Canadian Journal of Health Technologies

CADTH

February 2023 Volume 3 Issue 2

CADTH Reimbursement Recommendation

Durvalumab (Imfinzi)

Indication: In combination with gemcitabine-based chemotherapy, for the treatment of patients with locally advanced or metastatic biliary tract cancer

Sponsor: AstraZeneca Canada Inc.

Final recommendation: Reimburse with conditions

CADTH

ISSN: 2563-6596

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Summary

CADTH

What Is the CADTH Reimbursement Recommendation for Imfinzi?

CADTH recommends that Imfinzi should be reimbursed by public drug plans for the treatment of locally advanced or metastatic biliary tract cancer (BTC) if certain conditions are met.

Which Patients Are Eligible for Coverage?

Imfinzi in combination with gemcitabine plus platinum-based chemotherapy should only be covered to treat patients with locally advanced or metastatic BTC who have not received prior treatment. Patients receiving Imfinzi should be in relatively good health (i.e., have a good performance status, as determined by a specialist).

What Are the Conditions for Reimbursement?

Imfinzi should only be reimbursed when it is used in combination with gemcitabine and platinum-based chemotherapy, if prescribed by specialists with experience in managing BTC, and if the cost of Imfinzi is reduced. Imfinzi should not be reimbursed if it is used to treat patients with Ampulla of Vater (AoV) cancer.

Why Did CADTH Make This Recommendation?

- Evidence from a clinical trial demonstrated that treatment with Imfinzi plus gemcitabine and cisplatin live longer than patients treated with gemcitabine and cisplatin alone.
- Imfinzi meets some of the needs identified by patients. It is another treatment option that delays disease progression and has manageable side effects.
- Based on CADTH's assessment of the health economic evidence, Imfinzi does not represent good value to the health care system at the public list price. A price reduction is therefore required.
- Based on public list prices, Imfinzi is estimated to cost the public drug plans approximately $1.36 million over the next 3 years.

Additional Information

What Is BTC?

BTCs are rare cancers that occur in the bile duct system which includes the bile ducts within the liver and outside of the liver, as well as in the gallbladder. There are approximately 400 new BTC cases diagnosed in Canada each year, though this has increased over the past 20 years.

Unmet Needs in BTC

Treatment for locally advanced or metastatic BTC has not changed in the past 10 years, and there has been no improvement in treatment outcomes. There is a need for new, life-extending treatments that improve quality of life.

How Much Does Imfinzi Cost?

Treatment with Imfinzi is expected to cost approximately $11,733 for per cycle.

Recommendation

The CADTH pCODR Expert Review Committee (pERC) recommends that durvalumab be reimbursed in combination with gemcitabine plus platinum-based chemotherapy for the first-line treatment of patients with locally advanced (not amenable to surgery) 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 (TOPAZ-1) consisting of previously untreated adult patients with locally advanced or metastatic BTC demonstrated that treatment with durvalumab plus gemcitabine and cisplatin resulted in a statistically significant overall survival (OS) advantage compared to placebo plus gemcitabine and cisplatin (median OS, 12.9 months [95% CI, 11.6 to 14.1 months] versus 11.3 months [95% CI, 10.1 to 12.5 months]; HR, 0.76 [95% CI, 0.64 to 0. 91]). Additional analyses of OS at landmark 12- (54.3% versus 47.1%), 18- (34.8% versus 24.1%), and 24-months (23.6% versus 11.5%) were supportive of the survival advantage demonstrated by durvalumab plus gemcitabine and cisplatin. Durvalumab was also associated with an improvement in progression-free survival ([PFS] HR, 0.75 [95% CI, 0.63 to 0.89]), and a manageable toxicity profile with no additional serious safety concerns. The results of the TOPAZ-1 trial also suggested no detriment in health-related quality of life (HRQoL).

Durvalumab in combination with gemcitabine and cisplatin addresses an important therapeutic need for locally advanced or metastatic BTC, which has a poor prognosis. There have been no advances in treatment and therefore, minimal to no improvement in outcomes in the last decade. Patients and clinicians highlighted the need for treatments that prolong life, maintain quality of life (QoL), and reduce side effects compared to current treatments. Given the totality of the evidence, pERC concluded that durvalumab added to gemcitabine and cisplatin meets some of the needs identified by patients, including improvements in survival, and a similar toxicity profile to currently available treatments.

Using the sponsor submitted price for durvalumab plus gemcitabine and cisplatin and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for durvalumab plus gemcitabine and cisplatin was $665,692 per quality-adjusted life-year (QALY) gained compared with gemcitabine and cisplatin. Durvalumab plus gemcitabine and cisplatin is not cost-effective at a willingness-to-pay (WTP) threshold of $50,000 per QALY gained for adult patients receiving first-line treatment for locally advanced or metastatic BTC. A price reduction is required for durvalumab when used in combination with gemcitabine and cisplatin to be considered cost-effective at this threshold.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Treatment with durvalumab plus gemcitabine and platinum-based	Evidence from the TOPAZ-1 trial demonstrated that treatment with durvalumab plus gemcitabine	An attempt to histologically confirm diagnosis of BTC should

