CADTH

CADTH Reimbursement Review

Patient Input

PEMIGATINIB (TBC)

(Incyte Biosciences Canada Corporation)

Indication: Cholangiocarcinoma

CADTH received patient input from:
Canadian Organization for Rare Disorders, Canadian Liver Foundation and Cholangiocarcinoma Foundation

July 16, 2021

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CADTH

CADTH Reimbursement Review
Patient Input Template

Name of the Drug and Indication	**Pemigatinib (brand name : PEMAZYRE) for Cholangiocarcinoma fo=**
Name of the Patient Group	**Canadian Organization for Rare Disorders** **Canadian Liver Foundation** **Cholangiocarcinoma Foundation**
Author of the Submission	[redacted]
Name of the Primary Contact for This Submission	[redacted]
Email	[redacted]
Telephone Number	[redacted]

1. About Your Patient Group

Founded in 1969, the Canadian Liver Foundation (CLF) was the first organization in the world dedicated to supporting education and research into all forms of liver disease. Today, the CLF continues to be the only national health charity committed to reducing the incidence and impact for Canadians of all ages living with or at risk for liver disease. The CLF is the only registered charity in Canada directing funds specifically for liver disease research in all its forms and has invested more than $37 million in the scientific search for causes, preventative measures and potential treatments for liver disease. The CLF reaches millions of Canadians through our public and professional education programs, patient support programs and other awareness, fundraising and outreach efforts. Website: www.liver.ca

The Canadian Organization for Rare Disorders (CORD) is Canada's national network for organizations representing all those with rare disorders. CORD provides a strong common voice to advocate for health policy and a healthcare system that works for those with rare disorders. CORD works with governments, researchers, clinicians and industry to promote research, diagnosis, treatment and services for all rare disorders in Canada. Website: www.raredisorders.ca

Founded in 2006 by a family who lost a loved one to cholangiocarcinoma, the Cholangiocarcinoma Foundation's (CCF) mission is to find a cure and improve the quality of life for those affected by cholangiocarcinoma (bile duct cancer). CCF has grown to become the leading global resource in research, education, and public awareness. The CCF's objective is finding a cure which relies on . research that provides essential resources and knowledge for the field and innovative research that opens new pathways for diagnosis and drug discovery. Website: www.cholangiocarcinoma.org

2. Information Gathering

Recruitment: Responses reflect direct patient input from two sources: online survey and a virtual focus group. Recruitment for the survey was targeted specifically to patients and caregivers affected by bile duct cancer (cholangiocarcinoma), especially those with FGFR2 gene infusions or rearrangements" by the Canadian Organization for Rare Disorders (CORD), the Canadian Liver Foundation (CLF), and Cholangiocarcinoma Foundation (based in the USA) through their patient databases and social media. The Cholangiocarcinoma Foundation (CCF) recruited and facilitated the virtual focus group of three Canadian patients diagnosed with cholangiocarcinoma with FGFR2 infusions.

Responses: Patients provided input through survey available on Survey Monkey from 24 June to 11 July 2021. The introduction specified that the purpose of the survey was to provide patient input to the Canadian Agency for Drugs and Technologies in Health (CADTH); however both Canadians and non-Canadians were invited to take part. There were 32 respondents, with 27 who completed the entire survey, and the feedback reported here reflects those 27 complete responses. Among these, 12 (44%) identified as Canadian; 13 (48%) as American, and 2 (7%) as "Other." Canadian respondents reported home provinces as British Columbia, Alberta, Ontario, Quebec, and New Brunswick.

Among the 27 survey respondents, 15 (56%) identified as "diagnosed with bile duct cancer"; 10 (37%) as caregivers or family members; and two (7%) as having symptoms of bile duct cancer but not diagnosis). Additionally, 18 (67%) patients reported they had intrahepatic bile duct cancer; four (15%) had extrahepatic bile duct cancer; two (7%) had both forms; and three (11%) were unsure or preferred not to answer.

