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CADTH Reimbursement Recommendation

Pembrolizumab (Keytruda)

Indication: In combination with gemcitabine-based chemotherapy for the treatment of adult patients with locally advanced unresectable or metastatic biliary tract carcinoma.

Sponsor: Merck Canada Inc.

Final recommendation: Reimburse with conditions

Summary

What Is the Reimbursement Recommendation for Keytruda?

CADTH recommends that public drug plans reimburse Keytruda for the treatment of locally advanced unresectable or metastatic biliary tract carcinoma (BTC) if certain conditions are met.

Which Patients Are Eligible for Coverage?

Keytruda in combination with gemcitabine-based chemotherapy should only be covered to treat patients with locally advanced unresectable or metastatic BTC who have not received prior treatment or who have completed treatment with nongemcitabine-based neoadjuvant or adjuvant therapy more than 6 months ago. Patients receiving Keytruda should be in relatively good health (i.e., have a good performance status, as determined by a specialist).

What Are the Conditions for Reimbursement?

Keytruda should only be reimbursed if it is used in combination with gemcitabine-based chemotherapy if prescribed by specialists with experience in managing BTC and if the cost of Keytruda does not exceed the cost of durvalumab. Keytruda should not be reimbursed if it is used to treat patients with ampulla of Vater cancer.

Why Did CADTH Make This Recommendation?

- Evidence from a clinical trial demonstrated that patients treated with Keytruda plus gemcitabine and cisplatin live longer than those treated with gemcitabine and cisplatin alone.
- Keytruda meets some of the needs identified by patients. It is another treatment option that may prolong life and has manageable side effects.
- Based on CADTH's assessment of the health economic evidence, Keytruda represents good value to the health care system at the public list price. The committee determined that there is not enough evidence to justify a more significant cost for Keytruda compared with durvalumab throughout treatment.
- Based on public list prices, Keytruda is estimated to save the public drug plans approximately $20 million over the next 3 years. However, the actual budget impact is uncertain.

Additional Information

What Is BTC?

Biliary tract cancers are rare cancers that occur in the bile duct system, which includes the bile ducts within the liver and outside of the liver,

Summary

as well as in the gallbladder. There will be 1,263 new cases of locally advanced unresectable or metastatic BTC diagnosed in Canada in 2025. The length of survival for patients living in Canada with unresectable BTC is approximately 6 to 12 months.

Unmet Needs in BTC

Limited currently available treatment options are identified as a significant unmet need for patients with advanced BTC. New, life-extending treatments that improve quality of life are desired.

How Much Does Keytruda Cost?

Treatment with Keytruda is expected to cost $9,034.30 for the first 8 of the 21-day cycles and $9,018.70 for every cycle after that.

Recommendation

The pCODR Expert Review Committee (pERC) recommends that pembrolizumab in combination with gemcitabine-based chemotherapy be reimbursed for the treatment of adult patients with locally advanced unresectable or metastatic BTC only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One international, double-blind, randomized, phase III study (KEYNOTE-966, N = 1,069) consisting of patients with locally advanced, unresectable or metastatic BTC who are treatment naive in this setting demonstrated that treatment with pembrolizumab plus gemcitabine and cisplatin (hereafter referred to as pembrolizumab plus chemotherapy) likely results in a clinically significant increase in the probability of overall survival (OS) compared to placebo plus gemcitabine and cisplatin (hereafter referred to as placebo plus chemotherapy). The median OS was 12.7 months (95% confidence interval [CI], 11.5 to 13.6) in the pembrolizumab plus chemotherapy group versus 10.9 months (95% CI, 9.9 to 11.6) in the placebo plus chemotherapy group with a hazard ratio (HR) of 0.83 (95% CI, 0.72 to 0.95). The between-group differences in the Kaplan-Meier (KM)-estimated OS rates at 12 months and 24 months were 7.5% (95% CI, 1.6 to 13.4) and 6.8% (95% CI, 1.7 to 11.9), respectively, and therefore demonstrated a survival advantage with pembrolizumab plus chemotherapy. Assessment of health-related quality of life (HRQoL) suggested that adding pembrolizumab to chemotherapy may not result in any clinically significant difference compared to chemotherapy alone; however, the evidence had low certainty due to the large amount of missing data in the HRQoL assessment.

Patients and clinicians highlighted the need for accessible treatments that prolong life, alleviate symptoms, maintain patients' quality of life, and allow for convenient therapy administration. Given the totality of the evidence, pERC concluded that pembrolizumab added to gemcitabine-based chemotherapy meets some of the needs identified by patients, including improvements in survival (albeit modest), similar toxicity profile to chemotherapy alone, and maintaining HRQoL.

The sponsor-submitted network meta-analysis (NMA) results were insufficient to conclude that treatment with pembrolizumab plus chemotherapy differs from durvalumab plus chemotherapy in terms of efficacy or harm. At the sponsor-submitted price for pembrolizumab and publicly listed price for durvalumab, pembrolizumab (using a weight-based dosing or fixed dose for pembrolizumab) was less costly than durvalumab. Assuming pembrolizumab has similar efficacy as durvalumab, the total drug cost per patient throughout treatment with pembrolizumab should not exceed the total drug cost of therapy with durvalumab.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Pembrolizumab plus gemcitabine-based chemotherapy should only be initiated in adult patients with:	Evidence from the KEYNOTE-966 study demonstrated that treatment with pembrolizumab plus gemcitabine and	An attempt to histologically confirm the diagnosis of BTC should be made.

Reimbursement condition	Reason	Implementation guidance
1.1. Locally advanced unresectable or metastatic BTC, e.g., intra- and extrahepatic BTC, including mixed HCC-CCA or GBC. 1.2. First-line unresectable or metastatic disease at initial diagnosis or more than 6 months after the completion of prior nongemcitabine-based neoadjuvant/ adjuvant therapy. 1.3. Have good performance status.	cisplatin likely results in added clinical benefit in OS compared with gemcitabine and cisplatin alone in patients with locally advanced unresectable or metastatic BTC. Patients were excluded from the KEYNOTE-966 study if they had previous systemic therapy for advanced (metastatic) or unresectable (locally advanced) BTC (including intra-or extrahepatic CCA or GBC), except for neoadjuvant/adjuvant therapy, which was allowed. Patients with mixed HCC-CCA were eligible. The KEYNOTE-966 study included patients with an ECOG performance status of 0 or 1.	It would be reasonable for jurisdictions to consider reimbursement of pembrolizumab plus chemotherapy for patients who are currently receiving first-line gemcitabine-based chemotherapy with no evidence of disease progression; pembrolizumab may be initiated in these patients on a time-limited basis. pERC acknowledged that clinicians think it is reasonable to use pembrolizumab for patients with good ECOG performance status. The reimbursement criteria for pembrolizumab plus gemcitabine-based chemotherapy should be consistent with those used for durvalumab plus gemcitabine-based chemotherapy.
2. Pembrolizumab plus gemcitabine-based chemotherapy should not be used in patients with ampulla of Vater cancer.	Patients with ampulla of Vater cancer were excluded from the KEYNOTE-966 study.	—
Discontinuation		
3. Pembrolizumab plus gemcitabine-based chemotherapy should be discontinued upon the occurrence of any of the following: 3.1. Objective disease progression 3.2. Unacceptable toxicity 3.3. Completion of 24 months of treatment (e.g., 35 cycles at a dose of 200 mg every 3 week)s	Based on the input from clinical experts and the discontinuation criteria of the KEYNOTE-966 study, treatment with pembrolizumab plus gemcitabine-based chemotherapy should be discontinued if there is a disease progression based on the results of an imaging scan or intolerable AEs. In addition, patients in the KEYNOTE-966 study were treated with pembrolizumab for a maximum of 35 cycles (approximately 24 months).	—
4. Patients should be initially assessed clinically every 3 to 4 weeks, then with imaging and clinical assessments based on local standards.	As per usual care for patients receiving immunotherapy plus chemotherapy.	—
Prescribing		
5. Pembrolizumab plus gemcitabine-based chemotherapy should be prescribed by a clinician with expertise in managing BTC.	Based on input from the clinical experts, an oncologist with experience and knowledge of BTC management should prescribe treatment with pembrolizumab plus gemcitabine-based chemotherapy.	—
Pricing		
6. Pembrolizumab should be negotiated so that it does not exceed the drug program cost of	The sponsor-submitted indirect treatment comparison did not provide sufficient evidence to support a difference in overall	—