Reimbursement condition	Reason	Implementation guidance
chemotherapy should only be initiated in adult patients with: 1.1. Locally advanced (not amenable to surgery) or metastatic BTC, including intrahepatic, extrahepatic, and gallbladder cancer 1.2. First-line unresectable or metastatic disease at initial diagnosis, or greater than 6-months after the completion of adjuvant therapy or curative surgery. 1.3. Have good performance status.	and cisplatin resulted in statistically significant improvement of OS compared with gemcitabine and cisplatin alone in patients with previously untreated locally advanced or metastatic BTC. The TOPAZ-1 trial included patients with an ECOG performance status of 0 or 1.	be made. It would be reasonable for jurisdictions to consider reimbursement of durvalumab plus gemcitabine and platinum-based chemotherapy for patients who are currently receiving first-line chemotherapy with no evidence of disease progression; durvalumab may be initiated in these patients on a time-limited basis. pERC acknowledged that clinicians think it is reasonable to use durvalumab for patients with good ECOG performance status.
2. Treatment with durvalumab plus gemcitabine and platinum-based chemotherapy should not be used in patients with AoV cancer.	Patients with AoV cancer were excluded from the TOPAZ-1 trial. The CADTH review did not identify any evidence to demonstrate the safety and potential benefits in patients with ampullary carcinoma.	—
Discontinuation		
3. Treatment with durvalumab plus gemcitabine and platinum-based chemotherapy should be discontinued upon the occurrence of any of the following: 3.1. Objective disease progression 3.2. Unacceptable toxicity	In the TOPAZ-1 study, treatment with durvalumab was discontinued if a patient experienced disease progression, or intolerable or serious adverse events, which is aligned with clinical practice. However, in TOPAZ-1, treatment with durvalumab could be continued beyond disease progression at the discretion of the investigator if there was continued clinical benefit. The clinical experts noted that that it is unlikely that clinical benefit would be observed in the presence of progression based on the observed OS benefit.	—
4. Patients should be initially assessed clinically every 3 to 4 weeks, with imaging based on local standards.	Treatment response was evaluated q.6.w. (for the first 24 weeks) and q.8.w. (thereafter) in the TOPAZ-1 trial. Based on clinician input, patients would be assessed for changes in symptoms or functional status q.3.w., and for response to treatment every 9 to 12 weeks via cross sectional imaging.	—
Prescribing		
5. Durvalumab plus gemcitabine and platinum-based chemotherapy should be prescribed by a clinician with expertise in the management of BTC.	To ensure that durvalumab in combination with gemcitabine and cisplatin is prescribed only for appropriate patients, and that adverse effects are managed appropriately.	—

Reimbursement condition	Reason	Implementation guidance
Pricing		
6. A reduction in price	The ICER for durvalumab plus gemcitabine and cisplatin is $665,692 per QALY gained when compared with gemcitabine and cisplatin. A 93% reduction in the price of durvalumab would be required for durvalumab plus gemcitabine and cisplatin to be able to achieve an ICER of $50,000 per QALY gained compared to gemcitabine and cisplatin.	—
Feasibility of adoption		
7. The feasibility of adoption of durvalumab plus gemcitabine and platinum-based chemotherapy must be addressed	At the submitted price, the budget impact of durvalumab plus gemcitabine and cisplatin is expected to be greater than $40 million in years 1, 2, and 3.	—

AoV = ampulla of Vater; BTC = biliary tract cancer; ICER = incremental cost-effectiveness ratio; ECOG = Eastern Cooperative Oncology Group; OS = overall survival; pERC = pCODR Expert Review Committee; PS = performance status; q.3.w = every 3 weeks; q.4.w. = every 4 weeks; q.6.w. = every 6 weeks; q.8.w = every 8 weeks; QALY = quality-adjusted life-year.

Discussion Points

- pERC deliberated on durvalumab plus gemcitabine and cisplatin considering the criteria for significant unmet need 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 lack of promising emergent treatments in the last decade and limited effective treatment options available. The available evidence demonstrated that durvalumab plus gemcitabine and cisplatin led to a statistically significant improvement in median OS compared to gemcitabine and cisplatin. The committee considered the survival differences at the landmark OS analyses at 12-months (54.3% versus 47.1%), 18-months (34.8% versus 24.1%), and 24-months (23.6% versus 11.5%) to be suggestive of clinically meaningful improvements in OS over the follow-up of the TOPAZ-1 trial.
- pERC discussed the current treatment options for patients in this setting and acknowledged that the standard of care for locally advanced or metastatic BTC since 2010 has been gemcitabine and cisplatin, with no standard second-line treatment options. pERC noted that the majority of BTC patients do not reach second-line treatment as the disease rapidly progresses, and that second-line treatment with 5FU and oxaliplatin provides a modest survival benefit.
- Although the available evidence from the TOPAZ-1 trial is for the first-line setting (i.e., patients who are treatment naive in the metastatic setting), pERC discussed that it would be reasonable to fund the addition of durvalumab to patients already on first-line therapy with gemcitabine and platinum-based chemotherapy on a time-limited basis, as long as there has been no evidence of disease progression.
- pERC noted that the safety profile of durvalumab plus gemcitabine and cisplatin was similar to that of gemcitabine and cisplatin in the TOPAZ-1 trial, with no additional serious safety concerns and that adverse effects are anticipated to be clinically manageable.

