CADTH

CADTH REIMBURSEMENT REVIEW

Stakeholder Feedback on Draft Recommendation

pemigatinib (Pemazyre)

(Incyte Biosciences Canada Corporation)

Indication: Cholangiocarcinoma

December 16, 2021

CADTH

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Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	PC0252-000
Brand name (generic)	Pemazyre (Pemigatinib)
Indication(s)	For the treatment of adults with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma (CCA) with a FGFR2 fusion or other rearrangement.
Organization	The Canadian Gastrointestinal Oncology Evidence Network (CGOEN) and other cholangiocarcinoma-treating physicians
Contact information[a]	Dr. Vincent Tam Medical Oncologist [redacted]

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	☐
	No	☒

Please explain why the stakeholder agrees or disagrees with the draft recommendation. Whenever possible, please identify the specific text from the recommendation and rationale.

We disagree with the draft recommendation.

The prognosis of intrahepatic cholangiocarcinoma patients with FGFR2 fusions/rearrangements is poor. While the standard of care second-line treatment after progression on gemcitabine+cisplatin is currently a fluoropyrimidine-based regimen such as FOLFOX, the response rate and survival benefit of FOLFOX is small and some would argue whether it is clinically meaningful. Also, FOLFOX is an intravenous regimen requiring a central venous access device to administer, which comes at a significant cost to the healthcare system. The tolerability of FOLFOX in the second-line cholangiocarcinoma patient population is also questionable as most of these patients are more unwell and some have pre-existing neuropathy from cisplatin which could be worsened by oxaliplatin. An oral treatment option with less significant toxicities is more appropriate and this point appears to have been ignored.

In patients with FGFR2 fusions/rearrangements treated with pemigatinib the FIGHT-202 study showed an impressive response rate, disease control rate, and survival. A disease control rate of 82% and response rate of 35% likely leads to a meaningful delay in symptoms such as pain, bowel obstruction, gastric outlet obstruction, weight loss and liver failure. These are symptoms patients don't usually recover from with advanced cancer. Symptom control and quality of life also need to be considered in addition to survival benefit.

We agree with the clinical experts consulted by CADTH who noted *that "despite the high unmet need, conducting a randomized controlled trial in this setting with a targeted therapy, such as pemigatinib, compared to currently available therapies in second-line in Canadian clinical practice would likely not be feasible".* A randomized trial comparing pemigatinib to FOLFOX in FGFR2 fusion/rearrangement

positive cholangiocarcinoma certainly would be challenging to conduct given the rarity of these mutations. But, even if it was possible, such a trial would take a long period of time. As an example, the FIGHT 302 trial comparing pemigatinib to gemcitabine + cisplatin in first-line cholangiocarcinoma patients with FGFR2 rearrangement is currently being conducted. Nonetheless, the patients with this disease currently cannot wait for results from this clinical trial as they will not be alive at that time.

Due to the small number of cholangiocarcinoma patients who would be eligible for pemigatinib, poor prognosis and questionable clinical benefit with currently funded treatments, costs and toxicities associated with FOLFOX, we believe it would be beneficial for cholangiocarcinoma patients with FGFR2 fusions/rearrangements in Canada to have access to funded pemigatinib.

Further, we urge CADTH to develop a framework for assessing the value of drugs in settings with relatively small patient populations. HTA authorities requiring phase 3 trials in rare cancer settings essentially means that many important new therapies will simply not be funded -- as phase 3 trials will often not be feasible.

Expert committee consideration of the stakeholder input

2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes	☐
	No	☒

If not, what aspects are missing from the draft recommendation?

FOLFOX is an intravenous regimen requiring a central venous access device to administer, which comes at a significant cost to the healthcare system. The tolerability of FOLFOX in the second-line cholangiocarcinoma patient population is also questionable as most of these patients are more unwell and some have pre-existing neuropathy from cisplatin which could be worsened by oxaliplatin.

