CADTH REIMBURSEMENT REVIEW

Patient and Clinician Group Input

pembrolizumab (Keytruda)

(Merck Canada Inc.)

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

December 15, 2023

This document compiles the input submitted by patient groups and clinician groups for the file under review. The information is used by CADTH in all phases of the review, including the appraisal of evidence and interpretation of the results. The input submitted for each review is also included in the briefing materials that are sent to expert committee members prior to committee meetings.

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Patient Group Input

1. About Your Patient Group

The **Colorectal Cancer Resource & Action Network (CCRAN)** is a national not for profit patient advocacy group championing the health and wellbeing of Canadians touched by colorectal cancer and those at risk of developing the disease. It has **expanded its mandate** to serve cancer patients outside the colorectal cancer space by providing HTA patient evidence submissions within the oncology space for:

i. Patient groups who do not have the capacity to make these submissions or
ii. Within therapeutic areas where there currently exist no exclusive representative patient groups to complete a submission (such as the therapy currently under review).

CCRAN assumed the lead on a collective patient input submission for Pembrolizumab in combination with chemotherapy for the treatment of adult patients with locally advanced, unresectable, or metastatic biliary tract carcinoma (BTC). The following patient advocacy groups thoughtfully collaborated with CCRAN to ensure the advanced, unresectable or metastatic BTC patient/caregiver perspective was captured, represented and thoughtfully weaved throughout this submission:

- **Canadian Cancer Survivor Network (CCSN)**
- **GI Society (www.badgut.org)**

All patient groups are registered with CADTH.

2. Information Gathering

In collaboration with the two patient advocacy groups, CCRAN employed a multi-faceted outreach strategy to help secure the BTC patient/caregiver input.

On **September 10th, 2023** CCRAN reached out via email to 14 Canadian clinicians who treat BTC, some of whom belonged to centers that participated in the KN966 study, wherein we kindly requested assistance with patient/caregiver recruitment for CCRAN's BTC qualitative telephone interviews. We respectfully sent along a poster (please see **APPENDIX A**) for Clinicians to share with their advanced/metastatic BTC patients or their caregivers who had first had experience with the therapy under review, hoping they might be willing to share that experience via a telephone interview with CCRAN. Having heard from very few of the clinicians, follow up emails were subsequently resent on **September 29th** and **October 29th** which resulted in no patient recruitment due to all previously treated patients having passed from the pathology. We recognized this was going to be a challenging file with respect to securing the patient perspective.

On **September 24th, 2023**, CCRAN reached out to 20 international centers who participated in the KN966 study, as well as members of CCRAN's international medical and scientific advisory board for their assistance regarding patient recruitment. We reached out to 3 Australian Centers, 5 French Centers, 1 Center in Ireland, 1 Center in New Zealand, 3 in the United Kingdom, and 7 in the United States and sadly, we received a similar dismal response rate after having sent two follow ups (**September 30th and October 29th**).

On **October 29th, 2023**, CCRAN also reached out to the Canadian Cholangiocarcinoma Collaborative, hoping for a glimmer of assistance with respect to patient recruitment. Sadly, this effort did not result in any patient accrual.

CCSN designed and executed an online survey to help capture the advanced BTC patient experience with the disease, currently available treatments and the therapy under review. The online survey was administered between **October 20 – December 1, 2023**. The survey was promoted through CCSN's social media platforms as well as an email blast through their newsletter list. The GI Society also promoted it through their social media platforms as did CCRAN. Those

outreach efforts resulted in two respondents having fully completed the survey, identifying as patients, **one of whom had first hand experience with Pembrolizumab (Survey Respondent A)**. Please see **APPENDIX B**.

On **September 14th , November 1st , December 4th and December 11th** , CCRAN reached out to the U.S.-based patient advocacy group dedicated to supporting cholangiocarcinoma patients: Cholangiocarcinoma Foundation, requesting assistance with patient recruitment for our telephone interviews. Direct patient input through semi-structured qualitative interviews provides a comprehensive understanding of disease and treatment experience from the patient perspective and is crucial in helping to inform this submission.

This outreach effort resulted in four of the six patients interviewed by CCRAN (please see **APPENDIX C**). Two additional interviewees were secured through CCRAN's email and social media blasts. It is, however, important to note that **Caregivers A, B and C** represent deceased patients who have experience with gemcitabine/cisplatin, gemcitabine/cisplatin, and Pembrolizumab +cyclophosphamide + survivac respectively, in addition to the disease journey, all of whom reside in Canada. **Patients D, E and Caregiver F** are U.S.-based and have experience with Gem/Cis + Pembrolizumab (Pembro), Gem/Cis followed by Pembro, and Gem/Cis followed by Pembro respectively, in addition to the disease journey and additional treatment options. Demographics are as follows:

Respondent/ Demographic	**Caregiver A (Deceased Patient)**	**Caregiver B (Deceased Patient)**	**Caregiver C (Deceased Patient)**	**Patient D**	**Patient E**	**Caregiver F**
Age (@Dx)	40	58	69	72	40	69
Gender	Female Patient A	Female Patient B	Male Patient C	Female	Female	Male Patient F
Location	Canada	Canada	Canada	USA	USA	USA