Reimbursement condition	Reason	Implementation guidance
treatment, with the least costly immunotherapy reimbursed for the treatment of locally advanced unresectable or metastatic BTC.	survival, progression-free survival or adverse events between pembrolizumab and durvalumab, and no data were available to assess HRQoL. As such, insufficient clinical evidence justifies a cost premium for pembrolizumab over durvalumab for the indicated population.	
Feasibility of adoption		
7. The feasibility of the adoption of pembrolizumab must be addressed.	At the submitted price, the magnitude of uncertainty in the budget impact must be addressed to ensure the feasibility of adoption, given the difference between the sponsor's estimate of budget impact and CADTH's estimate(s).	—

AE = adverse event; BTC = biliary tract carcinoma; ECOG = Eastern Cooperative Oncology Group; GBC = gallbladder cancer; HCC-CCA = hepatocellular-cholangiocarcinoma; OS = overall survival; pERC = pCODR Expert Review Committee.

Discussion Points

- pERC deliberated on pembrolizumab plus gemcitabine-based chemotherapy considering the criteria for significant unmet needs that are described in section 9.3.1 of the Procedures for CADTH Reimbursement Reviews. pERC considered the severity of the condition, rapid progression, as well as the limited treatment options available to patients with locally advanced unresectable or metastatic BTC. The available evidence demonstrated that pembrolizumab plus chemotherapy resulted in an increase in median OS of 1.8 months compared to placebo plus chemotherapy, which was judged by the clinical experts to be clinically meaningful, considering the poor prognosis of patients with advanced BTC. This evidence was rated as moderate certainty using GRADE.
- pERC discussed that pembrolizumab plus chemotherapy has a manageable toxicity profile with no additional serious safety concerns. Evidence from the KEYNOTE-966 study suggested that treatment with pembrolizumab plus chemotherapy did not result in an increased risk of any adverse events (AEs) and likely did not result in increasing the risk of serious adverse events (SAEs), AEs leading to treatment discontinuation, or immune-mediated AEs when compared to placebo plus chemotherapy.
- pERC discussed the treatment options for this patient group and acknowledged that the current standard of care for locally advanced or metastatic BTC is durvalumab plus gemcitabine and cisplatin. At the time of the pERC deliberations, durvalumab plus gemcitabine-based chemotherapy has been funded in some jurisdictions in Canada. Pembrolizumab plus chemotherapy could be another treatment option for these patients.
- pERC noted no direct evidence demonstrating the comparative efficacy and safety between pembrolizumab plus chemotherapy and currently available treatments. Indirect evidence from the sponsor-submitted NMA was insufficient to conclude whether treatment of pembrolizumab plus chemotherapy differs in terms of OS or progression-free survival (PFS) or the odds of AEs when

compared to durvalumab plus chemotherapy due to the limitations associated with the NMA, such as sparse evidence from only 2 RCTs and imprecision of study results from the wide credible intervals for these outcomes.

- The pricing condition is based on the assumption of equal efficacy and safety between pembrolizumab and durvalumab. There is insufficient evidence to base conclusions around the long-term comparative effectiveness and safety of pembrolizumab versus durvalumab, and further price reductions may be warranted. In addition, the cost-effectiveness of pembrolizumab compared with chemotherapy alone in this population is unknown.

Background

BTC is a heterogeneous group of tumours originating in the biliary tree (cholangiocarcinoma) or the gallbladder and cystic duct (gallbladder cancer). Patients with early-stage BTC are usually asymptomatic; therefore most patients (60% to 85%) are diagnosed at the locally advanced unresectable or metastatic stages. Common symptoms of BTCs are jaundice, abdominal discomfort, malaise, hepatomegaly, weight loss, palpable abdominal mass, fever, night sweats, pruritis, dark urine, or clay coloured or light-coloured greasy stools. BTCs are rare and represent less than 1% of all cancers globally. BTCs are aggressive, and high mortality rates are reported in patients with BTCs. Data from Canada support that BTCs are a rare group of malignancies with poor prognosis. BTC comprises less than 0.5% of all cancer diagnoses annually in Canada. It was estimated that in 2025, there will be 1,403 new cases of total BTC and 1,263 new cases of locally advanced unresectable or metastatic BTC. The median survival for patients living in Canada with unresectable BTC is approximately 6 to 12 months.

While chemotherapy, mainly with gemcitabine plus cisplatin, was the first-line standard of care for patients with unresectable locally advanced or metastatic BTC over a decade ago, the combination of a programmed cell death protein ligand 1 (PD-L1) checkpoint inhibitor (durvalumab) and chemotherapy has been introduced in recent years, and an improvement in OS with durvalumab plus chemotherapy compared to chemotherapy alone has been demonstrated in a phase III randomized controlled trial (RCT). Durvalumab, in combination with gemcitabine-based chemotherapy, is the standard of care and is in widespread use throughout Canada for this particular patient population. Pembrolizumab is a high-affinity antibody against programmed cell death protein 1 (PD-1). By inhibiting the PD-1 receptor from binding to its ligands, pembrolizumab reactivates tumour-specific cytotoxic T lymphocytes in the tumour microenvironment. In Canada, pembrolizumab has been issued market authorization to treat various types of cancers. On April 12, 2024, pembrolizumab in combination with gemcitabine-based chemotherapy (herein referred to as pembrolizumab plus chemotherapy) was approved by Health Canada for the treatment of locally advanced, unresectable or metastatic BTC. The sponsor's reimbursement request is aligned with the Health Canada–approved indication. Pembrolizumab is available as a single-use vial of 100 mg pembrolizumab/4 mL (25 mg/mL) and is administered as an IV infusion over 30 minutes in combination with chemotherapy. The recommended dose of pembrolizumab for BTC treatment is either 200 mg every 3 weeks or 400 mg every 6 weeks (as IV

infusion) until disease progression, unacceptable toxicity or up to 24 months or 35 doses for 200 mg or 18 doses for 400 mg, whichever is longer, in patients without disease progression.

Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- a review of a phase III, randomized, double-blind, placebo-controlled trial (KEYNOTE-966) in patients with locally advanced, unresectable or metastatic BTC; 1 indirect treatment comparisons
- patients' perspectives gathered by 1 patient group: the Colorectal Cancer Resource & Action Network (CCRAN), in collaboration with the Canadian Cancer Survivor Network (CCSN) and Gastrointestinal (GI) Society
- input from public drug plans and cancer agencies that participate in the CADTH review process
- 2 clinical specialists with expertise in diagnosing and treating patients with BTC
- input from 1 clinician group: Ontario Health (Cancer Care Ontario) (OH-CCO) Gastrointestinal Cancer Drug Advisory Committee
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

Patient Input

One patient group, CCRAN, provided input to the review of pembrolizumab used in combination with chemotherapy for BTC. The CCRAN is a national not-for-profit patient advocacy group that collected inputs from patients and caregivers through a survey between October 20 and December 1, 2023, in collaboration with the CCSN and Gastrointestinal (GI) Society. The CCRAN also contacted the Cholangiocarcinoma Foundation, a US-based patient advocacy group dedicated to supporting patients with cholangiocarcinoma, to obtain additional patient input for this disease via telephone interviews, emails or social media blasts. In total, 4 patients and 4 caregivers provided feedback on their experience of BTC and the treatments. Among them, 5 had experience with pembrolizumab, which was given without chemotherapy, following previous chemotherapy, or in combination with chemotherapy. The number of cycles of pembrolizumab that these patients had received ranged from 2 to 40. Three patients or caregivers received chemotherapy but did not report experience with pembrolizumab.

Based on the patient input, inoperable or metastatic BTC and the currently available treatments significantly negatively impact patients' physical and psychosocial well-being, affecting their everyday life, work and family. The patients often face significant financial difficulties. According to the patients who had received treatment with pembrolizumab, improved cancer-induced symptoms, fewer side effects, improved quality of life and shorter infusion time were reported compared to other treatments.

The patient group input stated that the significant unmet need for patients with metastatic BTC is limited to currently available treatment options in this patient population. Important patient outcomes included improved quality of life, delayed onset of symptoms, reduced side effects compared to the current treatments, and prolonged overall and progression-free survival. The respondents stated that the introduction of novel, more effective, better tolerated and easily administered targeted therapies with equitable access is of paramount importance, particularly in the first-line setting.

Clinician Input

Input From Clinical Experts Consulted by CADTH

The clinical experts indicated that for patients with locally advanced unresectable or metastatic BTC, the most important goals of treatment are to prolong life, delay disease progression, alleviate symptoms and maintain patients' quality of life. The experts identified these unmet needs associated with the current treatments for advanced BTC: curative therapies are lacking and there are no biomarkers that can help with patient selection.

The clinical experts indicated that currently, durvalumab, in combination with chemotherapy, is widely used in the treatment of advanced BTC, and pembrolizumab will be the second immune checkpoint inhibitor to be used along with chemotherapy for these patients. The experts also noted that pembrolizumab would be used as a first-line treatment, and it is inappropriate to recommend that patients try other therapies before initiating pembrolizumab. Furthermore, the experts suggested that after a maximum of 8 cycles of combination therapy, treatment with pembrolizumab could be continued with or without gemcitabine.

The clinical experts noted that since no biomarkers have been identified in selecting patients suitable for the combination regimen, all patients with advanced BTC should be eligible for pembrolizumab plus chemotherapy if this is not contraindicated in these patients. For example, patients with good performance status and without comorbidities that may preclude them from receiving chemotherapy (e.g., cisplatin or carboplatin plus gemcitabine) are eligible. The experts noted that in clinical practice, patients on the treatments for advanced BTC would have regular imaging scans, such as CTs, to monitor their responses to the treatments. Other assessments include patients' functional status (e.g., ECOG performance status) and disease status. Usually, these assessments are reviewed every 2 to 3 months for patients with advanced BTC. The treating physicians consistently adopt this practice.

According to the clinical experts consulted by CADTH, treatment with a combination of pembrolizumab and chemotherapy will be discontinued if disease progression is detected based on the results of an imaging scan or if the patients experience any intolerable adverse effects related to the treatment.

The clinical experts noted that, in general, patients should be treated by a medical oncologist knowledgeable about BTC management, and they should receive treatment in any setting, such as a community or academic centre.

Clinician Group Input

One clinician group provided input for reviewing pembrolizumab in combination with chemotherapy: Ontario Health (Cancer Care Ontario) (OH-CCO) Gastrointestinal Cancer Drug Advisory Committee.

In general, the clinician group input was consistent with the feedback provided by the clinical experts consulted by CADTH for this review. CCO noted that the standard of care for patients with advanced BTC is gemcitabine plus cisplatin and gemcitabine plus carboplatin, and the treatment goals are prolonged life, delayed disease progression, and improved quality of life. CCO added that since there is only 1 available regimen with a poor duration of response, new regimens are required.

The clinician group stated that pembrolizumab can be safely added to the first-line chemotherapy, which is well tolerated, and all patients who align with the clinical trial criteria are best suited for the drug under review. The clinician group believes that clinical and/or radiologic progression, as per the discretion of the treating oncologist, determines whether a patient is responding to treatment in clinical practice, and treatment should be discontinued if there is disease progression and toxicity at the discretion of the treating oncologist. Additionally, the appropriate treatment setting would be a hospital (outpatient clinic) and a specialist is required.

Drug Program Input

The clinical experts consulted by CADTH provided advice on the potential implementation issues raised by the drug programs.

Table 2: Responses to Questions from the Drug Programs

Implementation issues	Response
Relevant comparators	
In the KEYNOTE-966 study, patients received pembrolizumab in combination with chemotherapy (gemcitabine and cisplatin). The comparator was chemotherapy alone (gemcitabine and cisplatin). In April 2023, durvalumab, in combination with chemotherapy, received a positive CADTH recommendation for the first-line treatment of patients with locally advanced (not amenable to surgery) or metastatic BTC. Other treatment options include chemotherapy alone, such as gemcitabine in combination with cisplatin. If a patient is not able to tolerate cisplatin-based chemotherapy, is it reasonable to combine pembrolizumab with alternative chemotherapy? If pembrolizumab is combined with alternative chemotherapy, should the chemotherapy continue for a maximum of 8 cycles or indefinitely?	The experts noted that the situation of patients who need alternative chemotherapy would be very rare as the majority of patients with advanced BTC would receive platinum-based chemotherapy, and cisplatin is commonly prescribed with gemcitabine. The experts indicated that if a patient is not able to tolerate cisplatin (for example, the patient has renal dysfunction), it is reasonable to offer other platinum-based treatments (i.e., carboplatin) in combination with gemcitabine. The clinical experts indicated that in clinical practice, the maximum number of cycles of chemotherapy that patients can receive is based on their tolerance to the treatment. pERC agreed with the clinical experts.
Considerations for initiation of therapy	
The KEYNOTE-966 study required histologic confirmation of unresectable locally advanced or metastatic extrahepatic	The clinical experts confirmed that histologic diagnosis of unresectable locally advanced or metastatic BTC is