A disease control rate of 82% and response rate of 35% likely leads to a meaningful delay in symptoms such as pain, bowel obstruction, gastric outlet obstruction, weight loss and liver failure. These are symptoms patients don't usually recover from with advanced cancer. Symptom control and quality of life need to be also considered in addition to survival benefit.

An oral treatment option with less significant toxicities and likely delaying onset of severe symptoms is more appropriate and these points appear to have been ignored.

This network of biliary cancer experts consider the FIGHT 202 data to be exciting and practice changing for this rare subset of terminal patients. To deny funding now disadvantages Canadian patients compared to other countries including in the U.S. where pemigatinib has been approved since April 2020 and is widely reimbursed, and in the U.K. where pemigatinib is listed on the National Health Service based on the NICE appraisal.

Clarity of the draft recommendation

3. Are the reasons for the recommendation clearly stated?	Yes	☒
	No	☐

If not, please provide details regarding the information that requires clarification.

4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☐
	No	☐

If not, please provide details regarding the information that requires clarification.

5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☐
	No	☐
If not, please provide details regarding the information that requires clarification.		

[a] CADTH may contact this person if comments require clarification.

Declaration for Vincent Tam

Clinician Information	
Name	*Vincent Tam*
Position	*Medical Oncologist, Tom Baker Cancer Centre*
Date	*20-12-2021*
☒	**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.

Conflict of Interest Declaration

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 Biosciences Canada	☒	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

CADTH Reimbursement Review

Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	PC0252
Name of the drug and Indication(s)	Pemigatinib for cholangiocarinoma
Organization Providing Feedback	PAG

1. Recommendation revisions Please indicate if the stakeholder requires the expert review committee to reconsider or clarify its recommendation.		
Request for Reconsideration	**Major revisions:** A change in recommendation **category** or patient **population** is requested	☐
	Minor revisions: A change in reimbursement **conditions** is requested	☐
No Request for Reconsideration	**Editorial revisions:** Clarifications in recommendation **text** are requested	☐
	No requested revisions	X

2. Change in recommendation category or conditions Complete this section if major or minor revisions are requested
None.

3. Clarity of the recommendation Complete this section if editorial revisions are requested for the following elements
a) Recommendation rationale
In Table 4 Summary of Economic Evaluation, in the “Treatment” row, PAG is suggesting adding the dosing schedule here as it helps to put the submitted price into context.
b) Reimbursement conditions and related reasons
None.
c) Implementation guidance
None.

CADTH Pemazyre Patient Response

Initial reactions to recommendation

As a patient advocacy organization for patients with rare conditions, having spoken directly with cholangiocarcinoma (CCA) patients with FGFR2 fusion in preparation for our Patient Submission, our initial reactions to the CADTH Recommendations for Reimbursement of pemigatinib (Pemazyre) were disappointment and distress. However, in reading through the rationale for rejection, we became increasingly overwhelmed by disbelief in the convoluted rationale for discounting the clinical trial evidence and patient testimonials and finally by despair that patients who were currently benefitting from Pemazyre risked discontinuation and those recently diagnosed who could have benefitted would probably never get the chance for the only directed therapy.

Joint Submission to CADTH

As presented in the joint submission from three patient organizations, Canadian Organization for Rare Disorders, Canadian Liver Foundation, the Cholangiocarcinoma Foundation, patients experience CCA as a major impact in their physical condition (pain, severe GI problems, neuropathy, insomnia) as well as significant impact on their overall quality of life, including daily living activities, relationships, sexual desire, and depression. Worse, because CCA is very aggressive and life-threatening in addition to being rare, many patients remain undiagnosed or misdiagnosed until the disease has progressed to an advanced level. And worst of all, again due to rarity, there have been no approved CCC-specific treatments and no evidence-based consensus on best practice guidelines, with surgery, chemotherapy, and radiation provided based on the judgment of the clinician. The identification of genetic mutations that could be treated with highly targeted therapies was a cause for hope and the outcomes for overall survival, progression free survival, and quality of life (as an oral therapy with few serious adverse effects) were strong enough to gain regulatory approval by Health Canada as well as other regulators and reimbursement in other jurisdictions.