In terms of stage at time of diagnosis, survey respondents were somewhat "evenly" split across Stage IIA/B (n=7); Stage IIIA/B (n=6), and Stage IV (n=6), with two diagnosed at Stage I and seven who did not know. Additionally, 10 respondents (37%) reported their cancer was diagnosed as resectable and 11 (41%) said it was not; importantly, however, 12 (44%) said they did not know.

In terms of time since diagnosis, respondents were distributed relatively evenly across timeframes, with 26% diagnosed between 2 to 5 years ago, 4% more than 5 years ago, and 22% each for "less than 6 months" ago, "6 to 12 months" ago, and "1 to 2 years" ago.

When asked whether they had a diagnosis of tumour gene mutations, four (15%) responded that they had been diagnosed with FGFR2 fusions; none had been diagnosed with either NTRK fusions or IDH1 mutations; four (15%) said they had been diagnosed with other gene mutations; four reported they had no diagnosis of gene mutations; and the largest grouping, 15 (56%) did not know.

Age at time of diagnosis was somewhat evenly distributed across four groupings, with 30% over 65 years old, 26% under 45 years of age, 22% between 45 and 54 years old, and 19% between 55 and 64 years old. Overall, 58% of patients were female and 42% male.

While the number of respondents is small, we thought it worthwhile to note some of the key differences between Canadian and USA respondents in terms of age at diagnosis, time since diagnosis, and stage at time of diagnosis (see Table 1). Notably, Canadian patients were both younger and older in terms of age at diagnosis. The "time since diagnosis" seems to be about the same across borders, with more Americans diagnosed in the last six months. However, Canadians seem to be diagnosed at a later stage of cancer development, with most at Stages III and IV while Americans somewhat more likely to be at Stage II. The terms cholangiocarcinoma and bile duct cancer will be used interchangeably throughout this submission.

Table 1: Characteristics of Respondents in Canada cf. USA														
Respondents	Age @ time of diagnosis				Time since diagnosis					Stage @ diagnosis				
	< 45	45-54	55-64	> 65	< 6 mos	6-12 mos	1-2 yrs	2-5 yrs	> 5 yrs	Stage I	Stage IIA/B	Stage IIIA/B	Stage IV	Don't know
Patients residing in Canada (n=12)	25%	8%	17%	43%	17%	25%	33%	25%	0%	8%	17%	33%	25%	17%
Patients residing in USA (n=13)	23%	31%	23%	23%	31%	23%	15%	23%	8%	8%	38%	15%	15%	23%
All respondents (n=25)	24%	20%	20%	32%	24%	24%	24%	24%	4%	8%	28%	24%	20%	20%

To supplement direct patient feedback, some information from an abstract presented at the Gastrointestinal Cancers Symposium in 2020 on the diagnostic journey and life impacts of cholangiocarcinoma is included.

3. Disease Experience

Disease experience was elicited in the survey through (1) an open-ended question asking respondents to describe the experience of the patient and caregivers and (2) ratings along a predefined matrix of "problems or issues experienced by persons due to bile duct cancer." Focus group members were also asked to describe their experience.

Overall, it was clear that cholangiocarcinoma has a major impact on the patients' quality of life, including daily activities and relationships, as well as their mental well-being. The experiences of Canadian and American patients were highly similarly so the combined results are reported here. Based on the matrix of options, the problems that were rated as having the most impact ("very much" and "much") were those related to "overall quality of life", further articulated as participation in activities or relationships, including "family, social, work, and school" and "intimacy or sexual desire." In terms of physical symptoms, "fatigue" was most problematic, rated as having "very much" or "much" impact by more than 80% of respondents. Likewise, about 80% reported experiencing "anxiety" "very much" to "somewhat" problematic. Other physical symptoms experienced by about two-thirds of respondents (67% to 72%) were "unintended weight loss" and "insomnia." Gastrointestinal problems, "abdominal pain" and "constipation" were reported by a similar percentage. About two-thirds experienced "somewhat" to "very much" issues with "depression" and about 50% had experiences of "neuropathy."