CCRAN anticipated this might be a difficult and challenging submission as it relates to the procurement of patient input due to the high mortality rates associated with this pathology. Couple that with the uncommon nature of the pathology and the limited number of patients accessing the therapy under review (through a trial setting) who may not be well enough or available to respond to our plea for patient input; we were prepared to pivot if need be. CCRAN diligently commenced the search for patient input months before the submission deadline but our tireless efforts were to no avail. Our efforts generated six patient/caregiver interviews:

- two of whom did not involve pembrolizumab,
- one of whom involved Pembrolizumab but no Gem/Cis
- one of whom involved the therapy under review
- two of whom involved Gem/Cis followed by Pembrolizumab therapy
- and the CCSN survey did generate one patient with experience with the therapy under review

To complete this critically important patient evidence submission, CCRAN was indeed required to pivot. We, therefore, decided to scour the literature and online public forums for patient reported outcomes (PROs) describing:

- their advanced BTC journey
- the treatments' (including the therapy under review) impact on their daily life, including physical, psychological functioning and well being

Some PROs in addition to the patient stories and testimonials were sought and incorporated into this submission in the most comprehensive manner possible to ensure the advanced, metastatic BTC patient voice is provided to help inform this committee's deliberations

3. Disease Experience

Biliary Tract Cancers (BTCs) are a group of heterogeneous malignancies that are broadly grouped based on the anatomical site from which they originate into subtypes which include:

- Intrahepatic cholangiocarcinoma (iCC)
- Extrahepatic cholangiocarcinoma (eCC)
- Gallbladder cholangiocarcinoma (GBC) and
- Ampulla of Vater cancer (AVC)

While BTCs may be uncommon, accounting for less than 1% of all new cancer cases worldwide, (Lancet, Vol 401, Issue 1039, 3-9 June 2023, pp1853-1865), the incidence is rising and, therefore, worthy of our attention and new interventions. It's important to distinguish between the various subtypes as each subtype has its own specific characteristics and variations in tumour biology, allowing for optimal management of the disease for every patient diagnosed with the disease. This is clearly reflected in our patient input collected through the qualitative data represented in **Appendix C**. Though, based on that patient input, biopsies are often technically difficult or result in inadequate tissue sampling, as nicely relayed by **Caregiver F**:

"***So, in hospital, he (my husband) had an ERCP and CT scan, which showed a blockage in his biliary tract but never had a successful biopsy to generate a pathology report. And never found cancer in his brushings***."

The prognosis is typically dismal for patients diagnosed with BTC. The five year survival rates are currently less than 5% for unresectable tumours (Hunter, LA et al Cancers 2021) but the prognosis for BTC is poor across **all** stages of disease, with 5 year survival rates of 5-30% [Oncol Ther (2021) 9:557-573]. Most of these cases are diagnosed at an inoperable or even at a metastatic stage, and for those patients whose disease is potentially surgically resectable, relapse rates are quite high. Hence, for patients with late stage disease, there are few, limited and ineffective treatment options to address this significant unmet need, requiring the introduction of a targeted and effective therapeutic. The causes of BTC are not known, but several risk factors for developing the different sub-types of this cancer have been identified, including conditions that cause long term inflammation of the bile ducts or gallbladder.

Our interviewed patients/caregivers reported having been diagnosed primarily through a series of scans consisting of CT, MR, (in some an Ultrasound) and ultimately ERCP to help facilitate biopsy. They all underwent cross-sectional imaging of the chest, abdomen and pelvis to help evaluate for metastatic disease extent. However, as previously mentioned, **Caregiver F** did advise that an official biopsy was never delivered for her husband due to "…***never having found cancer in his brushings….A CT scan showed a nebulous mass in the bile ducts. But not sure what it was so they treated empirically, believing it was cholangiocarcinoma.***"

Patients with BTC have reduced health related quality of life (HRQoL) due to a combination of tumour-and treatment-related signs or symptoms and the impact of these signs/symptoms on functioning in their lives. Tumour related signs and symptoms vary depending on tumour type, location and stage of the disease. The signs and symptoms reported by the caregivers and patients who participated in the telephone interviews included:

- Jaundice/yellow skin colour, abdominal pain/discomfort, backpain, reflux symptoms, dark urine, fatigue, lack of energy, weight loss, elevated liver function tests, sleep problems which included nights sweats, nausea and vomiting, GI symptoms, lack of appetite and general feeling of unwellness. These were consistent with the two patients who participated in CCSN's survey.

