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Reimbursement Recommendation

Pemigatinib (Pemazyre)

Indication: For the treatment of adults with previously treated, unresectable locally advanced or metastatic Cholangiocarcinoma with a FGFR2 fusion or other rearrangement.

Sponsor: Incyte Biosciences Canada Corporation

Recommendation: Reimburse with conditions

Summary

What Is the Reimbursement Recommendation for Pemazyre?

Canada's Drug Agency (CDA-AMC) recommends that Pemazyre be reimbursed by public drug plans for the treatment of adults with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma (CCA) with an *FGFR2* fusion or other rearrangement if certain conditions are met.

Which Patients Are Eligible for Coverage?

Pemazyre should only be covered to treat adult patients with advanced, metastatic, or surgically unresectable CCA confirmed by histology or cytology, have *FGFR2* abnormalities (fusions or other rearrangements), have received at least 1 prior systemic therapy, and are in relatively good health (as measured by performance status).

What Are the Conditions for Reimbursement?

Pemazyre should only be reimbursed if prescribed by clinicians with expertise in managing patients with gastrointestinal malignancies and if the cost of Pemazyre is reduced.

Why Did CDA-AMC Make This Recommendation?

- Evidence from a clinical trial demonstrated that Pemazyre helped shrink tumours in 37% of patients, and these responses lasted for about 9 months. The impact of Pemazyre on patients' quality of life could not be determined due to the study's design and fewer patients being available for assessment over time.
- The sponsor compared Pemazyre to other treatments. While Pemazyre showed better results for progression-free survival (PFS) and overall survival (OS), the analysis had significant limitations. Therefore, there's still uncertainty about the extent of the benefits pemigatinib offers for OS or PFS compared to other treatments.
- Patients identified a need for treatments that improve tumour response, delay disease progression, and improve quality of life. Pemazyre meets some of the needs identified by patients, including providing additional treatment options and achieving durable tumour responses with the potential to delay disease progression.
- Based on the CDA-AMC assessment of the health economic evidence, Pemazyre does not represent good value to the health care system at the public list price. A price reduction is therefore required.

Summary

- Based on public list prices, Pemazyre is estimated to cost the public drug plans approximately $64 million over the next 3 years. However, the actual budget impact is uncertain.

Additional Information

What Is CCA?

CCA is a type of cancer that forms in the bile ducts. It is a rare disease with approximately 400 new cases of CCA diagnosed each year in Canada. *FGFR2* genetic alterations are uncommon, occurring in 10% to 20% of patients with CCA. Approximately 10% of patients are expected to be alive 5 years after their diagnosis.

Unmet Needs in CCA

There is currently no standard of care for patients with CCA after unsuccessful first-line treatment. Available treatments for patients with CCA after unsuccessful first-line treatment have limited effectiveness and are associated with a number of side effects.

How Much Does Pemazyre Cost?

Treatment with Pemazyre is expected to cost, on average, $15,499 per 28 days (assuming 13.5 mg is administered orally once daily for 14 consecutive days followed by 7 days off therapy, in 21-day cycles).

Recommendation

This recommendation supersedes the pan-Canadian Oncology Drug Review Expert Review Committee (pERC) recommendation for this drug and indication dated April 2022.