There findings echo those reported in the 2020 GCS abstract presentation, where a survey of cholangiocarcinoma patients found they experienced considerable or serious impact on daily lives, work productivity, quality of life, mental health, and sexual functioning. Additionally, patients reported having experience symptoms on average about two years prior to a diagnosis.

Importantly, the qualitative responses from the focus group and survey participants provide invaluable insights on the emotional and psychological toll of a "rare cancer" on patients and families. As is the case with many rare cancers, patients experienced delayed diagnosis and misdiagnosis which then delayed or eliminated some treatment options and contributed significantly to the stress and anxiety experienced.

"Months of misdiagnosis, centered on colo-rectal investigation (scans & scopes) due to symptoms being diarrhea and inability to digest food properly (progressive food intolerance's), after becoming rapidly jaundice, focus was re-directed and bile duct cancer diagnosed."

"Doctor I first saw was extremely judgmental and focused on my weight and not on the cholangio....thankfully I knew I had to get to a second opinion and maybe a third. That is critical and thankfully my family doc helped me secure appts with several leaders in cholangiocarcinoma. I was glad I got cc in the USA where we don't have to fight for second opinions and then be declined."

"Brutal. My dad went to the emergency room twice for abdominal pain. Both times he was told it was muscular and take something for acid. After 3 months of pain, he finally found a doctor that touched his liver and felt a mass."

"The assumption that my husband is an alcoholic over and over again is annoying and disrespectful."

"Had I not asked to have my cysts in my liver looked at closer with an ultrasound my Cholangiocarcinoma would not have been diagnosed."

With cholangiocarcinoma, like many rare cancers, a diagnosis may often exacerbate rather than alleviate fears and anxieties, since there is little known about the condition and its prognosis, few specialists, few or no approved treatments, and often short life expectancy. Many patients do their own research but will then face barriers accessing promising options.

"Being diagnosed with a rare cancer is frightening and leads you down an uncertain path. There is very little information about the cancer itself, treatment options, and prognosis. It is unsettling to know that little research is being conducted for your particular cancer."

"Then 6 weeks of test to finally learn he had 1 year to live and we were told he could get chemo if wanted to try to maybe slow progression."

"Twin sister diagnosed with cat allergy by her GP. Intense itching and feeling unwell, vomiting. Stage 4 on diagnosis via A&E. Discovered it was cancer when an oncology secretary phoned to make an appt. Told terminal, emotional support zero. … No surgery or immunotherapy offered. No trials."

"Up front patient experience was horrible. The disease is rare and therefore Drs give death sentences and minimal information on trials and or immunotherapy available. Drs do not talk about biopsies for mutations. All this is needed for trials to potentially prolong our lives."

Respondents also reported having to do their own research to get a second opinion, access to appropriate tests, clinical trials, and treatment alternatives. It is not clear from such a small sample whether Canada lags other countries (USA in this case) in diagnosis and treatment but it is notable that the Canadian respondents report diagnosis at a later stage (III or IV) compared to Americans (Stage II).

"I went to my GP with a reoccurring pain in my upper right abdomen and after 3 months of tests I was diagnosed and giving 8 months to live. Sought second opinion and had surgery within 4 days of that meeting."

"We are in Canada. We had to do research about gene mutation test cause no one mentioned that. We research protocols to find some hope. Started one with maybe keytruda (or placebo) with gem-cis at McGill. We investigated another protocol at CHUM and were told to forget about it and go home try to enjoy the rest."

Finally, respondents spoke about the mental health impact on themselves and their concerns for their family and the lack of resources to address these.

"I feel alone, and scared, and hopeful."

"That's a game play every day. It's hard. Some days I can go on and some days it's just too hard. It is a struggle and my husband looks at me helplessly. Some days I am weak and some days I am good. It is a really tough game."

"I try to leave it at the back of my mind at all times. I just try to live life daily without thinking about it. I talked to a psychiatrist for a bit but it did not help a lot. It was hard with my daughter, I am afraid to leave her. She will be alone. That is the worst thing that is on my mind is leaving her behind."