"***Yes, he was fatigued, his urine was dark, and slightly jaundiced and this was July 2019. He had intermittent abdominal pain which led to him going to the hospital. Really it was the dark urine, fatigue and jaundice that led to us taking him to the emergency room***." (**Caregiver C)**

The impact of these symptoms on patients' lives included:

- Anxiety, inability to do daily, normal, activities, depressive mood, trouble meeting the needs of the family and financial difficulties, as evidenced by some of the patient input:

"…..Dry mouth, loss of appetite and fatigue… He had monthly ER visits due to fever, chills and vomiting as a result of repeated blocked stents, infections & fever… And an additional drain was added which caused weakness, incontinence and that required the addition of 2 drains. And again, this wasn't necessarily due to the treatments, but the disease…. He was unable to perform outdoor activities but was physically mobile inside the house, but that was all." (**Caregiver C**)

"***It started with normal fatigue, extremely bad night sweats, I would wake up and I would have to go in the shower because the bed would be soaked, I was overworked so I thought it was due to overworking and perimenopause and then approximately 6 months before diagnosis, I started getting nausea and vomiting frequently. I would say approximately 3 days a week the vomiting would affect me. It would be so spontaneous. I would have to throw up in my purse for example because of the spontaneity. I attributed it to the heat for example. Nothing else. The final symptom was extreme abdominal pain, right sided sharp pain***…***The fatigue and nausea were unbearable***…***I couldn't do anything***." (**Patient E**)

Patients' HRQoL tends to decline as the disease becomes more advanced. This may, in part, be associated with patients undergoing more invasive surgical procedures, systemic chemotherapeutic treatments and/or palliative treatments during the later stages of BTC. However, the advanced disease itself can most certainly impact the patient's quality of life due to debilitating symptoms. In addition to directly impacting QoL, the disease has also been found to adversely impact emotional well-being as well as physical and cognitive function. Patients with advanced BTC have a particularly high chance of developing obstructive complications. Many patients with extrahepatic biliary tract cancer present with jaundice due to biliary obstruction and for those patients who present with acute cholangitis due to malignant biliary obstruction, it can be life-threatening. Adequate biliary drainage is critical not only in managing acute cholangitis and symptoms related to jaundice, such as the annoying itch described by patients, but also in enabling the palliative systemic treatments. Three of our interviewees described how they or their loved ones were required to undergo stenting for their obstructive disease, insertion of biliary drains and described the complications that ensued, including the life-threatening cholangitis:

"***Every month up until April, that required replacing stents, 2 plastic stents were replaced until finally a metal stent was inserted in January 2021***." (**Caregiver C**)

"…***then at the end of September, I developed a biloma so they installed an external stent to help with the drainage of the bile. I was wearing 2 drains and 2 bags and on September 15th I spent 3 weeks in hospital related to issues with that….It was hell***." (**Patient D**)

"***On June 5, 2020, his hematologist found liver enzymes out of range and that's what led to a hospital admission due to cholangitis due to a biliary tract obstruction. …..He almost died. It was really touch and go.***" (**Caregiver F**)

4. Experiences With Currently Available Treatments

The current standard of care for first line treatment of advanced, unresectable or metastatic BTC is doublet chemotherapy: gemcitabine + cisplatin (Gem/Cis). Based on the patient input, this chemotherapy can certainly improve quality of life and prolong survival in select patients with advanced BTC. In others, particularly patients with already poor performance status or very advanced disease, systemic chemotherapy can lead to a rapid decline in HRQoL. Recently, a conditional positive funding recommendation was issued for the immune checkpoint inhibitor durvalumab in combination with Gem/Cis for the first line treatment of advanced/metastatic BTC (cholangiocarcinoma and gall bladder cancer only). Provincial jurisdictional listings are underway in Canada and, therefore, patient access is not yet readily or widely available. Patients who have good performance status and experience disease progression following first line chemotherapy may benefit from second line therapy. However, a minority of patients are fit enough for this option. The most common second line treatment option in Canada for patients with BTC who have progressed on Gem/Cis is FOLFOX, as evidenced by the patient input.

Caregiver A painfully recounted her daughter's brief journey with extra-hepatic cholangiocarcinoma when her daughter was diagnosed at the age of 40 years in June of 2020. Diagnosed with stage 4 disease (liver and stomach), her daughter received Gem/Cis for 5 months, which provided some response initially but by December 2020, the disease progressed quite rapidly. Her daughter then went on to access 5FU + Oxaliplatin, but that too provided no clinical benefit. It merely provided a slew of toxicities much like the first therapeutic protocol. The primary tumour was quite painful so they accessed external beam radiation but that too was deemed ineffective. In **Caregiver A's** words:

"***Second line therapy consisted of 5FU and oxaliplatin, but it did nothing and that was administered from January-March 2021…..Radiation did nothing as well in March 2021. ..She was very good about making sure she ate and we tried different drinks and foods during this time. But the worst part of the journey was the pain***… ***She eventually died my beautiful daughter***."

Caregiver B described his 58 year old wife's journey post-op. She managed to undergo surgical resection of her extra-hepatic cholangiocarcinoma and then adjuvant Gem/Cis which was ineffective because the disease had already spread to regional lymph nodes. Hence, **Caregiver B** believes the adjuvant therapy (Gem/Cis) was totally ineffective and the first line therapy which his wife underwent, FOLFOX, was not at all effective as well. While the Gem/Cis was relatively well tolerated, the FOLFOX was not well tolerated at all according to **Caregiver B.** ***"…there was discomfort and nausea. We discovered that hydration helped alleviate that somewhat.***"

Caregiver C described a tortuous and debilitating journey that his 69 year old father underwent with respect to his diagnosis and treatment for his stage 4 extra-hepatic cholangiocarcinoma. His father completed 4 cycles of Gem/Cis from January – March 2020, and achieved a reduction in tumour size and growth. The patient stayed on strict surveillance right up until September 2020 "***but was repeatedly admitted every 4-6 weeks to hospital due to bile duct blockages and infections and this delayed his re-initiation of his treatments from September to December***

2020. And before starting that, they added a PTC tube into the gall bladder to help drain the bile and help avoid any future blockages."

