytruda (pembrolizumab), powder for solution for infusion 50 mg, solution for infusion 100 mg/4mL vial. Kirkland (QC): Merck Canada; 2019. 2017.
6. EPAR assessment report: Keytruda. London (UK): European Medicines Agency; 2017: https://www.ema.europa.eu/en/documents/variation-report/keytruda-h-c-2830-ii-0023-g-epar-assessment-report-variation_en.pdf. Accessed 2019 Jun 19.
7. Merck responses to pCODR checkpoint meeting questions on pembrolizumab (Keytruda) for urothelial carcinoma [additional manufacturer's information]. Kirkland (QC): Merck Canada; 2019.
8. Keytruda® clinical rationale. In: pan-Canadian Oncology Drug Review manufacturer submission: Keytruda (pembrolizumab), powder for solution for infusion 50 mg, solution for infusion 100 mg/4mL vial. Kirkland (QC): Merck Canada; 2019.
9. Efficacy endpoints for selected sub-populations. In: pan-Canadian Oncology Drug Review manufacturer submission: Keytruda (pembrolizumab), powder for solution for infusion 50 mg, solution for infusion 100 mg/4mL vial. Kirkland (QC): Merck Canada; 2019.
10. Merck response to pCODR additional information request for the review of Keytruda (pembrolizumab) in the first-line treatment of locally advanced or metastatic urothelial carcinoma [additional manufacturer's information]. 2019 June 26.
11. Pembrolizumab for untreated PDL1-positive locally advanced or metastatic urothelial cancer when cisplatin is unsuitable. *Technology appraisal guidance*. London: National Institute for Health and Care Excellence (NICE); 2018: https://www.nice.org.uk/guidance/ta522. Accessed 2019 Jun 19.
12. Response to Request for Clarification dated 30 October 2018, KEYNOTE-052 [additional manufacturer's information]. . Kirkland (QC): Merck Canada; 2019.
13. Response to Request for Clarification dated 14 January 2019, KEYNOTE-052 [additional manufacturer's information]. . Kirkland (QC): Merck Canada; 2019.
14. Merck Sharp & Dohme Corp. NCT02853305: Study of pembrolizumab with or without platinum-based combination chemotherapy versus chemotherapy alone in urothelial carcinoma (MK-3475-361/KEYNOTE-361). *ClinicalTrials.gov*. Bethesda (MD): U.S. National Library of Medicine; 2016: https://clinicaltrials.gov/ct2/show/NCT02853305. Accessed 2019 Jun 19.

15. FDA alerts health care professionals and oncology clinical investigators about an efficacy issue identified in clinical trials for some patients taking Keytruda (pembrolizumab) or Tecentriq (atezolizumab) as monotherapy to treat urothelial cancer with low expression of PD-L1. Silver Spring (MD): U.S. Food & Drug Administration (FDA): https://www.fda.gov/Drugs/DrugSafety/ucm608075.htm Accessed 2019 Jun 19.
16. EMA restricts use of Keytruda and Tecentriq in bladder cancer. London (UK): European Medicines Agency: http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2018/05/WC500249798.pdf. Accessed 2019 Jun 19.
17. Merck Sharp & Dohme Corp. NCT03898180: Study of first-line pembrolizumab (MK-3475) with lenvatinib (MK-7902/E7080) in urothelial carcinoma cisplatin-ineligible participants whose tumors express programmed cell death-ligand 1 and in participants ineligible for platinum-containing chemotherapy (MK-7902-011/E7080-G000-317/ LEAP-011). *ClinicalTrials.gov*. Bethesda (MD): U.S. National Library of Medicine; 2019: https://clinicaltrials.gov/ct2/show/study/NCT03898180. Accessed 2019 Jun 19.
18. Flaig TW. The changing treatment landscape for metastatic urothelial carcinoma. *J Natl Compr Canc Netw*. 2018;16(5S):636-638.
19. Galsky MD, Hahn NM, Rosenberg J, et al. Treatment of patients with metastatic urothelial cancer "unfit" for cisplatin-based chemotherapy. *J Clin Oncol*. 2011;29(17):2432-2438.