"I've dealt with depression for a long time but I've been okay for a long time too. My concerns have been about my family. I am worried about my husband's mental health. I have my late night cry, many nights.

One of the most difficult parts is that I really feel fine and look fine, and it just seems very strange. You get through one day at a time. You keep going."

"My father's diagnosis was very grim, but we have seen more hope from Facebook support groups for people with CC. We are all very emotional but positive."

4. Experiences With Currently Available Treatments

Among the 27 survey respondents, 20 (74%) had or were currently receiving treatment, while seven (26%) had not received any treatment. Interestingly, only 67% of Canadians had received treatment while 85% of Americans had done so. Among the 20 who had received treatment, 60% had received surgery, 100% had or were currently receiving chemotherapy, and 20% had or were currently receiving radiation therapy. There was little or no different between Canadian and American responses. When presented with other potential treatments, only one patient (American) indicated receiving intra-arterial embolism and none of the Canadians or Americans had received any therapies targeted at specific gene mutations, with the exception of one Canadian who reported receiving pemigatinib (Pemazyre). In addition, two of the focus group participants (Canadian) were also receiving pemigatinib, all through special (compassionate) access from the manufacturer.

Given that bile duct cancer is very rare, highly aggressive, often diagnosed late, imminently life-threatening, and treatable with only a very few options, respondents were simply asked to describe in their own words the effectiveness of treatments experienced, tolerability of side effects, and their opinion as to whether treatment was "worthwhile"

There are two overarching themes regarding the experience of treatment that emerged from a content analysis of the responses. First, surgery, which is considered the 1st line option, was not always feasible or effective. Second, there are no chemotherapies specific for cholangiocarcinoma so patients experience considerable anxiety and uncertainty when undertaking course of treatment. There is limited reliable information about accessible treatment options on-line and many are highly reliant on their specialist to recommend and sometimes to source the best treatment option.

1. Resection (surgery) is worthwhile, if applicable, because it could "get rid" of the cancer. But it doesn't always work.

   "Surgery worthwhile as I was told by oncologist only way to cure this cancer is to cut it out"

   "Not effective. Resection done in august 2020 with good margins, not found anywhere else. Chemo done to "just be sure". May 2021 reoccurrence."

2. Given the short life expectancy and the few treatment options, chemotherapy can be worth the side effects if it can reduce symptoms and extend life.

   "The oncologist advised that 50% of patients diagnosed with this type of cancer, live up to 4 months; 10% up to 6 months and 5% up to a year."

   "The start of treatment (cisplatin and gemcitabine) with keytruda or placebo) really improved. Almost no more pain. No more need to take dilaudid."

   "Side effects are worth it if it will add years to your life. It's just hard to make plans around chemo because of side effects."

   "The treatments my husband received have been effective to date. The chemo was difficult to tolerate, but worth it since he is coming up on 3 years since diagnosis."

   "…the side effects on xeloda were tough...and I have developed trigger fingers in right hand quite bad requiring OT...and steroid injection...neuropathy in feet is bad...but I am alive and NED ...so thankful

   "Somewhat effective. It's been over 12 years since diagnosis. I will be starting Folfox in 2 days, so I believe it's worth trying."

5. Improved Outcomes

Responses on the effectiveness, side effectiveness, and value of available therapies point to the need for improved therapies and indeed improved outcomes but also convey the somewhat "resigned" and even "fatalistic" attitude of patients with rare conditions with limited research and development investment, few treatment options, and poor access to promising therapies. We identified the following themes on unmet needs.

1. There are not enough treatment options.

   "Chemo has shrunk my tumour however I am developing toxicity so have to discontinue soon. Surgery is not an option and I have no mutations radiation is next attempt but beyond that not sure what options I have."

   "There seems to be a lot more options in the USA then here in Canada, not sure how effective they are…"

   "Appalling options - death inevitable. It was worthwhile having some treatment as my sister was with us for a little longer, but it's an evil disease."

2. Quality of life is as important or more that quantity.

   "I am definitely into quality of life over quantity. So far I've done ok managing symptoms.