Patient D's first line therapy consisted of Gem/Cis + Pembro, hence we reserve the opportunity to comment on this patient in Section 6.

Patient E accessed Gem/Cis in first line treatment, then Y90, microwave ablation and SBRT for the management of her intra-hepatic cholangiocarcinoma. Pembro was introduced as a second line treatment which permitted her to assume a no evidence of disease status. When she underwent Gem/Cis, she shares:

"***I was not able to cook, was in bed/couch, slept 20 hours/day, I would watch tv but nothing else. I could go to the bathroom but nothing else. I was extremely tired, felt real crappy. I could not clean or go out to socialize….I could not entertain, or work. I had to sell my business; I owned a printing business which I hated selling but we were forced to do it because of my diagnosis. I had it for 25 years and ended up selling it all in a flash! The kids and my husband assumed the chores and responsibilities of the household. I would work 6 days a week but when I got sick, I could do nothing. I couldn't do homework with the girls, I couldn't take the girls to practice or anything else, I just stopped overnight***."

As for Ablation, Y90 and SBRT, **Patient E claims**: "..***the procedure (Ablation) was quite painful, and the recovery was harsh because of the procedure itself. The rest were ok***."

And **Caregiver F** recounted her 69 year old husband's stage 4 Hilar Cholangiocarcinoma journey with great detail. Her husband received Gem/Cis, ablation and FOLFOX for the treatment of his disease, in addition to biliary stents to assist with the malignant biliary obstruction. In **Caregiver F's** words:

"***Gem/Cis controlled it for a while, for approximately 7 months. FOLFOX did not – off after 2 months. The Gem/Cis was tolerable but he continued to have cholangitis periodically, but life was worth living for. He was compromised while on the gem/cis therapy. His quality of life was not what it was before the treatment. He had a lot of fatigue, nausea, he did not feel well on this therapy. His quality of life was terrible on FOLFOX and he decided he would rather die than continue it. He was on the couch and had extreme fatigue. He felt very sick, and he signed up for the "death with dignity" program in Washington to help with that. He never availed himself of it because he came off that therapy thankfully…and started Pembrolizumab."***

Following progression on Gem/Cis, many patients may not be well enough to receive a second line treatment protocol. Patients who are elderly or have a poor performance status are unable to tolerate chemotherapy, with their treatment limited to supportive care including decompression of the biliary tree through biliary stenting and ablation techniques. This most certainly highlights the significant **unmet need** for more effective and tolerable treatment options in BTC, particularly in the **first line setting**, when a response is most required and highly sought-after; and given the extremely poor prognosis for patients, it emphasizes the importance of patient centred outcomes such as quality of life and progression free survival in therapy selection.

5. Improved Outcomes

The telephone interviews serve as a means of capturing and providing a qualitative patient interview profile which led to the development of a series of recommendations based on the patient experience of BTC. Metastatic BTC patients or their caregivers were able to thoughtfully provide us with a comprehensive understanding of the disease and treatment experience and were then able to recommend improvements they wish to see achieved regarding newly developed therapeutics. Interviewed patients and caregivers stressed the importance of providing a targeted therapy for the first line treatment of metastatic BTC, which has **fewer side effects**, (i.e. no nausea, vomiting, fatigue etc.), allows for a **cure of the disease**, **improved quality of life**, and, if possible, **oral administration**. Equitable access for all was of paramount importance to **Caregivers A and B**, and **Caregiver C** emphasized the "***importance of transparency on***

the results of the ongoing clinical trials to potential patients who can make an informed decision before accepting any clinical trial."

When **Interviewees D, E and F** were asked if Pembrolizumab had any of the desired improvements of which they spoke, **Patient D** didn't really know if it would be her cure but she "***is hopeful because she is starting to see glimmers of hope and some signs of improvement in her cancer***." **Patient E** is absolutely convinced that Pembrolizumab has cured her because her last treatment of Pembrolizumab was in February 2018 and to this day she continues to be NED. **Caregiver F** wishes her husband had started the Pembrolizumab much sooner so that he could have avoided significant toxicity and avoided a great deal of adversity and maintains that it has significant clinical benefits.