Implementation issues	Response
cholangiocarcinoma (including mixed hepatocellular carcinoma and cholangiocarcinoma), gallbladder cancer, or intrahepatic cholangiocarcinoma. Is the histologic diagnosis of biliary tract cancer required for the patients to be eligible for treatment with pembrolizumab?	required for the patients to be eligible for treatment with pembrolizumab. pERC noted that an attempt to histologically confirm the diagnosis of BTC should be made. pERC acknowledged that the clinical experts noted that occasionally, a diagnosis of BTC is made without histologic confirmation, and the current treatment paradigm of gemcitabine plus platinum-based chemotherapy would be given if no histological confirmation is possible.
Should the criteria for pembrolizumab plus chemotherapy be similar to that of durvalumab plus chemotherapy for patients with locally advanced unresectable or metastatic BTC?	The clinical experts indicated that the criteria for pembrolizumab plus chemotherapy should be similar to that of durvalumab plus chemotherapy for patients with locally advanced unresectable or metastatic BTC. pERC agreed with the clinical experts.
Are patients who completed 2 years of treatment with pembrolizumab and had experienced disease progression or recurrence eligible for re-treatment with pembrolizumab for up to one year (17 cycles when given every three weeks)? If re-treatment is permitted, would this be pembrolizumab monotherapy or in combination with chemotherapy?	The clinical experts noted that for patients who have completed 2 years of treatment with pembrolizumab but experience disease progression or recurrence, they are eligible for re-treatment with pembrolizumab for up to one year (17 cycles if given every 3 weeks). The treating oncologist should decide whether pembrolizumab is used as monotherapy or combined with gemcitabine-based chemotherapy. The patient's response and possible toxicity from previous chemotherapy should also be considered. pERC agreed with the clinical experts.
Considerations for discontinuation of therapy	
If disease progression is identified during a drug holiday, can the treatment with pembrolizumab and chemotherapy be resumed? If a patient cannot tolerate the chemotherapy combination, can they continue with pembrolizumab alone? Is there a minimum number of chemotherapy cycles that must be given concurrently with pembrolizumab?	pERC agreed with the clinical experts that re-treatment with pembrolizumab following progression during a drug holiday would be reasonable. pERC acknowledged that some patients must discontinue the chemotherapy portion after 1 cycle, due to toxicity or intolerance, therefore pERC considered that a minimum of one cycle of chemotherapy to be reasonable.
Considerations for prescribing therapy	
For consistency, jurisdictions would plan on implementing pembrolizumab as weight-based dosing up to a cap (e.g., 2 mg/kg every 3 weeks to a maximum dose of 200 mg or 4 mg/kg every 6 weeks to a maximum of 400 mg), similar to other indications.	This is a comment from the drug programs to inform pERC deliberations.
Generalizability	
Should patients with ECOG performance status of 2 or greater be eligible for treatment with pembrolizumab plus gemcitabine and cisplatin?	The clinical experts indicated that in the KEYNOTE-966 trial, only patients with ECOG performance status 0 or 1 were included, and those with ECOG performance status 2 were excluded. Patients with ECOG PS 2 may still be treated with pembrolizumab plus gemcitabine and cisplatin in clinical practice. pERC agreed with the clinical experts and indicated that it is

Implementation issues	Response
	reasonable to use pembrolizumab for patients with good ECOG PS.
Should patients with ampullary cancer be eligible for this treatment?	The clinical experts indicated that in the KEYNOTE-966 study, patients with ampullary cancer were not eligible for treatment with pembrolizumab plus gemcitabine and cisplatin. In clinical practice, this type of cancer is treated differently than BTC. Therefore, ampullary cancer should not be considered for treatment with pembrolizumab. pERC agreed with the clinical experts.
Should pembrolizumab be added to patients who are currently on or who have just completed a first-line chemotherapy regimen?	In patients who are currently receiving first-line chemotherapy with no evidence of disease progression, pERC and the clinical experts felt that it is reasonable to add pembrolizumab to the patients' treatment.
Funding algorithm (oncology only)	
Drug may change place in therapy with the currently available comparator drugs.	This is a comment from the drug programs to inform pERC deliberations.
Care provision issues	
Pembrolizumab is already prepared and administered at facilities throughout Canada. Health care professionals have extensive experience with it. Preparation and administration time for pembrolizumab are relatively reasonable and would not be expected to increase health system resources significantly. However, there is an additional cost related to drug wastage since there is only 1 vial size available.	This is a comment from the drug programs to inform pERC deliberations.
System and economic issues	
At the time of this recommendation, the pCPA negotiations for durvalumab have concluded.	This is a comment from the drug programs to inform pERC deliberations.

BTC = biliary tract carcinoma; ECOG PS= Eastern Cooperative Oncology Group Performance Status; PCPA = pan-Canadian Pharmaceutical Alliance; pERC = pan-Canadian Oncology Drug Review Expert Review Committee.

Clinical Evidence

Systematic Review

Description of Studies

One phase III double-blind RCT (KEYNOTE-966, N = 1,069) met the inclusion criteria for the systematic review conducted by the sponsor. This study evaluated the efficacy and safety of the combination of pembrolizumab and chemotherapy versus placebo plus chemotherapy in patients with locally advanced, unresectable or metastatic BTC. Patients were randomized at a 1:1 ratio to either pembrolizumab in combination with gemcitabine and cisplatin (chemotherapy) or placebo in combination with chemotherapy. More specifically, patients randomized to pembrolizumab received pembrolizumab 200 mg by IV infusion once every 3 weeks for a maximum of 35 cycles; both patients randomized to pembrolizumab and placebo

received treatment in combination with gemcitabine (1,000 mg/m^2 on days 1 and 8 of each cycle every 3 weeks; no maximum duration) and cisplatin (25 mg/m^2 by IV infusion on days 1 and 8 of each cycle; maximum duration 8 cycles). The primary efficacy end point in the KEYNOTE-966 study was OS. Other relevant outcomes in this study included PFS, HRQoL measured by the EORTC QLQ-C30 and EORTC QLQ-BIL21 questionnaires, and safety. Overall, the patients' baseline characteristics were balanced between treatment groups. The trial randomized approximately equal proportions of males and females (n for male = 552; 51.6%). Most randomized patients were white (n = 524; 49.0%), had a median age of 64.0 years (range: 23 to 85), had ECOG performance status score of 1 (n = 582; 54.4%), and were from a non-Asian region (n = 583; 54.5%). Most patients had metastatic disease (n = 943; 88.2%) with an intrahepatic site of origin (n = 633; 59.2%). Approximately 30% of these patients received prior surgery (n = 319; 29.8%).