   "The oncologist also stated that the life expectancy might not change with treatment. The only reason that mom had undergone radiation, is the radiologist advised it might actually control the pain. The life experience remained the same."

3. Given the ability to diagnosis gene mutations, there needs to be more research to develop more targeted therapies.

   "I wish we had more options and it seems like now everyone is wanting to target FGFR which is only about 10% I believe of all patients...wish companies would move on and attempt to target other mutations that don't have a lot of meds...."

   "From our experiences, chemo might not be a first option when there are more treatment options than before, especially when chemo alone doesn't seem very effective for bile duct cancer. Yet, taking oral drugs such as FGFR2 inhibitors or TKI secure much better quality of life without travelling to hospitals according to busy schedule."

   "The treatments take a toll on the physical capabilities but they are worthwhile. Since it is a genetic mutation we remain hopeful that the right targeted therapy will be developed."

6. Experience With Drug Under Review

Given that a second targeted therapy for FGFR2 gene fusions (infigratinib or Truseltiq) was also being reviewed at this time by Health Canada (on the Project ORBIS collaborative framework), it made sense to ask about both of these drugs in this survey. Overall, about 12 (44%) of survey respondents did not know or were unsure they had been informed about targeted therapies for (any) gene mutations. About one-third (n=9) reported they had heard of either pemigatinib or infigratinib, or both, with a slightly higher proportion of Americans claiming knowledge that did Canadians. Two of the survey respondents (one Canadian and one American) and two of the focus group participants (both Canadian) reported direct experience with pemigatinib; none had experience with infigratinib. The focus group participants seemed to have accessed pemigatinib through compassionate access from the company.

"I had the FGFR2 mutation, so my doctor did what he could – I am on Pemazyre now – I don't know what he had to jump through or do to get it here, but it took 3-4 months before he could give me the drug."

Overall, respondents indicated they had to go through a period of adjustment (to get the right dosage) but overall had very little challenge dealing with the side effects of pemigatinib.

"First cycle was tough at 13.5 mg with multiple side effects, lowered to 9 for 2nd and 3rd cycles - this reduced side effects somewhat but not all. I am currently trying alternating 9/4.5 and all side effects have

stopped except hair loss, while it is still falling out some places have started to grow back (weird). Feeling a lot better daily not having to deal with certain side effects, outlook on life hasn't changed much as I know my time is limited. As I only have 1 daughter it is hard on her as she doesn't have a sibling to talk with, she already had anxiety and depression before I was diagnosed."

"I was okay for the most part with Pemazyre – I lost most of my hair, the first dosage was headaches, diarrhea, sore knuckles in fingers. I've tolerated most of it."

Those survey respondents who indicated some knowledge about the targeted therapies were asked to discuss their expectations for the medication and what they believed or hoped it would do for them. Several also indicated that their expectations were based on feedback and discussions in cholangiocarcinoma (CC) support groups.

1. The first overriding theme that emerged was the "realistic but hopeful" expectation that the therapy would stabilize or reduce tumour size and disease progression.

   "I am currently on Pemazyre … I am hoping for reduction in size of nodules and no new growth or at least stability."

   "My expectations are that they will be as effective as possible at shrinking or stopping the growth of tumours."

   "I have seen great success with patients on Pemazyre....i know someone who was on the trial and has done exceptionally well on it."

   "Hope they would give remission and/or stability."

   "Just help and maybe control disease for a certain amount of time, which would be a lot!"

2. The second emergent theme was the hope that these therapies would stimulate development of more targeted therapies.

   "I follow several CC support groups and read about folks who take these meds. Those who participate in these studies strongly encourage all CC patients to get genomic testing and apply for appropriate programs. Pemazyre seems especially well accepted. I have the IDH2 mutation and strongly hope for a targeted medication to treat it."

   "I was hoping for a second generation of FGFR2 inhibitors for when patients develop resistance to the current FGFR2."

   "I believe of all patients...wish companies would move on and attempt to target other mutations that don't have a lot of meds...."