Additionally, all interviewees stressed how important it was to undergo genomic profiling of BTCs. They maintained that genomic profiling has found BTCs to be target-rich malignancies, and can identify clinically relevant or potentially actionable genetic mutations that can improve patient outcomes – mutations such as IDH1, FGFR2, NTRK Fusions, BRAF, RET, MSI, and HER2 may help to achieve the desired outcomes patients seek. However, genomic profiling was not offered to them and was a diagnostic tool they had to seek out on their own, as an out of pocket expense:

"***Her cancer was not tested until Feb 2021. When the results came back, there were no trials available for her which was DEPRESSING. Her mutations were: -BRAF-G469R, PTEN-E99fs*8, ARID1A-S674fs*69, TP53 splice site, 993+1G>A. There was 1 disease relevant gene with no reportable trial FGFR2***." (**Caregiver A**)

"***Yes. I asked about that (genomic profiling) in the Fall of 2020 when it was clear that the cancer had returned. I was advised by the oncologist that they did not do that yet. As that did not sit well with me, I pressed the issue and was eventually approved for the tumour sample to be sent to Boston (Foundation One) for testing. Biomarker testing was undertaken at a cost of about $5,000. It discovered mutations in STK11 and MDM2. It was deemed that there were no trials available that would offer any benefit***." (**Caregiver B**)

"***Yes. Foundation One testing which resulted in MSI High biomarker finding. Testing was done late 2020, Report on Jan 2021***." (**Caregiver C**)

In light of the poor prognosis associated with metastatic BTC, there is an **urgent need** to prioritize patient centered outcomes such as quality of life, together with overall survival. According to the qualitative patient input, the **therapy under review addresses and provides these desired improvements:**

"*I wish my husband had started Pembro earlier, because his cancer grew and did a lot of damage that can now not be eliminated. If he had started earlier, it would have stopped the cancer earlier, and he would not have suffered as much and would have responded optimally. No portal hypertension and would not have had so many cholangitis episodes. And not so many plastic or metal stents. This therapy should be approved and provided to patients and their caregivers." (Caregiver F)*

CCSN's **Survey Respondent B** is a Canadian female patient with late stage disease who received radiation and chemotherapy to treat her BTC. She expressed how important it would be to provide new treatments that maintain **quality of life, delay onset of symptoms, reduce side effects from current medications, prolong life and provide a cure to the cancer.** When asked to rate on a scale of 1-10 how much of an improvement would be required from a new treatment to make it better than her current treatments, the respondent replied with a rating of **7, indicating that significant efforts would be required to promote improvement**. And when asked how her life might be different with these improvements, the respondent shared, "***Being able to plan things as I would have no side effects. Feel normal***." And finally, when asked what considerations she makes when balancing the advantages and disadvantages of a treatment, she replied, "***Try to coordinate with friends for the things I need i.e.. Transportation, groceries and medications."***

6. Experience With Drug Under Review

Caregivers A and B who lost their daughter and wife respectively to BTC, passionately conveyed the urgent need for more effective treatments and combinations for BTC. Their deceased loved ones had accessed Gem/Cis in the first line and adjuvant setting respectively, which they both expressed had been ineffective at regressing the disease or preventing a recurrence on any meaningful level. Hence, both family members succumbed to the disease in 1 and 2 years respectively. Both urged and stressed the importance of introducing Pembrolizumab into the treatment algorithm to help improve patient outcomes.

Caregiver C's father accessed the IMV clinical trial in the second line setting that included **Pembrolizumab + Cyclophosphamide + DPX-Survivac vaccine** after having been treated with 4 cycles of Gem/Cis. He underwent treatment for 11 months, wherein he achieved a fairly good tumour response (50% shrinkage), and good quality of life. According to his son, his appetite, mood and mobility were the key indicators of clinical response, which improved for the first 6 months while on the trial. There were some treatment interruptions, however, due to blocked stents and infections. In **Caregiver C's** own words:

"***My father's Pembrolizumab would stop any time he was admitted and treated in the ER for blocked stents leading to an infection. Once he was clinically and medically doing better, his treatments would resume. He developed ascites in late Dec 2021 and clinically declined with extreme fatigue and weight loss***."

In terms of any treatment-induced side effects while on the clinical trial: **Caregiver C** recalls fatigue, loss of appetite, and dry mouth having been a nuisance but does admit that these side effects were likely attributable to the previous chemotherapy regimen his father had undergone. He also admits that the cancer-induced symptoms experienced before starting the trial had been somewhat resolved due to the trial medications. These included: rashes, itchiness, loss of appetite, and dry mouth. He believed his father's quality of life would have ranked a **6 out of a possible 10** while on the clinical trial which included the Pembrolizumab. **Caregiver C** maintains this was a positive metric as his father had been suffering multiple ER visits due to biliary obstructions and infections that were negatively compromising his father's journey but the trial had managed to stabilize him and provide him with a satisfactory quality of life.

Caregiver C spoke to the profound psychological impact the disease had on his father and how the therapy under review managed to overcome some, if not much, of this toll:

"***As a patient, my father was determined and felt encouraged there was a fighting chance to manage and possibly beat this disease by accessing targeted therapy. The rarity of this disease made him feel like a lonely warrior and he was happy to know there was more research being done to provide alternate options…. As a caregiver, Immunotherapy… can provide a psychological boost to the patient and their families. We strongly believe the psychology of the patient also has an impact on how they will respond to treatment. The introduction of targeted therapy specific to a genetic mutation as a 1st line treatment needs further encouragement and advancement***."