Efficacy Results

The KEYNOTE-966 study met its primary end point at the final analysis (data cut-off [DCO]: December 15, 2022). The results suggested that treatment with pembrolizumab plus chemotherapy may be associated with prolonged OS, compared with treatment with placebo plus chemotherapy: median OS 12.7 months (95% CI, 11.5 to 13.6) versus 10.9 months (95% CI, 9.9 to 11.6). The HR for OS was 0.83 (95% CI, 0.72 to 0.95, P = 0.0034). Although the between-group difference in median OS was 1.8 months, given the poor prognosis in patients with advanced BTC (with a median OS less than 12 months), an improvement of 1.8 months in median survival is considered a clinically meaningful benefit, according to the clinical experts consulted by CADTH. The between-group differences in the Kaplan-Meier (KM)-estimated OS rates at 6, 12, 18, and 24 months were 7.0% (95% CI, 2.0 to 12.0), 7.5% (95% CI, 1.6 to 13.4), 5.0% (95% CI, −0.5 to 10.5), and 6.8% (95% CI, 1.7 to 11.9), respectively. These estimates were affected by imprecision; the 95% CIs included the potential for trivial effects, based on a threshold for a clinically important between-group difference of 5% as informed by the clinical experts consulted by CADTH. Results of prespecified subgroup analyses based on various patient baseline characteristics were consistent with that in the overall population.

PFS measured with RECIST 1.1 was 1 of the key secondary end points in the KEYNOTE-966 study. At DCO of December 15, 2021, the median PFS was 6.5 months (95% CI, 5.7 to 6.9) with pembrolizumab plus chemotherapy and 5.6 months (95% CI, 5.1 to 6.6) with placebo plus chemotherapy. According to the multiplicity scheme, the corresponding HR was 0.86 (95% CI, 0.75 to 1.00), P = 0.0225, which did not meet the prespecified efficacy boundary for a statistically significant PFS benefit for pembrolizumab plus chemotherapy. In the analysis of PFS, the proportional hazards assumption for PFS was formally tested and visually examined to ensure its validity on PFS. No violation of this assumption was found. The between-group difference in KM-estimated PFS rates were 6.2% (95% CI 0, to 12.4), 5.7% (95% CI, −0.5 to 11.9), 5.6% (95% CI, −0.4 to 11.6), 6.3% (95% CI, 0.2 to 12.4), and 3.5% (95% CI, −2.8 to 9.8) for 6, 9, 12, 15 and 18 months, respectively. At 6 months of follow-up, the results showed that pembrolizumab plus chemotherapy may increase the KM-estimated probability of PFS when compared with placebo plus chemotherapy; however, the clinical importance of the increase (6.2%) is uncertain, and the 95% CI included the possibility of no difference between treatments. At 18 months, the evidence was very uncertain about the effect of pembrolizumab plus chemotherapy when compared with placebo plus chemotherapy on the KM-estimated probability of PFS (3.5%), owing to imprecision (the confidence interval included the potential that either

treatment could be favoured) and indirectness (due to uncertainty in the adequacy of RECIST 1.1 to measure PFS). Although PFS is typically considered a surrogate for OS in oncology trials, assessing PFS in patients with BTC is complex and may not accurately reflect the PFS benefit gained in patients with BTC.

HRQoL was measured using the EORTC QLQ-C30 and EORTC QLQ-BIL21 questionnaires, the latter of which is specific to patients with CCA and GBC. HRQoL measures were included as exploratory outcomes in the KEYNOTE-966 study. At week 18, approximately 60% of the patients completed the assessment and contributed to the analysis of HRQoL data. As such, the results are at risk of bias due to missing outcomes data. At week 18, the between-group differences in the least squares mean (LSM) changes from baseline in the EORTC QLQ-C30 Global health status (GHS)/QoL, Physical Functioning, and Role Functioning subscale scores were 0.04 (95% CI, −2.52 to 2.60, P = 0.9773), 1.24 (95% CI, −1.42 to 3.90, P = 0.3596), and 2.68 (95% CI, −0.76 to 6.11, P = 0.1264), respectively. The difference in the LSM changes from baseline in the EORTC QLQ-BIL21 Jaundice and Pain subscale scores were 0.26 (95% CI, −1.35 to 1.87, P = 0.7535) and −1.87 (95% CI, −4.26 to 0.53, P = 0.1265), respectively. Based on the between-group minimally important differences (MIDs) for these 2 instruments (EORTC QLQ-C30: ranged from 5 to 10 points for most scales; EORTC QLQ-BIL21: MID not identified for patients with BTC, however it can be extrapolated from other cancer types), HRQoL results suggested that compared to placebo plus chemotherapy, adding pembrolizumab to chemotherapy did may not result in any clinically important difference in the subscale scores for Global health status, Physical Functioning and Role Functioning in EORTC QLQ-C30, and the subscale scores for Jaundice and Pain in EORTC QLQ-BIL21.

Harms Results

The proportion of patients experiencing 1 or more AEs in KEYNOTE-966 was well balanced between the 2 treatment groups, which suggested that adding pembrolizumab to existing chemotherapy is not associated with added risk of adverse events: 99.1% versus 99.6% for any AEs, 52.2% versus 49.3% for SAEs, and 26.1% versus 22.8% for treatment discontinuation due to AEs, for the comparisons between pembrolizumab plus chemotherapy and placebo plus chemotherapy. For patients treated with pembrolizumab, commonly reported any AEs were neutrophil count decreased (62.4%), anemia (61.1%), nausea (44.0%), platelet count decreased (39.9%), fatigue (35.3%) and constipation (35.2%), and for patients treated with placebo, commonly reported any AEs included decreased neutrophil count (61.2%), anemia (58.6%), nausea (46.1%), decreased platelet count (39.7%), fatigue (32.2%) and constipation (35.6%). Commonly reported SAEs were cholangitis (5.9%), pyrexia (5.7%), platelet count decreased (3.6%), biliary tract infection (3.2%), anemia (2.5%), sepsis (2.5%), biliary obstruction (2.3%), neutrophil count decreased (2.1%), and pulmonary embolism (2.1%) in patients treated with pembrolizumab, and were cholangitis (4.5%), biliary tract infection (3.4%), sepsis (3.0%), biliary obstruction (3.0%), ascites (2.4%), pyrexia (2.2%), and liver abscess (2.1%) in patients treated with placebo. The most common reasons for treatment discontinuation due to AEs were decreased neutrophil count (3.6%) and decreased platelet count (3.6%) in patients treated with pembrolizumab, and were neutrophil count decreased (3.0%) in patients treated with placebo.

The proportion of patients with AEs resulting in death was 5.9% (31 patients) in the pembrolizumab plus chemotherapy group and 9.2% (49 patients) in the placebo plus chemotherapy group. Patients in the

pembrolizumab plus chemotherapy group reported more AEs of particular interest compared to those in the comparator group, 22.1% versus 12.9%. For the immune-mediated AEs (immune-mediated enterocolitis, hepatitis or lung disease), although it did not appear that pembrolizumab plus chemotherapy resulted in clinically important increases in these events based on a threshold for a clinically important between-group difference of 5 to 10% as informed by the clinical experts consulted by CADTH, few events were reported in the KEYNOTE-966 study, which adds uncertainty to these results. No unusual safety signals were observed for the treatment of pembrolizumab plus chemotherapy. The frequency, type, and severity of harms were consistent with pembrolizumab monotherapy and the harms were not exacerbated by combining pembrolizumab with chemotherapy. According to the clinical experts consulted by CADTH, the AEs observed in the KEYNOTE-966 study are manageable in clinical practice.