20. Galsky MD, Chen GJ, Oh WK, et al. Comparative effectiveness of cisplatin-based and carboplatin-based chemotherapy for treatment of advanced urothelial carcinoma. *Ann Oncol*. 2012;23(2):406-410.
21. De Santis M, Bellmunt J, Mead G, et al. Randomized phase II/III trial assessing gemcitabine/carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer who are unfit for cisplatin-based chemotherapy: EORTC study 30986. *J Clin Oncol*. 2012;30(2):191-199.
22. Bellmunt J, de Wit R, Vaughn DJ, et al. Pembrolizumab as second-line therapy for advanced urothelial carcinoma. *N Engl J Med*. 2017;376(11):1015-1026.
23. Rosenberg JE, Hoffman-Censits J, Powles T, et al. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. *Lancet*. 2016;387(10031):1909-1920.
24. Necchi A, Pond GR, Raggi D, et al. Efficacy and safety of gemcitabine plus either taxane or carboplatin in the first-line setting of metastatic urothelial carcinoma: a systematic review and meta-analysis. *Clin Genitourin Cancer*. 2017;15(1):23-30.e22.
25. Canadian Cancer Statistics Advisory Committee. Canadian cancer statistics 2018. Toronto (ON): Canadian Cancer Society; 2018: cancer.ca/Canadian-Cancer-Statistics-2018-EN. Accessed 2019 Jun 19.
26. Park JC, Citrin DE, Agarwal PK, Apolo AB. Multimodal management of muscle-invasive bladder cancer. *Curr Probl Cancer*. 2014;38(3):80-108.
27. Spiess PE, Agarwal N, Bangs R, et al. Bladder cancer. *J Natl Compr Canc Netw*. 2017;15(10):1240-1267.
28. Bajorin DF, Plimack ER, Siefker-Radtke AO, et al. KEYNOTE-052: Phase 2 study of pembrolizumab (MK-3475) as first-line therapy for patients (Pts) with unresectable or metastatic urothelial cancer ineligible for cisplatin-based therapy [abstract]. *J Clin Oncol*. 2015;33(15 Suppl 1):Presented at: American Society of Clinical Oncology Annual Meeting; 2015 May-June; Chicago, IL.
29. Balar A, Bellmunt J, O'Donnell PH, et al. Pembrolizumab (pembro) as first-line therapy for advanced/unresectable or metastatic urothelial cancer: preliminary results from the phase 2 KEYNOTE-052 study [abstract]. *Ann Oncol*. 2016;27(Suppl 6): Presented at: European Society for Medical Oncology Congress; 2016 Oct; Copenhagen, DK.
30. Balar AV, Castellano DE, O'Donnell PH, et al. Pembrolizumab as first-line therapy in cisplatin-ineligible advanced urothelial cancer: results from the total KEYNOTE-052 study

population [abstract]. *J Clin Oncol*. 2017;35(6 Suppl 1):Presented at: Genitourinary Cancers Symposium; 2017 Feb; Orlando, FL.
31. Grivas P, Plimack E, Balar AV, et al. Pembrolizumab (pembro) as first-line therapy in cisplatin-ineligible advanced urothelial cancer (UC): outcomes from KEYNOTE-052 in senior patients (pts) with poor performance status [abstract]. *Ann Oncol*. 2017;28 (Suppl 5):v301. Presented at: European Society for Medical Oncology Congress; 2017 Sept; Madrid, ES.
32. O'Donnell PH, Grivas P, Balar AV, et al. Biomarker findings and mature clinical results from KEYNOTE-052: first-line pembrolizumab (pembro) in cisplatin-ineligible advanced urothelial cancer (UC) [abstract]. *J Clin Oncol*. 2017;35(15 Suppl 1):Presented at: American Society of Clinical Oncology Annual Meeting; 2017 June; Chicago, IL.