Patient D, Patient E and **Caregiver F** are U.S.-based citizens who were happy to participate in our telephone interviews, having accessed Gem/Cis + Pembrolizumab, Gem/Cis followed by Pembrolizumab, Gem/Cis followed by Pembrolizumab, respectively. Each achieved a remarkable clinical and radiographic response, describing the improvement in cancer-induced symptoms and quality of life.

Patient D is a 72 year old female diagnosed with intra-hepatic cholangiocarcinoma on August 14, 2023, with metastases to the lungs and sacrum. She commenced first line treatment of **Gem/Cis + Pembrolizumab** on November 2, 2023. She has received two cycles of the therapy to date and has experienced **no side effects** whatsoever and claims to be doing very well on the protocol. "***I have had no side effects whatsoever. None, at all***." Her quality of life rating score is an **8 out of a possible 10.** She claims "***her treatments have been really great***"**.** She has not received any radiographic imaging as of the date of the interview but does believe she is responding to the therapy because her healthcare providers had recommended and scheduled her for the removal of one of her biliary drains, which was no longer required:

"***There have been no CT scans yet because it is too early but I can tell you I feel really good and well after having started this therapy. I believe this is encouraging and reveals that I am responding to this therapy. Plus, this coming Monday, they will be removing one of my drains. That's the best news ever!..... Getting my drain out Monday is such a good sign. What a lift off my shoulders it is. That, in and of itself, is such a good sign because to me, it's a sign that I am responding to the therapy."***

Patient E is a 47 year old female diagnosed with intra-hepatic cholangiocarcinoma at the age of 40 on August 10, 2016, with metastases to the liver and local lymph nodes. She underwent 16 cycles of Gem/Cis, whose infusions she had difficulty tolerating, but every scan showed noticeable improvement; Yttrium 90 (Y90) for her liver metastases which regressed her liver metastases; followed by microwave ablation for 4 tumours in her liver which were nicely treated; followed by 7 cycles of Pembrolizumab which allowed her to acquire a no evidence of disease (NED) status. There was a questionable finding in her last scan of a possible liver metastasis which was treated with SBRT in September 2018. To date, she **remains NED** and attributes her good health and NED status to Pembrolizumab. **Patient E** accessed the Pembrolizumab through the manufacturer's Patient Support Program and received it from October 2017 through to February 2018 as a 2nd line therapy. She maintains strongly that she experienced no side effects whatsoever and "***felt great while I was on it, just fantastic***". She assigned a quality of life rating score of **9 out of a possible 10**. She comments on the side effects and ease of use:

"*..**it was fantastic and great! But it did kill my thyroid. It could attack other organs, i.e. it compromised thyroid function. That was the only side effect I got from it….Ease of use? Oh, yes, it was. The gem/cis infusions were 5-6 hours long. But the Keytruda infusion was so short - I was in and out in an hour. The number of side effects were negligible in comparison to gem/cis. I had none***."

And when **Patient E** was asked what has she been able to accomplish because of having been able to access the therapy under review, she articulately replied:

"***If someone asked me back in August of 2016 if I thought I would be alive today, my answer would have been no. But I am alive, healthy and leading a normal life today-something I never thought was possible. So, I guess the answer to your question is, ya, I have been able to live! Live my life which I never thought I could do past just a few brief months which I was given. That has to be the most remarkable achievement or accomplishment I would say, all because of Keytruda***."

Caregiver F is a caregiver to a 72 year old Hilar cholangiocarcinoma patient diagnosed at the age of 69 in September of 2020 with lymph node involvement. **Caregiver F's** husband received Gem/Cis with concurrent ablation as first line therapy followed by second line FOLFOX. In August of 2021, her husband was nearing end of life, so a recommendation was made by the patient's medical oncologist to attempt Pembrolizumab. Thankfully, the patient did access it wherein an immediate response was observed, both clinically and radiographically. According to **Caregiver F**,

the patient is alive and well today thanks to Pembrolizumab. The Pembrolizumab was accessed through the compassionate access program in August 2021 and has managed to stay on it ever since. **Caregiver F** explains that her husband has had a difficult disease journey, having experienced "***horrible bouts of cholangitis, requiring hospitalizations due to disease-induced symptoms such as fevers, pain etc.***". ***"His quality of life was so poor, we couldn't get a handle on it. His obstructions required stents, both plastic and metal, and frequent replacement of those stents. It was so hard…***"

Caregiver F's husband has received 40 cycles of Pembrolizumab to date and she claims that his quality of life is not what it used to be but "***that may be due to the cancer damage. But we don't know which is which. He has fatigue, nausea, aches in his body - this we believe is due to Pembro (the aches). We just can't tell***." She ranks his quality of life a **5** out of a possible 10 "***because he is at 50% of where he used to be before his diagnosis***."