Critical Appraisal

In the KEYNOTE-966 study, patients' baseline demographic and disease characteristics were generally balanced between the 2 treatment groups. However, patients in the pembrolizumab plus chemotherapy group performed relatively better than those in the placebo plus chemotherapy group. This imbalance is likely attributed to chance and does not introduce bias. The clinical experts consulted by CADTH noted that this imbalance would not significantly impact result interpretation.

A multiplicity testing procedure was applied to OS, PFS and overall response rate to control for the type I error rate in the study and across interim analyses. However, other efficacy outcomes were analyzed without multiplicity adjustment, for example, HRQoL assessment using the EORTC QLQ-C30 and EORTC QLQ-BIL21. Nevertheless, there were no statistically significant results in any relevant domains.

HRQoL was assessed using disease-specific instruments, and 1 was specifically designed for patients with BTC. A MID specific for patients with BTC was not identified from the literature; however, a range of potential between-group MIDs was established based on clinical trials of 9 different cancer types and may be used to determine the clinical relevance of the study findings for HRQoL. On the other hand, the completion rates of these 2 questionnaires were approximately 60% in the 2 treatment groups. As such, the risk of bias due to missing outcomes data and its impact on study findings is uncertain.

External Validity

Based on feedback from the clinical experts consulted by CADTH, the eligibility criteria and baseline characteristics of patients randomized in the KEYNOTE-966 study generally reflected a study population that was consistent with the patients in clinical practice in Canada that would receive combination therapy of pembrolizumab plus chemotherapy. However, the study population may be somewhat healthier. The clinical experts noted that the study results from KEYNOTE-966 could be generalized to patients with advanced BTC in Canada who would be treated with pembrolizumab plus chemotherapy.

GRADE Summary of Findings and Certainty of the Evidence

For pivotal studies and RCTs identified in the sponsor's systematic review, GRADE was used to assess the certainty of the evidence for outcomes considered most relevant to inform CADTH's expert committee deliberations. A final certainty rating was determined as outlined by the GRADE Working Group.

Following the GRADE approach, evidence from RCTs started as high-certainty evidence. It could be rated down for concerns related to study limitations (which refer to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias.

When possible, certainty was rated in the context of an important (nontrivial) treatment effect; if this was not possible, certainty was rated in the context of the presence of any treatment effect (i.e., the clinical importance is unclear). In all cases, the target of the certainty of evidence assessment was based on the point estimate and where it was located relative to the threshold for a clinically important effect (when a threshold was available) or to the null. The threshold for a clinically important effect was 5% to 10% for OS (as informed by the clinical experts consulted by CADTH) and null for PFS (due to uncertainties in the measurement and interpretation of the outcome). The threshold for a clinically important effect for the EORTC QLQ-C30 and EORTC QLQ-BIL21 scores was set according to the presence or absence of an important impact based on thresholds identified in the literature. The certainty of the evidence was summarized narratively for some harm events (e.g., immune-mediated AEs) due to the unavailability of the absolute difference in effects.

The selection of outcomes for the GRADE assessment was based on the sponsor's Summary of Clinical Evidence, consultation with clinical experts, and input received from patient and clinician groups and public drug plans. The following list of outcomes was finalized in consultation with expert committee members:

- probability of OS at 12, 18, and 24 months
- probability of progression-free survival at 6 and 18 months
- change from baseline in EORTC QLQ-C30 scores at 18 weeks
- change from baseline in EORTC QLQ-BIL21 scores at 18 weeks
- any AEs
- any SAEs
- AEs leading to treatment discontinuation
- risk of immune-mediated AEs (enterocolitis, hepatitis, lung disease).

Results of GRADE Assessment

Table 3 presents the GRADE summary of findings for pembrolizumab in combination with chemotherapy versus placebo in combination with chemotherapy in the study population.

Table 3: Summary of Findings for Pembrolizumab in Combination with Chemotherapy Versus Placebo in Combination with Chemotherapy for Patients with Locally Advanced Unresectable or Metastatic BTC

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Placebo plus chemotherapy	Pembrolizumab plus chemotherapy	Difference		
Efficacy (ITT population)							
Overall survival							
Probability of OS at 12 months Median follow-up: 25.6 months as of DCO on December 15, 2022	1,069 (1 RCT)	NR	[redacted]	[redacted]	[redacted]	Moderate[a]	Pembrolizumab plus chemotherapy likely results in a clinically important increase in overall survival probability at 12 months compared to placebo plus chemotherapy.
Probability of OS at 18 months Median follow-up: 25.6 months as of DCO on December 15, 2022	1,069 (1 RCT)	NR	[redacted]	[redacted]	[redacted]	Moderate[b]	Pembrolizumab plus chemotherapy likely results in a clinically important increase in overall survival probability at 18 months compared to placebo plus chemotherapy.
Probability of OS at 24 months Median follow-up: 25.6 months as of DCO on December 15, 2022	1,069 (1 RCT)	NR	[redacted]	[redacted]	[redacted]	Moderate[c]	Pembrolizumab plus chemotherapy likely results in a clinically important increase in overall survival probability at 24 months compared to placebo plus chemotherapy.
Progression-free survival							
Probability of PFS at 6 months Median follow-up: 13.6	1,069 (1 RCT)	NR	[redacted]	[redacted]	[redacted]	Low[d]	Pembrolizumab plus chemotherapy may increase the probability

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Placebo plus chemotherapy	Pembrolizumab plus chemotherapy	Difference		
months as of DCO on December 15, 2021							of progression-free survival at 6 months compared with placebo plus chemotherapy. The clinical importance of this increase is uncertain.
Probability of PFS at 18 months Median follow-up: 13.6 months as of DCO on December 15, 2021	1,069 (1 RCT)	NR	[redacted]	[redacted]	[redacted]	Very low[e]	The evidence is very uncertain about the effect of pembrolizumab plus chemotherapy on the probability of progression-free survival at 18 months when compared with placebo plus chemotherapy.
HRQoL (PRO analysis set)							
EORTC QLQ-C30 (global health status score)							
LS Mean change from baseline (0 [severe impairment] to 100 [good health]), points (95% CI) Follow-up: 18 weeks	985 (1 RCT)	NA	−2.51	−2.47 (−4.45 to −0.49)	0.04 (−2.52 to 2.60)	Low[f]	Pembrolizumab plus chemotherapy may result in little to no difference in LSM change from baseline in the Global Health Status score compared to placebo plus chemotherapy.
EORTC QLQ-C30 (physical functioning score)							
LS Mean change from baseline (0 [severe impairment] to 100 [good health status]),	985 (1 RCT)	NA	−7.66	−6.42 (−8.34 to −4.49)	1.24 (−1.42 to 3.90)	Low[g]	Pembrolizumab plus chemotherapy may result in little to no difference in LSM change from baseline in the Physical Functioning

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Placebo plus chemotherapy	Pembrolizumab plus chemotherapy	Difference		
points (95% CI) Follow-up: 18 weeks							score compared to placebo plus chemotherapy.
EORTC QLQ-C30 (role functioning score)							
LS Mean change from baseline (0 [severe impairment] to 100 [good health]), points (95% CI) Follow-up: 18 weeks	985 (1 RCT)	NA	−9.69	−7.02 (−9.59 to −4.45)	2.68 (−0.76 to 6.11)	Low[h]	Pembrolizumab plus chemotherapy may result in little to no difference in LSM change from baseline in the Role Functioning score compared to placebo plus chemotherapy.
EORTC QLQ-BIL21 (jaundice score)							
LS Mean change from baseline (0 [no or low symptom burden] to 100 [severe symptoms]), points (95% CI) Follow-up: 18 weeks	972 (1 RCT)	NA	−0.12	0.14 (−1.14 to 1.42)	0.26 (−1.35 to 1.87)	Low[i]	Pembrolizumab plus chemotherapy may result in little to no difference in LSM change from baseline in the Jaundice score compared to placebo plus chemotherapy.
EORTC QLQ-BIL21 (pain score)							
LS Mean change from baseline (0 [no or low symptom burden] to 100 [severe symptoms]), points (95% CI) Follow-up: 18 weeks	972 (1 RCT)	NA	−4.07	−5.94 (−7.83 to −4.05)	−1.87 (−4.26 to 0.53)	Low[j]	Pembrolizumab plus chemotherapy may result in little to no difference in LSM change from baseline in the Pain score compared to placebo plus chemotherapy.