3. Third, not exactly a theme, but it would be unconscionable not include the hope that these therapies, because they are targeted, could have long-lasting benefits and perhaps even a cure.

   "Hopefully they will prove to be effective in treatment and cure for CC."

7. Companion Diagnostic Test

Access to targeted therapies requires diagnostic testing for specific genomic mutations to ensure the appropriate patients have access to the right therapy.

8. Anything Else?

These respondents are typical of the bile duct cancer community, where diagnosis is often incidental and delayed, referral to the right specialists is by chance rather than directed, treatment options are few and mostly ineffectual, access is made worse by the lack of knowledge among treaters and their unavailability in many settings, and little hope is offered. The identification of gene mutations and the development of therapies that target these are the best news possible at this time.

Survey respondents were provided a brief overview about the FGFR2 gene mutation and how it works in bile duct cancer, a brief description of the two targeted therapies for FGFR2 mutations and the clinical trial results with each. They were asked to rate "…how important is it for bile duct cancer patients with FGFR2 fusions to have an option to access targeted therapies, if it is appropriate for them?"

All (100%) respondents indicated it was "very important" to have targeted therapies available. Some of the supporting comments were as follows.

"We need many options as everyone reacts differently with each treatment."

"These meds can be a huge game changer and have proven success in trials. Patients with FGFR MUST be given access to these meds."

"All cancer patients live on hope and these medications provide a substantial dose of that."

Finally, all respondents were given the opportunity to provide any additional recommendations or comments.

"We need to educate more about this cancer in Canada, there are very few oncologists that specialize in the treatment as it is rare."

"I am so glad that research on this cancer being done. This cancer is devastating lives, and young lives at that. At 70 years old, I feel I still have living to do and would happily try something that would help prolong my life if it doesn't mean quality of life is ruined. Targeted therapy sounds so much less invasive and more helpful in curing this cancer."

"No question, if it works on some people, it's still worth a try. Our drug approval systems are slow, that is the real problem. None of us can wait. This is an issue with time. We don't have time to waste."

"We need options. Options are what get us through. If I can get another 8 months of therapy that is doing some harm to the active cells, I will take it and hopefully during that time, a miracle would come along."

"It would be awesome. I benefited somewhat. Definitely, we need options. Hopefully it will be all available to us at some point. We should all be able to get it.

"There needs to be more research done to find a cure. Money from the government should be used as it is used in other research for different cancers."

"Canadians should have more options. It's a shame, I read posts about people in India complaining about their limited options and it's the same for us in Canada. I wish I was in the US."

"These targeted therapies will help other people with cancer who currently do not have treatment or whose treatment does not work. The more research we do on targeted therapies and the more access people have to these therapies the more we will be able to advance in this field."

Appendix: Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the CADTH reimbursement review process, 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.**

   This submission was completed by the staff and volunteers of CORD, the CLF, and the CCF. Outside input for this submission came from the patients and caregivers who participated in interviews and those who responded to the online survey.

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.**

   Data collection and analysis was completed by the staff and volunteers of CORD, the CLF, and the CCF.

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.**

   The Canadian Liver Foundation (CLF) is committed to bringing liver research to life for all Canadians through liver research, education, patient support and advocacy. The CLF receives funding from a variety of sources with the majority coming from donations from individuals across the country. We use these funds to support CLF liver awareness, education, patient support and research grant programs.

   The CLF receives some program funding in the form of unrestricted educational grants from pharmaceutical companies. Grant agreements are established in support of activities initiated by the CLF and prohibit the funder from having any input or influence in program objectives or deliverables.

Canadian Liver Foundation

Company	Check Appropriate Dollar Range			
	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
None				
None				
None				

Canadian Organization for Rare Disorders

Company	Check Appropriate Dollar Range			
	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
None				

Cholangiocarcinoma Foundation

Company	Check Appropriate Dollar Range			
	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Incyte Corporation				X
Taiho Oncology				X
QED Therapeutics				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: Durhane Wong-Rieger
Position: President & CEO
Patient Group: Canadian Organization for Rare DIsorders
Date: July 16, 2021