- pERC noted an apparent mismatch between the Health Canada indicated population and the population reflected in the pharmacoeconomic analysis. The Health Canada product monograph for durvalumab does not specify the line in which it must be used; however, the available evidence from the TOPAZ-1 trial is only available for first-line use. Consequently, the comparative clinical efficacy, and therefore cost-effectiveness, of durvalumab in subsequent lines is unknown. Input received by clinical experts suggested that it was highly unlikely that durvalumab would be used in subsequent lines, as no effective alternative treatments are currently available, and rather durvalumab plus gemcitabine and cisplatin is expected to shift the current treatment paradigm.
- pERC discussed the statistical significance of the results and noted that despite the amendment in the testing method for the primary end point at the final analysis, the prespecified alpha was met, and therefore, the results were considered statistically significant.
- According to the product monograph, for individuals with weight of 30 kg or less, the recommended dosing is 20 mg/kg q.3.w. for 8 cycles, followed by monotherapy at 20 mg/kg every 4 weeks until weight increases to greater than 30 kg. In TOPAZ-1, patients received durvalumab at a flat dose of 1,500 mg q.3.w. in combination with gemcitabine and cisplatin for up to 8 cycles, followed by 1,500 mg every 4 weeks as a single drug until disease progression or unacceptable toxicity. The estimated price reduction and budget impact were calculated using a dose of 1,500 mg (assumed mean body surface area of 1.8 m^2 and mass of 75 kg).

Background

BTC refers to a heterogeneous group of gastrointestinal adenocarcinomas in the liver, gallbladder, and bile ducts. There are 4 subtypes of BTC including intrahepatic cholangiocarcinoma (IHCC), extrahepatic cholangiocarcinoma (EHCC), gallbladder cancer (GBC), and AoV cancer. While BTCs comprise less than 1% of all cancers, they account for 10% to 15% of primary liver cancers, which are the12th and 18th most common cancer in males and females in Canada, respectively (2021). The most common subtype of BTC is GBC. Intrahepatic cholangiocarcinoma occurs in approximately 10% to 20% of BTC cases, while EHCC occurs in 30% to 40% of BTC cases. The incidence of BTCs varies globally, depending on various risk factors, with an incidence of cholangiocarcinoma and GBC in Europe, US, and Australasia of 0.3 to 3.5 per 100,000 and 1.6 to 2.0 per 100,000, respectively, though incidence rates are said to be increasing. While there are few Canadian estimates for BTC, 1 study estimated the average national incidence rate of GBC and extrahepatic BTCs in Canada at 30.92 cases per 1,000,000 individuals per year (approximately 3 per 100,000), which was observed to be increasing between 1994 and 2012. In Canada and the US, there are approximately 400 and 5,000 new cases of cholangiocarcinoma diagnosed each year, respectively. Though these estimates are nearly 20 years old and may not be reflective of current incidence rates. Prognosis for patients with BTCs is poor, with estimated US 5-year survival rates for EHCC of 30%, 24%, and 2%, and IHCC of 15%, 6%, and 2% for local, regional, and distant metastatic disease. Survival rates for GBC are similar, with 5-year survival of 8% and 7% for stages IIIA and IIIB, and 4% and 2% for stages IVA and IVB.

Symptoms of BTCs are often nonspecific and include nausea, emesis, anorexia, weight loss, abdominal pain, and jaundice. As such, up to 90% of BTC cases are inoperable at the time of diagnosis, and the majority of patients present with locally advanced or metastatic BTC.

Symptoms often reflect the location of the cancer, with IHCC patients often presenting with nonspecific symptoms including fever, weight loss and/or abdominal pain, while patients with EHCC present with jaundice due to biliary obstruction.

For patients with locally advanced or metastatic BTC, platinum-based chemotherapy, most commonly the combination of gemcitabine (1,000 mg/m^2) plus cisplatin (25 mg/m^2), has remained the preferred first-line standard of care (SOC) regimen for patients with advanced BTC for over 10 years. There is currently no standard second-line treatment option for patients with locally advanced or metastatic BTC who experience disease progression following first-line treatment. Palliative treatment options include 5-fluorouracil (5-FU) or capecitabine monotherapy, 5-FU, leucovorin and irinotecan (FOLFIRI), or 5-FU, folinic acid (leucovorin) and oxaliplatin (FOLFOX). Pemigatinib also has Health Canada market authorization with conditions for the treatment of adults with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or other rearrangement, though it recently received a do not reimburse CADTH recommendation and is not funded in Canada.

Durvalumab has been approved by Health Canada in combination with gemcitabine-based chemotherapy, for the treatment of patients with locally advanced or metastatic BTC. Durvalumab is a fully humanized immunoglobulin G1 kappa monoclonal antibody that selectively blocks the interaction of programmed cell death-ligand 1 with programmed cell death protein 1 and CD80. It is available as 50 mg/mL concentrate for solution for infusion and the dosage recommended in the product monograph is 1,500 mg in combination with gemcitabine-based chemotherapy every 3 weeks, followed by 1,500 mg every 4 weeks as monotherapy until disease progression or unacceptable toxicity. Durvalumab is also indicated for the treatment of locally advanced, unresectable, stage III non–small cell lung cancer, and extensive stage small cell lung cancer. In addition, durvalumab has received marketing authorization with conditions for the treatment of locally advanced or metastatic urothelial carcinoma, pending the results of clinical trials. Durvalumab has been previously reviewed by CADTH for the treatment of patients with locally advanced, unresectable non–small cell lung cancer following curative intent, platinum-based chemoradiation therapy, for up to a maximum of 12 months, as well as for first-line treatment of adult patients with ES-SCLC, in combination with etoposide and either carboplatin or cisplatin.