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Placebo plus chemotherapy	Pembrolizumab plus chemotherapy	Difference		
Harms (safety analysis set)							
Any AEs							
Proportion of patients with any AEs Median follow-up: 25.6 months as of DCO on December 15, 2022	1,063 (1 RCT)	NR	[redacted]	[redacted]	[redacted]	High[k]	Pembrolizumab plus chemotherapy results in little to no difference in the proportion of patients who experience any AEs compared to placebo plus chemotherapy.
Any SAEs							
Proportion of patients with any SAEs Median follow-up: 25.6 months as of DCO on December 15, 2022	1,063 (1 RCT)	NR	[redacted]	[redacted]	[redacted]	Moderate[l]	Pembrolizumab plus chemotherapy likely results in little to no clinically important difference in the proportion of patients who experience SAEs compared to placebo plus chemotherapy.
Any AEs leading to treatment discontinuation							
Proportion of patients with any AEs leading to treatment discontinuation Median follow-up: 25.6 months as of DCO on December 15, 2022	1,063 (1 RCT)	NR	[redacted]	[redacted]	[redacted]	Moderate[m]	Pembrolizumab plus chemotherapy likely results in little to no clinically important difference in the proportion of patients who experience any AEs leading to treatment discontinuation compared to placebo plus chemotherapy.

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Placebo plus chemotherapy	Pembrolizumab plus chemotherapy	Difference		
Immune-mediated enterocolitis							
Proportion of patients with immune-mediated enterocolitis Median follow-up: 25.6 months as of DCO on December 15, 2022	1,063 (1 RCT)	NR	[redacted]	[redacted]	[redacted]	Moderate[n]	Pembrolizumab plus chemotherapy likely results in little to no clinically important difference in the number of patients who experience immune-mediated enterocolitis compared to placebo plus chemotherapy.
Immune-mediated hepatitis							
Proportion of patients with immune-mediated hepatitis Median follow-up: 25.6 months as of DCO on December 15, 2022	1,063 (1 RCT)	NR	[redacted]	[redacted]	[redacted]	Moderate[o]	Pembrolizumab plus chemotherapy likely results in little to no clinically important difference in the number of patients who experience immune-mediated hepatitis compared to placebo plus chemotherapy.
Immune-mediated lung disease							
Proportion of patients with immune-mediated lung disease Median follow-up: 25.6 months as of DCO on December 15, 2022	1,063 (1 RCT)	NR	[redacted]	[redacted]	[redacted]	Moderate[p]	Pembrolizumab plus chemotherapy likely results in little to no clinically important difference in the number of patients who experience immune-mediated lung disease compared to placebo plus chemotherapy.

AE = adverse event; BTC = biliary tract carcinoma; CI = confidence interval; DCO = data cut-off; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EORTC QLQ-BIL21 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-BIL21; FA = final analysis; HRQoL = health-related quality of life; IA1 = first interim analysis; ITT = intention to treat; LS = least square; NA = not applicable; NR = not reported; OS = overall survival; PFS = progression-free survival; PRO = patient-reported outcome; RCT = randomized controlled trial; RR = relative risk; SAE = serious adverse event.

Note: Study limitations (which refer to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias were considered when assessing the certainty of the evidence. All serious concerns in these domains that led to the rating down of the level of certainty are documented in the table footnotes.

[a]Rated down 1 level for serious imprecision. The clinical experts consulted by CADTH considered a 5% between-group difference clinically important. The 95% CI includes the potential for a trivial effect. The between-group differences were requested from the sponsor to aid interpretation and were not part of the sponsor's analysis plan.

[b]Rated down 1 level for serious imprecision. The clinical experts consulted by CADTH considered a 5% between-group difference clinically important. The 95% CI includes the potential for a trivial effect. The between-group differences were requested from the sponsor to aid interpretation and were not part of the sponsor's analysis plan.

[c]Rated down 1 level for serious imprecision. The clinical experts consulted by CADTH considered a 5% between-group difference clinically important. The 95% CI includes the potential for a trivial effect. The between-group differences were requested from the sponsor to aid interpretation and were not part of the sponsor's analysis plan.

[d]Rated down 1 level for serious indirectness. Per the sponsor, RECIST 1.1 is not the best measure of PFS in this patient population. Rated down 1 level for serious imprecision. There is no known MID, so the null was used for the threshold. The 95% CI included the possibility of no difference. Between-group differences were requested from the sponsor to aid interpretation and were not part of the sponsor's analysis plan.

[e]Rated down 1 level for serious indirectness. Per the sponsor, RECIST 1.1 is not the best measure of PFS in this patient population. Rated down 2 levels for very serious imprecision. There is no known MID, so the null was used for the threshold. The 95% CI included the possibility of no difference and harm. Between-group differences were requested from the sponsor to aid interpretation and were not part of the sponsor's analysis plan.

[f-h] Rated down 2 levels for very serious study limitations due to risk of bias due to missing outcomes data (data were available for 635 patients at week 18). The between-group MID of EORTC QLQ-C30 subscales ranges from 5 to 10 points for most scales. Statistical testing for this outcome was not adjusted for multiplicity in the study and should be considered supportive evidence.

[i-j] Rated down 2 levels for very serious study limitations due to risk of bias due to missing outcomes data (data were available for 635 patients at week 18). There is no known MID; however, it was judged that the entire 95% CI likely included trivial effects. Statistical testing for this outcome was not adjusted for multiplicity in the study and should be considered supportive evidence.

[k]Evidence was not rated down.

[l-m] Rated down 1 level for serious imprecision. There is no established MID. The point estimate suggests little to no difference, and the 95% CI included the possibility of important harm. Between-group differences were requested from the sponsor to aid interpretation and were not part of the sponsor's analysis plan.

[n-p] Rated down 1 level for serious imprecision. There is no established MID; however, since the baseline risk for these immune-mediated AEs was very low in the KEYNOTE-966 study, rating down for imprecision for the certainty of evidence can be more conservative.

Sources: Clinical Study Report for KEYNOTE-966 and additional information provided by the sponsor. Details included in the table are from the sponsor's Summary of Clinical Evidence.