She does maintain that a number of his cancer-induced symptoms have resolved since having started the Pembrolizumab: "***weight loss, ascites, night sweats, and the cholangitis episodes has been less frequent***". **Caregiver F** describes the Pembrolizumab as being a shorter and convenient infusion in comparison to the FOLFOX and Gem/Cis:

"..***Yes, because it is a shorter infusion. When he was on FOLFOX, they recommended he ice his feet and hands to reduce neuropathy. Now, he is nowhere near as miserable. Gem/Cis is really long and tiresome, this therapy is not. And he doesn't get any mouth sores like he used to get with the other treatments***."
In terms of what this protocol has allowed the patient to fulfill: **Caregiver F** thoughtfully explained that her husband was forced to retire once receiving his diagnosis of BTC. He was a University Professor contributing to research in the field of sociology. Once he started to ameliorate, he continued his research and worked with students because this was his life's work and passion that provided him fulfillment. In **Caregiver F's** words:

"…***then back on it while on pembrolizumab. What a joy that has been. That is an accomplishment! Especially, knowing how compromised he has been…..He is still alive, and he would definitely be dead today were it not for pembrolizumab. His quality of life is acceptable to him now. He got to live because of this treatment***."

Caregiver F emphasized the need to introduce the immunotherapy earlier on in the patient's disease journey, such that patients with advanced BTC may have durable immune responses and prolonged survival, in the event the immune checkpoint inhibitor, pembrolizumab, is combined with first line Gem/Cis: ***"…unfortunately, he started the Pembro after the cancer had already progressed and done some damage. It was delivered in third line so it***

was a bit later than when it should have been delivered. It could have made a huge difference if it had been delivered earlier….. If he had started earlier, it would have stopped the cancer earlier, and he would not have suffered as much and would have responded optimally. No portal hypertension and would not have had so many cholangitis episodes. And not so many plastic or metal stents."

CCSN's **Survey Respondent A** is a U.S.-based metastatic BTC female patient who is currently NED. She has experience with Pembrolizumab, in addition to Gem/Cis, Taxotere, and therapies such as a liver resection, 3 lung VATS, thoracotomy, and adoptive t-cell therapy. The adverse effects she incurred when taking the Pembrolizumab were fatigue and joint aches, but managed just fine according to her. When describing the advantages of Pembrolizumab, **Survey Respondent A** shared: "***Pembrolizumab allowed the targeted t-cell treatment to work effectively. After taking the Pembro my tumours completely disappeared and that is the last treatment I had over 6 years ago***." In comparison to other therapies, the respondent replied in each area of symptom management, side effects, ease of use, and disease progression that Pembro was "***much better***".

Patients value having access to new therapies that have few side effects, can improve their QoL, allow them to be engaged in society, functioning and contributing members of the work force, if possible, and are able to be committed to their families and friends. This is commonly expressed by patients and caregivers throughout various tumour types, including BTC, but a critical unmet need exists for patients with metastatic BTC who face limited treatment options that can extend progression free survival, overall survival and more importantly, can improve QoL in a truly meaningful way. The immunotherapy under review provides patients with a treatment with minimal side effects, improved quality of life, durable and sustained response compared to the chemotherapy regimen, and increased longevity. To have observed the magnitude of the response in **Patients D, E, F** and **Survey Respondent A** confirms that the therapy under review (specifically, the Pembrolizumab) is effective and amenable for long term administration. Funding the therapeutic aligns well with the input captured within this submission and its appendices.

7. Anything Else?

Direct patient input through semi-structured qualitative telephone interviews has provided a comprehensive understanding of the BTC disease and treatment experience, from both the patient and caregiver perspective. More importantly, patients or their caregivers interviewed throughout this process provided in-depth experiential information as to why the addition of Pembrolizumab to chemotherapy or post chemotherapy was critically important in the patient's BTC journey. Over the last decade, there have been no newly developed and approved novel targeted therapies for advanced, unresectable or metastatic BTC in Canada, save the approval of Durvalumab in 2022 by Health Canada but its reimbursement is still in progress. Hence, advanced, unresectable or metastatic BTC continues to have an overall dismal prognosis, and patients frequently suffer from poor HRQoL. In these patients, the prevention and easing of suffering due to tumour and treatment-related symptoms is of primary importance. The introduction of novel, effective, easily administered and less toxic targeted therapeutics is of paramount importance. This was made abundantly clear by our interviewees.

The patient input has nicely demonstrated that tumour growth, even minimal tumour growth, can lead to disease symptoms causing significant deterioration in quality of life and can necessitate stent placements or their changes. These are associated with complications requiring hospitalization, including bleeding, perforation, cholangitis and infection. These are the unique circumstances and needs of patients with BTC that must be taken into consideration when managing their disease, but more importantly, when looking to assess new therapeutics. Quality of life matters to patients diagnosed with metastatic BTC and must be considered in the value assessment of a new drug therapy, especially if quality of life and/or major toxicity can be improved, as nicely demonstrated in the cases of **Patients C, D, E, F, and Survey Respondent A.** Our patient input maintains that the addition of Pembrolizumab does not increase treatment-induced toxicity, nor does it reduce quality of life, but instead provides a prolonged survival benefit (**Caregiver C, Patient D, Patient E, Caregiver F and Survey Respondent A**) with ease of use. Hence, we respectfully recommend that the therapeutic be added to the current landscape of systemic treatments for advanced, unresectable or metastatic BTC in Canada, as the first line treatment for this patient population in combination with chemotherapy.