Sources of Information Used by the Committee

To make their recommendation, pERC considered the following information:

- a review of 1 phase III RCT in patients with previously untreated, unresectable, locally advanced, or metastatic BTC
- patients' perspectives gathered by patient groups, the Canadian Cancer Survivor Network with participation from the Canadian Liver Foundation, Canadian Organization for Rare Disorders, Cholangiocarcinoma Foundation, Colorectal Cancer Resource and Action Network, Gastrointestinal Society, and Regroupement québécois des maladies orphelines.
- input from public drug plans and cancer agencies that participate in the CADTH review process

- 2 clinical specialists with expertise diagnosing and treating patients with locally advanced or metastatic BTC
- input from 2 clinician groups, including the Canadian Gastrointestinal Oncology Evidence Network, and the Ontario Health Cancer Care Ontario Gastrointestinal Cancer Drug Advisory Committee
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

Patient Input

Patient group input for the review of durvalumab was provided as a joint submission by the Canadian Cancer Survivor Network (CCSN) with participation from the Canadian Liver Foundation, Canadian Organization for Rare Disorders, Cholangiocarcinoma Foundation, Colorectal Cancer Resource and Action Network (CCRAN), Gastrointestinal Society, and Regroupement québécois des maladies orphelines. The CCSN is a national network of patients, families, survivors, friends, community partners, funders, and sponsors who have come together to promote the best SOC for patients with cancer.

The CCSN and participating patient groups conducted an online survey between July 18 and August 2, 2022 to collect quantitative data on durvalumab. A total of 58 individuals who responded to the survey; of which 12 had experience with durvalumab, 25 did not have experience with durvalumab, and 17 identified as a caregiver. Of the 58 survey respondents, 21 were living in Canada, 35 were living in the US, and 1 each were living in the UK and Spain. Additionally, the CCRAN conducted 7 interviews between July 7 and July 22, 2022 in 4 patients and 3 caregivers in Canada and the US who have experience with durvalumab.

In the CCSN survey, 29 respondents disclosed their disease stage, including 18 late-stage or metastatic, 4 middle-stage, 3 early stage, and 4 unknowns. Respondents to the CCSN survey reported abdominal pain, loss of appetite and weight loss, nausea and vomiting, itching, dark urine, fever, jaundice, and light coloured, greasy stools as symptoms impacting their QoL and day-to-day life due to BTC. Caregivers indicated that caring for their loved one with BTC has impacted their lifestyle, including feeling emotionally drained, experiencing challenges in managing medications and medical appointments, and being unable to plan ahead. The most used treatments reported by the CCSN survey respondents included gemcitabine plus cisplatin, immunotherapy, radiation, surgical therapy, targeted therapy, and FOLFOX. Most CCSN respondents reported tiredness, difficulty sleeping, hair loss, nausea and vomiting, muscle weakness, numbness and tingling of the arms and legs, and diarrhea as adverse effects associated with treatment. Although most respondents indicated no issues with accessing treatments, travel costs, limited availability in the community, and financial hardship due to cost were noted as challenges.

Most respondents with durvalumab experience in the CCSN survey indicated durvalumab had little to no difference in symptom management, side effects, ease of use, or in disease progression in comparison to other therapies received for BTC. Respondents reported fatigue, constipation, white blood cell count and platelet count decreases, anemia, and others as side effects of durvalumab. In the CCRAN interviews, 4 patients and 3 caregivers described their experience with durvalumab for BTC. Patients accessed durvalumab via compassionate

access, clinical trials, private insurance coverage, and via out-of-pocket expenses. Most CCRAN interviewees reported little to no side effects associated with durvalumab and that their cancer had regressed with treatment. Further, CCRAN respondents indicated that durvalumab was easier to use with a shorter duration of infusion compared to other treatment options. There was a consensus among patients that durvalumab should be made available to eligible patients.

Aside from providing access to a new treatment option, respondents to surveys reported that new treatments should maintain QoL, prolong life, provide a cure, reduce side effects from current treatment, delay the onset of symptoms, and be easy to use. When asked to describe how much of an improvement would be needed from a new treatment to make it better than current treatments, the consensus was that prolonged life with similar or reduced side effects to current treatments was most important, while QoL and ease of access remain as normal as possible.

Clinician Input

Input From Clinical Experts Consulted by CADTH

First-line therapy for advanced BTC has remained gemcitabine and cisplatin since the results of the ABC-02 study in 2010; however, the median OS is less than 12 months, thus the experts considered prolonged survival an important unmet need for patients with locally advanced or metastatic BTC. The clinical experts highlighted that surgery is currently the only curative treatment for BTC; however, the disease is often detected in advanced stages and is usually inoperable at diagnosis. Aside from the current SOC of gemcitabine and cisplatin, patients with relatively poor performance status, often receive single drug gemcitabine. The experts noted that patients commonly progress following first-line treatment, and there is currently no standard second-line treatment available. There are no predictive biomarkers for locally advanced or metastatic BTC. Therefore, according to the clinical experts, patients most suitable for gemcitabine and cisplatin are those with preserved organ function and good performance status, regardless of the presence of cancer-related symptoms. Conversely, patients least suitable for durvalumab plus gemcitabine and cisplatin are those with a contraindication to immunotherapy. The experts also felt that it would not be appropriate to recommend other treatments before initiating treatment with durvalumab.

The experts noted that, in clinical practice, patients would be assessed every 3 weeks, during routine follow-up for changes in symptoms such as fatigue and pain, and clinical and functional status, and response to treatment would be assessed every 9 to 12 weeks via imaging. The experts also noted that tumour marker assessments of c antigen (CA) 19-9 are often evaluated and followed for those with adequate biliary decompression and elevated CA 19-9 levels. Per the experts, durvalumab would be discontinued at clinical or radiologic progression, or confirmed by worsening symptoms, or unacceptable immune-related toxicity. The clinical experts stated that durvalumab should only be prescribed by medical oncologists and administered by qualified nurses under the supervision of a medical oncologist in a systemic treatment unit.