The CDA-AMC pERC recommends that pemigatinib be reimbursed for the treatment of adults with previously treated, unresectable locally advanced or metastatic CCA with an *FGFR2* fusion or other rearrangement only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One single-arm, open-label, phase II trial (FIGHT-202) demonstrated that treatment with pemigatinib resulted in clinically meaningful benefit based on durable tumour responses in adult patients with previously treated, unresectable locally advanced or metastatic CCA with an *FGFR2* fusion or other rearrangement. The FIGHT-202 trial achieved the predetermined threshold for a positive outcome (lower limit of the 95% confidence interval [CI] for objective response rate [ORR] > 15%) in cohort A (N = 107). ORR was assessed by an independent radiological review committee using central genomics laboratory results and required confirmation of complete response (CR) and partial response (PR) at least 4 weeks after the initial assessment. The proportion of patients with an objective response was 35% (95% CI, 26.50% to 45.35%) and the median duration of response (DOR) was 7.49 months (95% CI, 5.65 to 14.49 months) with a median follow-up time of 15.44 months. At the final analysis (median follow-up time was 45.4 months), the objective response was 37% (95% CI, 27.94% to 46.86%) and the median DOR was 9.13 months (95% CI, 6.01 to 14.49 months), in addition, the median OS was 17.48 months (95% CI, 14.36 to 22.93 months) and the median PFS was 7.03 months (95% CI, 6.08 to 10.48 months). pERC considered these response outcomes to be clinically meaningful in a rare patient population with limited standard of care options and a setting where conducting phase III trials might not be feasible. pERC was unable to draw any conclusions on the effect of pemigatinib on health-related quality of life (HRQoL) based on the available evidence given the noncomparative, open-label design of the trial, and the substantial decline in patients available to provide assessments over time. Due to the noncomparative design of the FIGHT-202 trial, the estimate of the relative treatment effect of pemigatinib compared with other relevant treatment options is uncertain. The sponsor submitted an indirect treatment comparison (ITC) of pemigatinib to relevant comparators in Canada (mFOLFOX regimen [modified leucovorin calcium {folinic acid} + fluorouracil + oxaliplatin] plus active symptom control [ASC] and ASC alone), while the results of the ITC favoured pemigatinib for PFS and OS in comparison with mFOLFOX plus ASC as well as with ASC alone, there were significant limitations of the analysis. Overall, uncertainty remains around the magnitude of the additional benefit that pemigatinib provides for OS or PFS versus comparators.

pERC acknowledged the rarity of CCA that is *FGFR2*-positive and the significant unmet need for additional treatment options in this setting given the severe nature of this disease and its substantial morbidity. Patients identified a need for treatments that improve tumour response, delay disease progression, improve HRQoL, are orally administered, and have acceptable toxicity levels. Given the totality of the evidence, pERC

concluded that pemigatinib meets some of the needs identified by patients, including providing additional treatment options and achieving durable tumour responses with the potential to delay disease progression. Furthermore, pemigatinib is orally administered and has an acceptable toxicity profile.

The cost-effectiveness of pemigatinib is highly uncertain due to the high degree of uncertainty of the magnitude of clinical benefit of pemigatinib compared with ASC alone and mFOLFOX plus ASC. As such, a base-case cost-effectiveness estimate was unable to be determined in adult patients with previously treated, unresectable, locally advanced, or metastatic CCA with an *FGFR2* fusion or rearrangement.

The committee considered exploratory analyses conducted by CDA-AMC which reflect more appropriate assumptions but remain highly uncertain given the absence of robust comparative data on PFS and OS for pemigatinib versus ASC alone and mFOLFOX plus ASC. In CDA-AMC reanalyses, the incremental cost-effectiveness ratio for pemigatinib relative to ASC alone and mFOLFOX plus ASC was estimated to be $252,718 and $261,226 per quality-adjusted life-year (QALY) gained, respectively, using the sponsor-submitted price for pemigatinib and publicly listed price for all other drugs. Pemigatinib was therefore not considered cost-effective at a $50,000 per QALY gained willingness-to-pay threshold. Price reductions exceeding 95% would be required for pemigatinib to achieve an incremental cost-effectiveness ratio of $50,000 per QALY gained. The price reduction is influenced by the cost of testing, which is estimated to be $38,000 to identify a single patient eligible for treatment with pemigatinib. If testing costs were $0, a price reduction of 77% (versus ASC alone) and 72% (versus mFOLFOX and ASC) would be required to achieve cost-effectiveness at a willingness-to-pay per QALY gained of $50,000.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Treatment with pemigatinib should be initiated in adults who have all of the following: 1.1. Histologically or cytologically confirmed advanced, metastatic, or surgically unresectable CCA with *FGFR2* abnormalities (fusions or other rearrangements).	The results of cohort A of the FIGHT-202 trial achieved the predetermined threshold for a positive outcome (lower limit of the 95% CI for ORR > 15%) in patients with characteristics listed in this condition. Cohort A included patients with *FGFR2* fusions or rearrangements and was the focus of this review.	—
2. Patients must have received at least 1 line of prior systemic therapy.	The Health Canada indication specifies that pemigatinib be used in patients who have been previously treated for unresectable locally advanced or metastatic CCA with an *FGFR2* fusion or other rearrangement. In addition, patients enrolled in the FIGHT-202 trial had to have a documented disease progression after at least 1 line of prior systemic therapy.	pERC noted that patients who are intolerant to first-line treatment would be eligible for pemigatinib.
3. Patients must have good performance status.	Patients with ECOG PS of greater than 2 were excluded from the FIGHT-202 trial.	—