Patient response to CADTH rejection for reimbursement

Patient experience: CADTH acknowledged the joint patient group input specifying the detrimental effects of CCC as well as the expectations for improved therapy, namely improved prognosis, quality of life, tumour response, and disease progression. However, the committee suggests in their overall recommendation that “pERC was uncertain whether pemigatinib meets the need given the limitations associated with the evidence reviewed.” This is an unacceptable rationale for denial. Two overarching points. First, the evidence was of sufficient quality, based on the clinical trials, for the regulatory to approve the therapy for the specific patient population (CCC with FGFR2 fusions). Second, it is clear that the patient perspective has not been incorporated into the assessment process. The patients who testified were very certain about the impact, and this was not balanced against the “limitations” cited.

We acknowledge the concerns based on the heterogeneity across study designs and populations. A solution is to conduct (post-hoc) subgroup analyses recognizing the sample sizes will be even smaller and no traditional statistical analyses would be appropriate. But trends and themes could indeed be identified that could be further tested with subsequent studies or,

better, real-world evidence. These forms of "managed access" entry programs must be considered as viable options for these types of conditions and treatments, especially where the disease is aggressive, progressive to death, and effective validated options are limited or non-existent.

We were certainly disappointed and dismayed that pERC (CADTH) acknowledged, up front, that "given the rarity of FGFR2 positive CCA, … a randomized controlled trials in this setting with pemigatinib was likely not to be feasible…"
Nevertheless, they go on to criticize the evidence from the Phase II trials using a traditional lens of common drugs, including: "use of ITC in lieu of direct comparative evidence" and "the limitations and inherent biases of small non-comparator studies and their risk of providing unreliable efficacy estimates." The results and analyses are only found wanting if one is expecting data from RCTs with large samples and long-term follow up.

This response is all the more ironic given the very recently published note on "How CADTH Uses Patient Perspectives" where example after example is touted as evidence that patient input has an impact on CADTH decision making. We reference specific examples from this document on patient input "to understand what it is like to live with illness, as experienced by patients." Also, "to appreciate the goals of treatment and what it means for these to be met or missed." And, most relevant here, "to help interpret clinical trial results."

So, do patient submissions make a difference in the assessments and recommendations, or not? CORD was hoping to speak with additional patients who had experience with Pemazyre to supplement our previous testimonials, but the timing was too tight to connect and obtain consent. However, we were able to connect with one of the Patient Support Program managers and got very important feedback on patient responses not just to Pemazyre but also to the value of "hassle-free" access. We provide a summary of the feedback.

According to one patient, "Prior to enrolling [in the PSP], I thought I was going to sell my house so I could spend my last Christmas with family. I did not believe was I going to be able to get any help with the medication. I felt so bad that I would not be able to provide any toys to my grandchildren." This 60-year-old patient had had several different treatments prior to Pemazyre, which she received as part of the (extended) clinical trials. Upon completion she was continuing to receive support through a company-sponsor patient support program. The patient is stable on the treatment and has been on the same dosage for the past eight months.

Overall, among the 10 patients enrolled in the PSP, all are very grateful to be able to continue access to Pemzyre. "I can focus getting better and not worry about paying for these medicines. "I can focus on my family and spending time with them." "Thank you so many times over."

Reconsideration

We urge CADTH (pERC) to reconsider their assessment and analysis using the lens of an ultra-rare condition that is very severe, progressive, life-ending with no other effective treatments. We urge them to consider the evidence within the framework of Phase II clinical trials as the only option and therefore to consider the limitations within a framework of what they do tell us about the potential efficacy and safety, and importantly, how they can be used under monitored settings, with the goal of collecting evidence, including patient-centred outcomes, in

real-world settings. We are certain this will open up opportunities for appropriate patients with CCA and FGFR2 fusions.

Submission by:

Durhane Wong-Rieger

Canadian Organization for Rare Disorders

[redacted]