Clinician Group Input

Two clinician groups provided input for the review of durvalumab: the Canadian Gastrointestinal Oncology Evidence Network (CGOEN), represented by 7 clinicians, and the Ontario Health Cancer Care Ontario (OH-CCO) Gastrointestinal Cancer Drug Advisory Committee (DAC), represented by 5 clinicians. The CGOEN is a virtual network of Canadian

gastrointestinal oncology clinicians who contribute to the knowledge of gastrointestinal cancer and its treatments. The OH-CCO DAC provides evidence-based clinical and health system guidance on drug-related issues.

Both clinician groups noted that current treatment goals for patients with unresectable, metastatic BTC include extending patients' lives, delaying disease progression, and maintaining QoL. The CGEON indicated that cisplatin plus gemcitabine is the only currently available treatment option for patients with unresectable BTC, though the OH-CCO DAC also indicated that carboplatin and gemcitabine may be used in first line. Clinical experts from CGEON noted that the majority of BTC patients do not reach second-line treatment as the disease rapidly progresses, and that second-line treatment with 5FU and Oxaliplatin provides a modest survival benefit and is poorly tolerated. Experts highlighted that none of the molecularly targeted drugs for BTC are funded in Canada. Thus, both clinician groups emphasized that the limited number of treatment options, and the moderate survival benefit provided by gemcitabine and cisplatin treatment demonstrates a significant unmet need for more effective treatments in this setting.

Given the lack of available options, both clinician groups indicated that there was no rationale that patients try other treatments before initiating durvalumab plus gemcitabine and cisplatin, and that the addition of durvalumab to the current SOC would not affect the sequencing of subsequent therapy. The CGEON and OH-CCO DAC inputs indicated that all patients with unresectable BTC who align with the clinical trial criteria would be most suited for treatment with durvalumab. Patients least suitable for treatment were identified as those with contraindications to immunotherapy, inadequate liver or renal function, or Eastern Cooperative Oncology Group (ECOG) performance status of 3 or more. The CGEON and OH-CCO DAC both indicated that in clinical practice, clinical condition and/or radiologic progression are used to determine response to treatment. The CGEON indicated that a clinically meaningful response to treatment would be maintenance or improvement in QoL and prolongation of survival, while disease progression or intolerance would be factors for discontinuing treatment. The groups agreed that durvalumab would be administered in any setting where standard chemotherapy is delivered, under the supervision of a specialist. The OH-CCO DAC agreed with the weight-based dosing method with a cap since it is consistent with other disease site regimens and noted that flat-dosing results in overtreatment.

Drug Program Input

Input was obtained from the drug programs that participate in the CADTH reimbursement review process. The following were identified as key factors that could potentially impact the implementation of a CADTH recommendation for durvalumab:

- considerations for relevant comparators
- considerations for initiation of therapy
- considerations for continuation or renewal of therapy
- considerations for discontinuation of therapy
- considerations for prescribing of therapy
- generalizability of trial populations to the broader populations in the jurisdictions
- system and economic issues
- potential need for a provisional funding algorithm.

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

Drug program implementation questions	Response
Relevant comparators	
The comparator arm of the TOPAZ-1 trial was gemcitabine plus cisplatin. This is a funded therapy and is considered standard of care for the first-line treatment of patients with locally advanced or metastatic BTC. If there are concerns about a patient's renal function, carboplatin or oxaliplatin may be substituted for cisplatin. For patients with a poor performance status, gemcitabine monotherapy may be used as first-line treatment. If a patient is not able to tolerate cisplatin-based chemotherapy, is it reasonable to combine durvalumab with alternate chemotherapy?	In considering the current available evidence, Health Canada indication and clinical expert opinion, pERC concluded that reimbursement of durvalumab should only be with gemcitabine and platinum (cisplatin, carboplatin and oxaliplatin) based therapy.
Considerations for initiation of therapy	
Is histologic diagnosis of BTC required to be eligible for durvalumab? Is a diagnosis of BTC ever made without histologic confirmation?	pERC noted that an attempt to histologically confirm diagnosis of BTC should be made. pERC acknowledged that the clinical experts noted that occasionally, 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.
Can durvalumab be restarted if treatment was stopped for reasons other than disease progression?	pERC agreed with the clinical experts that as long as durvalumab was not stopped for immune-related toxicities, then restarting durvalumab is reasonable.
Considerations for continuation or renewal of therapy	
What is the recommended type and frequency of follow-up for patients on durvalumab maintenance?	pERC stated that initial clinical assessment and imaging should be conducted based on local standards.
Considerations for discontinuation of therapy	
In the trial, treatment could be continued beyond disease progression at the discretion of the investigator if there was continued clinical benefit. What are the criteria for discontinuing durvalumab?	pERC agreed with the clinical experts that durvalumab should be discontinued when there is objective evidence of disease progression, or severe immune-related toxicity. Given the modest improvement in OS, the clinical experts stated that it is unlikely that clinical benefit would be observed in the presence of progression. The clinical experts also noted that if durvalumab was discontinued, they would also consider discontinuing treatment with gemcitabine and cisplatin (if during chemotherapy phase), unless toxicities were specific to individual treatments.
If there is progression during a drug holiday, can treatment be resumed? If retreatment with durvalumab is permitted in this scenario, would therapy consist of durvalumab monotherapy or durvalumab plus chemotherapy? Is there a minimum number of cycles of chemotherapy that	pERC agreed with the clinical experts that retreatment with durvalumab following progression during a drug holiday would be reasonable, however, would only be conducted when in combination with chemotherapy, and not given as monotherapy. It was also noted that this would only be considered in cases where patients had evidence of progression but were still well enough to receive treatment with chemotherapy.