Economic Evidence

Cost and Cost-Effectiveness

Table 4: Summary of Economic Information

Component	Description
Type of economic evaluation	CMA
Target population	Patients with locally advanced unresectable or metastatic BTC who would be eligible to receive immunotherapy as a first-line treatment in combination with chemotherapy
Treatment	Pembrolizumab plus chemotherapy (gemcitabine and cisplatin)
Dose regimen	Pembrolizumab: 200 mg every 3 weeks, or 400 mg every 6 weeks, up to 24 months (35 cycles for q.3.w. or 18 cycles for q.6.w.) or until disease progression or unacceptable toxicity. Gemcitabine: 1,000 mg/m^2 days 1 and 8 of a 21-day cycle until disease progression or unacceptable toxicity. Cisplatin: 25 mg/m^2 days 1 and 8 of a 21-day cycle for up to 8 cycles.
Submitted price	Pembrolizumab: $4,400.00 per 100 mg/4 mL vial for IV infusion
Submitted treatment cost	Pembrolizumab plus chemotherapy (as regimen) $9,034.30 for the first 8 21-day cycles and $9,018.70 every 21 days after[a]
Comparator	Durvalumab plus chemotherapy (gemcitabine and cisplatin)
Perspective	Canadian publicly funded health care payer
Time horizon	Lifetime (20 years)
Key data source	Key assumption of equal treatment efficacy and safety of pembrolizumab plus chemotherapy and durvalumab plus chemotherapy based on unpublished NMA conducted by the sponsor
Costs considered	Drug acquisition and treatment administration costs

Key limitations	• The assumption of comparable clinical efficacy and safety between pembrolizumab and durvalumab is uncertain. There was insufficient evidence to determine if the 2 regimens were different in terms of OS, PFS, or AEs, and no data were available to assess HRQoL.
	• Chemotherapy alone was inappropriately excluded as a relevant treatment comparator as it is still used in clinical practice for the indicated population. As such, the cost-effectiveness of pembrolizumab plus chemotherapy relative to chemotherapy alone is unknown. At the time of the review, durvalumab had received a list recommendation from CADTH, was undergoing negotiation at the pCPA and was not listed by participating drug plans.
	• Treatment costs are uncertain, mainly owing to the sponsor's extrapolations of OS and PFS (affecting durvalumab plus chemotherapy) and the assumption that pembrolizumab would be administered with fixed dosing:
	  ◦ The sponsor's extrapolations of OS and PFS resulted in a higher proportion of patients remaining on treatment with durvalumab plus chemotherapy relative to pembrolizumab plus chemotherapy. Given the underlying assumption of similar efficacy and safety to justify a CMA, the ToT between the 2 treatment regimens should be similar. Based on clinical experts consulted for the review, there is no reason for treatment compliance, dose delays, dose reductions to manage toxicity, or dose re-escalations to differ between the 2 regimens based on the available evidence.
	  ◦ Input from participating public drug plans indicated that jurisdictions would likely implement weight-based dosing.

Component	Description
CADTH reanalysis results	• CADTH conducted a reanalysis correcting the price of cisplatin, assuming weight-based dosing of pembrolizumab, assuming gemcitabine was administered up to a maximum of 8 cycles when used in combination with pembrolizumab or durvalumab, using a Gompertz distribution to extrapolate OS, using a Gamma distribution to extrapolate PFS, assuming 0% wastage of unused product (i.e., perfect vial sharing), and setting RDI to 100% for all treatments. • The CADTH base case suggests that pembrolizumab plus chemotherapy is associated with cost savings of $58,930 over a lifetime horizon (20 years) when compared with durvalumab plus chemotherapy, driven by the assumption that pembrolizumab would be administered with weight-based dosing. The cost-effectiveness of pembrolizumab plus chemotherapy relative to chemotherapy alone is unknown. • As the price negotiations for durvalumab were still ongoing at the time of the submission, CADTH conducted threshold analyses to determine the price of durvalumab at which pembrolizumab would no longer be considered cost-saving (i.e., cost-neutral). Assuming weight-based dosing of pembrolizumab, if the price reduction of durvalumab is greater than 42%, pembrolizumab would no longer be cost-saving. Assuming pembrolizumab is administered with fixed dosing, if the price reduction of durvalumab is greater than 18%, pembrolizumab would no longer lead to cost savings.

CMA = cost-minimization analysis; BTC = biliary tract carcinoma; ITC = indirect treatment comparison; NMA = network meta-analysis; OS = overall survival; PFS = progression-free survival; q.3.w = every 3 weeks; q.6.w = every 6 weeks; RDI = relative dose intensity; ToT = time on treatment.

[a]Cycle costs consider relative dose intensities, vial sharing, 5% vial wastage, and assuming a body surface area of 1.8 m^2.

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis: relevant comparators were omitted, treatment costs are uncertain, allocating market share to clinical trials is not appropriate, the market uptake of pembrolizumab plus chemotherapy is uncertain, the budget impact of patients diagnosed in years 1 to 3 is not fully captured, and poor modelling practices were employed.

CADTH reanalyses assumed pembrolizumab is administered with weight-based dosing, assumed gemcitabine is administered up to a maximum of 8 cycles when used in combination with pembrolizumab or durvalumab, aligned ToT for the durvalumab plus chemotherapy regimen with CADTH's revisions made to the cost-minimization analysis, assumed no vial wastage, set RDI to 100% for all treatments, and set the clinical trial market share to 0%.

The CADTH base case reflects an assumption of future practice (i.e., if durvalumab is reimbursed and becomes the standard of care for most patients). Under this assumption, the budget impact of reimbursing pembrolizumab for use by adult patients with locally advanced unresectable or metastatic BTC, in combination with gemcitabine and cisplatin, is expected to result in cost savings of $1,797,999 in year 1, $7,680,385 in year 2, and $10,831,246 in year 3, for a 3-year total of $20,309,629. CADTH conducted an exploratory analysis to determine the budget impact of reimbursing pembrolizumab based on currently available comparators (i.e., chemotherapy alone). Based on current practices, pembrolizumab is expected to result in an added cost of approximately $95,024,704 over 3-years. Should the uptake of pembrolizumab, the availability or the price of durvalumab paid by participating plans differ from the CADTH base case, the 3-year budget impact could range between a cost savings of $20,309,629 and an added cost of $95,024,704.

The estimated budget impact is highly sensitive to the price, availability, and uptake of durvalumab. If durvalumab negotiations were concluded with price reductions above 43%, pembrolizumab would no longer be cost-saving.

pERC Information

Members of the Committee

Dr. Maureen Trudeau (Chair), Mr. Daryl Bell, Dr. Philip Blanchette, Dr. Kelvin Chan, Dr. Matthew Cheung, Dr. Michael Crump, Dr. Jennifer Fishman, Mr. Terry Hawrysh, Dr. Yoo-Joung Ko, Dr. Christian Kollmannsberger, Dr. Catherine Moltzan, Ms. Amy Peasgood, Dr. Anca Prica, Dr. Adam Raymakers, Dr. Patricia Tang, Dr. Marianne Taylor, and Dr. W. Dominika Wranik.

Meeting date: May 8, 2024

Regrets: One expert committee member did not attend.

Conflicts of interest: One expert committee member did not participate due to conflict of interest considerations.

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