Interviewed patients and caregivers wished to relay their final thoughts regarding the incorporation of Pembrolizumab in the first line treatment of BTC:

"***Since it has been approved for other cancers, the idea that it should be considered for approval for this type of cancer should be strong and compelling. Please approve it***!" **Patient D**

"***I am living proof that by combining Pembrolizumab + Chemotherapy, it greatly increases a patient's chances for survival. I am almost 5 years NED and I still read forums and support pages for people currently battling Cholangiocarcinoma and it is heartbreaking to see the lack of information available to these people with regards to targeted therapies like Pembrolizumab + Chemotherapy. I would really like to see this treatment approved for patients who need and qualify for it because much like me, I saw firsthand how it can change a***

patient's disease course. It works. Patients should not be denied the chance to live longer and better lives."
Patient E

Incorporating Pembrolizumab into the first line treatment of advanced, unresectable or metastatic BTC in combination with Gem/Cis, will most surely help to address a high unmet need for the BTC patient population – the addition of an immunotherapeutic that is capable of maintaining QoL, prolonging longevity, and achieving a durable response. This is a particularly meaningful goal for this patient population and their caregivers. The is well supported in our submission and within our appendices: efficacy and safety are echoed throughout the patient interview data as patients speak to the addition of the immune checkpoint inhibitor to standard of care chemotherapy in the treatment of their metastatic BTC. The clinically meaningful survival benefits reported by our interviewed patients (some of whom achieved an NED status) in the absence of any new safety signals, supports the combination of Pembrolizumab, gemcitabine and cisplatin as a first line treatment option for patients diagnosed with advanced, unresectable or metastatic biliary tract cancer. We, therefore, strongly support and urge that a positive funding recommendation be issued for Pembrolizumab in combination with chemotherapy for the first line treatment of patients with advanced, unresectable or metastatic BTC. We believe a positive funding recommendation aligns well with the identified patient input and need for a new, effective, easily and quickly administered treatment option that is capable of maintaining the patient's quality of life, durable response, and increased survival.

Appendix: Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the CADTH CDR and pCODR programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

1. Did you receive help from outside your patient group to complete this submission? If yes, please detail the help and who provided it.

No

2. Did you receive help from outside your patient group to collect or analyze data used in this submission? If yes, please detail the help and who provided it.

No

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Merck				X

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

Name: Filomena Servidio-Italiano

Position: President & CEO

Patient Group: Colorectal Cancer Resource & Action Network (CCRAN)

Date: December 30, 2023

Clinician Group Input

CADTH Project Number: PC0344-000

Generic Drug Name (Brand Name): Pembrolizumab (Keytruda)

Indication: For the treatment of adult patients with locally advanced unresectable or metastatic biliary tract carcinoma (BTC), in combination with chemotherapy

Name of Clinician Group: Ontario Health (CCO) Gastrointestinal Cancer Drug Advisory Committee

Author of Submission: Dr. Erin Kennedy, Dr. Rachel Goodwin

1. About Your Clinician Group

OH-CCO's Drug Advisory Committees provide timely evidence-based clinical and health system guidance on drug-related issues in support of CCO's mandate, including the Provincial Drug Reimbursement Programs (PDRP) and the Systemic Treatment Program.

2. Information Gathering

Information was gathered by email.

3. Current Treatments and Treatment Goals

The standard of care is CISGEM and CARBOGEM. The treatment goals would be prolonged life, delayed disease progression, and improved quality of life.

4. Treatment Gaps (unmet needs)

4.1. Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

There is only one available regimen and the duration of response is poor. Therefore, new regimens are required.

5. Place in Therapy

5.1. How would the drug under review fit into the current treatment paradigm?

Pembrolizumab can be safely added to first line chemotherapy and is well tolerated.

5.2. Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

Patients best suited for the drug under review would be all patients who align with the clinical trial criteria.

5.3 What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

Clinical and/or radiologic progression as per the discretion of the treating oncologist.

5.4 What factors should be considered when deciding to discontinue treatment with the drug under review?

Treatment should be discontinued if there is disease progression and toxicity at the discretion of the treating oncologist.

5.5 What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

The setting would be hospital (outpatient clinic) and a specialist is required.

6. Additional Information

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7. Conflict of Interest Declarations

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

1. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

   OH-CCO provided a secretariat function to the group.

2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

   No.

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. **Please note that this is required for each clinician who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Name: Dr. Erin Kennedy

Position: Ontario Health (CCO) Gastrointestinal Cancer Drug Advisory Committee lead

Date: 13-12-2023

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 1: Conflict of Interest Declaration for Clinician 1

Company	Check appropriate dollar range*

	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Add company name				
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 2

Name: Dr. Rachel Goodwin

Position: Ontario Health (CCO) Gastrointestinal Cancer Drug Advisory Committee member

Date: 12-11-2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 2: Conflict of Interest Declaration for Clinician 2

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Merck	X			
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.