Drug program implementation questions	Response
must be given with durvalumab (e.g., what if the patient must discontinue the chemotherapy portion after 1 cycle)?	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 of therapy	
In the trial, patients received durvalumab at a flat dose of 1,500 mg q.3.w. in combination with gemcitabine and cisplatin for up to 8 cycles, followed by 1,500 mg q.4.w. as a single drug until disease progression or unacceptable toxicity. If a patient's weight fell to ≤ 30 kg they received a weight-based dose equivalent to 20 mg/kg of durvalumab q.3.w. in combination with chemotherapy, followed by 20 mg/kg q.4.w. as a single drug. Jurisdictions use weight-based dosing for IO therapies up to a cap. Can weight-based dosing up to a cap be used in place of flat-dosing for patients weighing more than 30 kg? If weight-based dosing up to a cap can be used, what mg/kg dose(s) of durvalumab should be used when given in combination with chemotherapy q.3.w. and then as a single drug q.4.w.? Should the weight-based dosing be 15 mg/kg up to 1,500 mg q.3.w. in combination with chemotherapy, followed by 20 mg/kg up to 1,500 mg q.4.w. as a single drug, vs. 20 mg/kg q.3.w. in combination with chemotherapy and then q.4.w. as a single drug?	There is no evidence to support weight-based dosing or to inform the appropriate dose cap of durvalumab in patients with locally advanced or metastatic BTC because this was not evaluated in the TOPAZ-1 trial. The clinical experts stated that flat-based dosing is preferred from a clinical standpoint and reflects how durvalumab was administered in the clinical trial. pERC and the clinical experts also noted that very few patients weigh less than 30 kg, and it is unlikely that they may be treated with chemotherapy at this weight.
Generalizability	
Should durvalumab be considered in patients with ECOG PS 2 or greater, or in patients with AoV cancer, as these patients were excluded from the trial?	pERC and the clinical experts stated that patients with ECOG 2 or greater were not eligible for the TOPAZ-1 trial. pERC acknowledged that clinicians think it is reasonable to use durvalumab for patients with good ECOG performance status. pERC and the clinical experts noted that AoV cancers are treated differently than BTC, therefore should not be considered for treatment with durvalumab.
Should durvalumab be added to patients 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 durvalumab may be initiated in these patients. However, if patients have already completed their first-line chemotherapy regimen, durvalumab should not be added.
System and economic issues	
PAG has potential concerns regarding feasibility of adoption.	Comment from the drug programs to inform pERC deliberations.

AoV = ampulla of vater; BTC = biliary tract cancer; ECOG = Eastern Cooperative Oncology Group; IO = immuno-oncology; OS = overall survival; PAG = Provincial Advisory Group; pERC = pCODR Expert Review Committee; PS = performance status; q.3.w. = every 3 weeks; q.4.w. = every 4 weeks.

Clinical Evidence

Description of Study

TOPAZ-1 was a double-blind, placebo-controlled, international, randomized, phase III study to evaluate the efficacy and safety of adding durvalumab to the established chemotherapy regimen of gemcitabine and cisplatin in patients with previously untreated, unresectable, locally advanced, or metastatic BTC or recurrent disease. Patients were randomized 1:1 to either durvalumab 1,500 mg (n = 341) or placebo (n = 344) via IV infusion (on day 1; every 3 weeks [q.3.w.]) in combination with cisplatin 25 mg/m^2 and gemcitabine 1,000 mg/m^2 (each administered on days 1 and 8; q.3.w.), for up to 8 cycles, followed by 1,500 mg durvalumab or placebo via IV infusion every 4 weeks (q.4.w.) until clinical progression (or RECIST 1.1-defined radiological progressive disease [PD]), unacceptable toxicity, withdrawal of consent, or another discontinuation criterion. The primary end point of the TOPAZ-1 trial was OS, with secondary end points of PFS, overall response rate (ORR), duration of response (DOR), disease control rate, and HRQoL and treatment tolerability.

Baseline characteristics of the TOPAZ-1 trial were well balanced between treatment groups; however, according to the clinical experts, the trial may have enrolled a healthier group of patients with a lower ECOG performance status compared to the Canadian population. In TOPAZ-1, patients were mostly Asian (56.4%), with an even balance of males (50.4%) and females (49.6%), a median age of 64 years, and most had initially unresectable disease ([redacted]). Most patients had IHCC ([redacted]), followed by GBC ([redacted]), and EHCC ([redacted]). There were 3 planned data cutoffs (DCOs); 2 interim analyses and 1 final analysis, though the second interim analysis (IA-2) was considered the final analysis. As of the most recent DCO (February 25, 2022), the median follow-up of the TOPAZ-1 trial was [redacted] months and [redacted] months for durvalumab and placebo groups for OS.