Reimbursement condition	Reason	Implementation guidance
Discontinuation		
4. Treatment with pemigatinib should be discontinued upon the occurrence of the following: 4.1. documented disease progression 4.2. unacceptable toxicity.	This review identified no evidence that continuing treatment with pemigatinib in patients whose disease has progressed is effective. Patients who are unable to complete treatment with pemigatinib due to unacceptable toxicity would likely not be able to receive further treatment with pemigatinib.	—
Prescribing		
5. Pemigatinib should only be prescribed by clinicians with expertise and experience in the treatment of GI malignancies.	To ensure that pemigatinib is prescribed only for appropriate patients	—
Pricing		
6. A reduction in price.	The cost-effectiveness of pemigatinib is highly uncertain due to the high degree of uncertainty of the magnitude of clinical benefit of pemigatinib compared with mFOLFOX plus ASC and ASC alone. Based on an exploratory analysis, the ICER for pemigatinib vs. mFOLFOX plus ASC and ACS alone was estimated to be $261,226 and $252,718 per QALY gained, respectively. Price reductions exceeding 95% are required to achieve an ICER of $50,000 per QALY gained. This price reduction is influenced by the cost of testing, which is estimated to be $38,000 to identify a single patient eligible for treatment with pemigatinib. If testing costs were $0 then to be cost-effective relative to mFOLFOX plus ACS, a 72% price reduction for pemigatinib is needed or 77% vs. ACS alone.	—
Feasibility of adoption		
7. The feasibility of adoption of pemigatinib must be addressed.	At the submitted price, the magnitude of uncertainty in the budget impact must be addressed to ensure the feasibility of adoption, given the difference between the sponsor's estimate and the CDA-AMC estimate(s).	—
8. The organizational feasibility of conducting *FGFR2* genetic testing must be addressed.	*FGFR2* testing is required to determine eligibility for initiation of treatment with pemigatinib. pERC acknowledged that *FGFR2* genetic testing might not be available in all jurisdictions in Canada, and that requiring *FGFR2* molecular testing to determine eligibility to receive treatment is anticipated to impact laboratory, molecular, and pathology resources.	

ASC = active symptom control; CCA = cholangiocarcinoma; CDA-AMC = Canada's Drug Agency; CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group Performance Status; GI = gastrointestinal; ICER = incremental cost-effectiveness ratio; mFOLFOX = modified leucovorin calcium (folinic acid) + fluorouracil + oxaliplatin; ORR = objective response rate; pERC = pan-Canadian Oncology Drug Review Expert Review Committee; QALY = quality-adjusted life-year; vs. = versus.