33. Castellano D, Grivas P, Plimack E, et al. Pembrolizumab (pembro) as first-line therapy in elderly patients (pts) with poor performance status with cisplatin-ineligible advanced urothelial cancer (UC): results from Keynote-052 [abstract]. *Eur Urol*. 2018;17 (2):e124-e125. Presented at: European Association of Urology Annual Congress; 2018 March; Copenhagen, DK.
34. Merck Sharp & Dohme Corp. NCT02335424: Study of pembrolizumab (MK-3475) in participants with advanced urothelial cancer (MK-3475-052/KEYNOTE-52). *ClinicalTrials.gov*. Bethesda (MD): U.S. National Library of Medicine; 2019: https://clinicaltrials.gov/ct2/show/NCT02335424. Accessed 2019 Jun 19.
35. Pembrolizumab 25mg/mL concentrate for solution for infusion and 50mg powder for concentrate for solution for infusion (Keytruda®). Glasgow (UK): Scottish Medicines Consortium: https://www.scottishmedicines.org.uk/media/3692/pembrolizumab-keytruda-final-august-2018-for-website.pdf. Accessed 2019 Jun 19.
36. Lorenzi M, Arndorfer S. First-line treatment of cisplatin-ineligible advanced/unresectable or metastatic urothelial carcinoma: technical report. In: pan-Canadian Oncology Drug Review manufacturer submission: Keytruda (pembrolizumab), powder for solution for infusion 50 mg, solution for infusion 100 mg/4mL vial. Kirkland (QC): Merck Canada; 2019.
37. Vuky J, Batar AV, Castellano D, et al. Updated efficacy and safety of KEYNOTE-052: a single-arm phase 2 study investigating first-line pemborlizumab in cisplatin-ineligible advanced urothelial cancer [poster ASCO 2018]. In: pan-Canadian Oncology Drug Review manufacturer submission: Keytruda (pembrolizumab), powder for solution for infusion 50 mg, solution for infusion 100 mg/4mL vial. Kirkland (QC): Merck Canada; 2019.
38. Ishak KJ, Proskorovsky I, Benedict A. Simulation and matching-based approaches for indirect comparison of treatments. *Pharmacoeconomics*. 2015;33(6):537-549.
39. Caro JJ, Ishak KJ. No head-to-head trial? Simulate the missing arms. *Pharmacoeconomics*. 2010;28(10):957-967.
40. Jansen JP, Trikalinos T, Cappelleri JC, et al. Indirect treatment comparison/network meta-analysis study questionnaire to assess relevance and credibility to inform health care decision making: an ISPOR-AMCP-NPC Good Practice Task Force report. *Value Health*. 2014;17(2):157-173.
41. Bladder Cancer: Diagnosis and Management. NICE Guideline, No. 2. National Collaborating Centre for Cancer (UK).London: 2015 Feb.
42. Buyse M. Statistical validation of surrogate outcome measures. Trials. 2011;12(Suppl 1):A93-A93.
43. El-Khoueiry AB, Melero I, Yau T, et al. Impact of antitumor activity on survival outcomes, and nonconventioanl benefit, with nivolumab in patients with advanced hepatocellular carcinoma: subanalyses of checkmate 040 [poster ASCO-GI 2018]. In: pan-Canadian Oncology Drug Review manufacturer submission: Keytruda (pembrolizumab), powder for solution for infusion 50 mg, solution for infusion 100 mg/4mL vial. Kirkland (QC): Merck Canada; 2019.
44. Fradet Y, Bellmunt J, De Wit R, et al. Pembrolizumab (pembro) versus investigator's choice (paclitaxel, docetaxel, or vinflunine) in recurrent, advanced urothelial cancer (UC): 2-year

follow-up from the phase 3 KEYNOTE-045 trial. Journal of Clinical Oncology Conference. 2018;36(15 Supplement 1).
45. Keytruda_Health Canada_Module 2.5. In: pan-Canadian Oncology Drug Review manufacturer submission: Keytruda (pembrolizumab), powder for solution for infusion 50 mg, solution for infusion 100 mg/4mL vial. Kirkland (QC): Merck Canada; 2019. 2017.