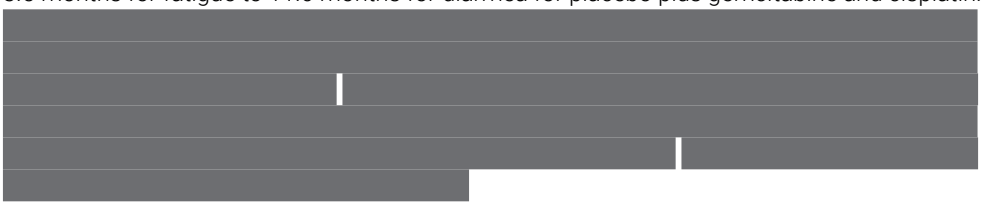
Efficacy Results

As of the final efficacy analysis of TOPAZ-1 (IA-2, DCO August 11, 2021), the median OS was 12.8 months (95% CI, 11.1 to 14.0 months) in the durvalumab plus gemcitabine and cisplatin group, and 11.5 months (95% CI, 10.1 to 12.5 months) in the placebo plus gemcitabine and cisplatin group. Durvalumab plus gemcitabine and cisplatin was associated with a prolonged OS compared to placebo plus gemcitabine and cisplatin (hazard ratio [HR], 0.80 [95% confidence interval [CI], 0.66 to 0.97]; P = 0.021). With an additional 6.5-months follow-up (DCO February 25, 2022), the median OS was 12.9 months (95% CI, 11.6 to 14.1 months) for durvalumab plus gemcitabine and cisplatin, and 11.3 months (95% CI, 10.1 to 12.5 months) for placebo plus gemcitabine and cisplatin, and durvalumab plus gemcitabine and cisplatin remained favoured over placebo plus gemcitabine and cisplatin (HR, 0.76 [95% CI, 0.64 to 0.91]). Results for OS rate were consistent at IA-2 and the 6.5-months follow-up, with landmark OS rates at 12 months, 18 months, and 24 months of 54.3% versus 47.1%, 34.8% versus 24.1%, and 23.6% versus 11.5%, respectively.

At IA-2, the key secondary end point of PFS was in line with the primary end point. Durvalumab plus gemcitabine and cisplatin was associated with a prolonged PFS compared to placebo plus gemcitabine and cisplatin (HR, 0.75 [95% CI, 0.63 to 0.89]; P = 0.001), with a median PFS of 7.2 months (95% CI, 6.7 to 7.4 months) for durvalumab plus gemcitabine and cisplatin, and 5.7 months (95% CI, 5.6 to 6.7 months) for placebo plus gemcitabine and cisplatin. Results for PFS were not available at the 6.5-months additional follow-up DCO.

ORR was a secondary end point of the TOPAZ-1 study but was a primary outcome at the first interim analysis (IA-1). [redacted]. At IA-2, the ORR was 26.7% for durvalumab plus gemcitabine and cisplatin, and 18.7% for placebo plus gemcitabine and cisplatin (OR, 1.60 [95% CI, 1.11 to 2.31], P = 0.011). The statistical test for this outcome was not adjusted for multiplicity, so there is an increased risk of type I error. Only 7 (2.1%) patients in the durvalumab plus gemcitabine and cisplatin, and 2 (0.6%) patients in the placebo plus gemcitabine and cisplatin groups achieved a complete response. No results for ORR were available at the 6.5-month update. The median DOR was 6.4 months ([redacted]) in the durvalumab plus gemcitabine and cisplatin group and 6.2 months ([redacted]) in the placebo plus gemcitabine and cisplatin group.

Secondary end points for HRQoL consisted of the time to deterioration and improvement rates for the European Organisation for Research and Treatment of Cancer (EORTC) 30-Item Cancer Quality-of-Life Questionnaire (QLQ-C30) and EORTC 21-Item Cholangiocarcinoma and Gallbladder Cancer Quality-of-Life Questionnaire (QLQ-BIL21). For global health status (GHS)/QoL, the median time to deterioration was 7.4 months (95% CI, 5.6 to 8.9 months) for durvalumab plus gemcitabine and cisplatin compared to 6.7 months (95% CI, 5.6 to 7.9 months) for placebo plus gemcitabine and cisplatin. The median time to deterioration in functional groups ranged from 5.6 months to 10.1 months with durvalumab plus gemcitabine and cisplatin and 6.5 months to 10.0 months for placebo plus gemcitabine and cisplatin. The median time to deterioration in multiple and single symptom items ranged from 3.0 months for fatigue to 18.2 months for diarrhea with durvalumab plus gemcitabine and cisplatin and 3.5 months for fatigue to 11.0 months for diarrhea for placebo plus gemcitabine and cisplatin.



The median time to symptom deterioration on the EORTC QLQ-BIL21 ranged from 3.5 months to 11.7 months for durvalumab plus gemcitabine and cisplatin, and 3.7 months to 14.2 months with placebo plus gemcitabine and cisplatin. The proportion of patients experiencing improvement in symptom domains ranged from [redacted] to [redacted] for durvalumab plus gemcitabine and cisplatin, and from [redacted] to [redacted] for placebo plus gemcitabine and cisplatin.

Harms Results

As of the final analysis (IA-2), the overall incidence of treatment-emergent adverse events (TEAEs) in the TOPAZ-1 study was comparable between durvalumab plus gemcitabine and cisplatin and placebo plus gemcitabine and cisplatin groups (336 [99.4%] versus 338 [98.8%]). The most frequent TEAEs for both durvalumab plus gemcitabine and cisplatin and placebo plus gemcitabine and cisplatin included anemia (163 [48.2%] versus [redacted]), and nausea ([redacted] versus [redacted]), with differences of at least 5% only observed between durvalumab and placebo groups for nausea. Grade 3 or 4 AEs were reported at a similar frequency between treatment groups, with a total of 250 (74.0%) and 257 (75.1%) in the durvalumab plus gemcitabine and cisplatin and placebo plus gemcitabine and cisplatin, respectively. The most common grade 3 or 4 AEs included anemia ([redacted]), decreased neutrophil count (21.0% versus 25.7%), and neutropenia (20.1% versus 21.1%). The incidence of serious adverse events (SAEs) was similar between durvalumab plus gemcitabine and cisplatin and placebo plus gemcitabine and cisplatin ([redacted] versus 151 [44.2%]), with the most common SAE being cholangitis in

both groups (versus [5.0%]). The proportion of patients who discontinued treatment due to TEAE was in the durvalumab plus gemcitabine and cisplatin group, and 15.2% in the placebo plus gemcitabine and cisplatin group, driven mainly by , and in the placebo groups. Deaths due to adverse events (AEs) were reported in 13 (3.8%) patients in the durvalumab plus gemcitabine and cisplatin group, and 14 (4.1%) patients in the placebo plus gemcitabine and cisplatin group, with most deaths in the durvalumab group due to and , and in the placebo group.

The incidence of notable harms including immune-mediated AEs (imAEs), infusion-related reactions (IRRs), infections, and gastrointestinal (GI) events was generally more frequent in the durvalumab plus gemcitabine and cisplatin group than the placebo group. At the final analysis, imAEs were identified for 43 (12.7%) patients in the durvalumab plus gemcitabine and cisplatin group and 16 (4.7%) patients in the placebo plus gemcitabine and cisplatin group, of which 8 (2.4%) and 5 (1.5%) patients experienced grade 3 or 4 imAEs. IRRs were reported in and patients in the durvalumab plus gemcitabine and cisplatin and placebo plus gemcitabine and cisplatin groups, respectively. Infections and infestations occurred in patients in the durvalumab plus gemcitabine and cisplatin group, and patients in the placebo plus gemcitabine and cisplatin group. Gastrointestinal disorders occurred in and patients in the durvalumab plus gemcitabine and cisplatin and placebo plus gemcitabine and cisplatin groups, respectively. Immune-mediated GI events occurred in and 1 (0.3%) patients in the durvalumab plus gemcitabine and cisplatin, and placebo plus gemcitabine and cisplatin groups, respectively.

Economic Evidence

Table 3: Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Partitioned Survival Model (PSM)
Target population	Adult patients receiving first-line treatment for locally advanced or metastatic BTC
Treatment	Durvalumab plus gemcitabine and cisplatin
Submitted price	Durvalumab, 50 mg/ mL, single-use vial for IV solution: $7.82 per mg ($939 per 120 mg vial, $3,911 per 500 mg vial)
Treatment cost	$11,577 per cycle
Comparator	Gemcitabine and cisplatin
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (20 years)
Key data source	A phase III randomized, double-blinded, placebo-controlled clinical trial assessing the safety and efficacy of durvalumab plus gemcitabine and cisplatin compared with gemcitabine and cisplatin for patients with advanced BTC.

Component	Description
Key limitations	• The population in the sponsor's pharmacoeconomic evaluation was adult patients receiving durvalumab in first-line setting, which does not reflect the full Health Canada indication. The cost-effectiveness of durvalumab plus gemcitabine and cisplatin in subsequent lines of treatment is unknown. • The long-term clinical efficacy of durvalumab was uncertain. Approximately 68.9% of OS gains from durvalumab predicted in the model occurred through extrapolation beyond the time frame of the TOPAZ-1 trial (maximum duration of follow-up: approximately 2.75 years for OS). • Nearly half of estimated incremental life years (48%) associated with durvalumab were accrued in the postprogression health state, which lacked face validity. • The sponsor adopted relative dose intensities to account for missed doses or treatment interruptions, which inappropriately reduced drug costs. • The health utilities were uncertain because the analysis of EQ-5D-5L data, which was collected as an exploratory end point in the TOPAZ trial, was not controlled for multiplicity prone to type I error. The sponsor also assumed that age does not have an impact on health utility, which likely biased QALYs in favour of durvalumab.
CADTH reanalysis results	• To address the limitations, CADTH made the following revisions to the sponsor's pharmacoeconomic model: adopted a Spline Odds (1 Knot) function to estimate OS; assumed 100% relative dose intensity; and, used age-based utilities. • In the CADTH base case, durvalumab plus gemcitabine and cisplatin was associated with an ICER of $665,692 per QALY gained (incremental costs: $169,097; incremental QALYs: 0.26) compared with gemcitabine and cisplatin alone in first-line treatment. • A price reduction of at least 93% would be needed for durvalumab when used in combination with gemcitabine and cisplatin to be cost-effective at a WTP threshold of $50,000 per QALY gained.

BTC = biliary tract cancer; ICER = incremental cost-effectiveness ratio; LYs = life years; OS = overall survival; PSM = Partitioned Survival Model; QALY = quality-adjusted life-year; WTP = willingness to pay.

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis. The population considered in the budget impact analysis did not reflect the full Health Canada indicated population. The market share of durvalumab was underestimated. The use of relative dose intensity to estimate actual drug costs was inappropriate. The markups, dispensing fees and treatment duration estimates were uncertain.

In reanalysis, CADTH adopted a relative dose intensity of 100%, increased the market share of durvalumab and excluded markups and dispensing fees. Based on the CADTH reanalysis, the 3-year budget impact to the public health care payer of introducing durvalumab was $135,947,567 (year 1: $42,645,066; year 2: $45,307,337; year 3: $47,995,164).

pERC Information

Members of the Committee

Dr. Maureen Trudeau (Chair), Mr. Daryl Bell, Dr. Jennifer Bell, Dr. Matthew Cheung; Dr. Winson Cheung, Dr. Michael Crump, Dr. Leela John, Dr. Christian Kollmannsberger, Mr. Cameron Lane, Dr. Christopher Longo, 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: December 7, 2022

Regrets: None

Conflicts of interest: None