Discussion Points

- **Criteria for significant unmet need are met:** pERC noted that there was uncertainty with the clinical evidence; therefore, the committee deliberated on pemigatinib considering the criteria for significant unmet need described in the Procedures for Reimbursement Reviews on the CDA-AMC website. Patient groups, clinician inputs, and the clinical experts consulted by CDA-AMC highlighted that CCA is an aggressive biliary tract cancer (BTC) with poor prognosis. Other than standard of care chemotherapy, there are currently no standard funded regimens for adult patients with previously treated, unresectable locally advanced or metastatic CCA with an *FGFR2* fusion or other rearrangement. Considering the rarity and severity of the condition, and the absence of clinically effective alternatives, the committee concluded that the available evidence reasonably suggests that pemigatinib has the potential to delay disease progression, although the available evidence is associated with uncertainty.
- **Feasibility randomized controlled trial (RCT):** pERC agreed with the clinical experts that the responses observed in the FIGHT-202 trial were clinically meaningful and durable in patients treated in a second-line treatment setting. pERC noted the number of challenges in interpreting the trial results due to the limitations in the study design. However, pERC agreed with the clinical experts that, despite the significant unmet need in this patient population, conducting an RCT of pemigatinib compared with palliative chemotherapy would not be feasible.
- **HRQoL:** Patients and clinicians highlighted maintenance or improvement in HRQoL as an important outcome and treatment goal in adult patients with previously treated, unresectable, locally advanced, or metastatic CCA with an *FGFR2* fusion or other rearrangement. The results for HRQoL from the FIGHT-202 trial were inconclusive due to the single-arm, open-label design, and the small number of patients completing assessments at the specified time point. As a result, pERC could not conclude that pemigatinib would meet this important need. Additionally, there were no HRQoL outcomes evaluated in the ITCs, and the comparative effect of pemigatinib on HRQoL versus other active treatments remains unknown.
- **Generalizability of the results:** pERC discussed the generalizability of the FIGHT-202 trial results with patients with extrahepatic *FGFR2*-positive CCA. pERC considered that results observed in cohort A are likely generalizable to patients with extrahepatic *FGFR2*-positive CCA given that patients with intrahepatic and extrahepatic CCA are managed in a similar way in clinical practice, *FGFR2* is the target of the mechanism of action of pemigatinib, and there is no biological rationale to assume that pemigatinib would not provide benefit with an acceptable safety profile to patients with extrahepatic CCA. pERC also noted that *FGFR2* fusions are rare in nonintrahepatic CCA.
- **Cohorts in FIGHT-202 study:** pERC discussed that patients in the FIGHT-202 trial were assigned to 3 cohorts based on their *FGF-FGFR* status: cohort A (*FGFR2* fusions or rearrangements), cohort B (*FGF-FGFR* alterations other than *FGFR2* fusions or rearrangements), and cohort C (negative for *FGF-FGFR* alterations). This pERC recommendation focuses on cohort A (*FGFR2* fusions or rearrangements), as cohorts B and C were not included in the requested reimbursement criteria

and were not submitted for approval to Health Canada, thus falling outside the scope of this recommendation.

- **Indirect evidence:** pERC discussed the sponsor-submitted ITCs in the form of an unanchored matching-adjusted indirect comparison (MAIC). The results of the ITC favoured pemigatinib for PFS and OS in comparison with mFOLFOX plus ASC as well as with ASC alone. pERC noted that there were several limitations identified with the sponsor's submitted MAIC, including heterogeneity across study designs and populations and the inability to adjust for all potential confounders and prognostic variables in the MAIC. pERC also noted that *FGFR2* might be a prognostic factor, and that the control groups from the ABC-06 trials were for all comers, and therefore the ITC was not accounting for the potential influence of the imbalance of *FGFR2* between the FIGHT-202 trial and the control groups from the ABC-06 trials. pERC noted that given the absence of robust comparative data on PFS and OS, the ability to interpret the relative treatment effects observed between pemigatinib and leucovorin calcium (folinic acid) + fluorouracil + oxaliplatin (FOLFOX) plus ASC and ASC alone was limited, and no firm conclusions could be drawn on how pemigatinib compared with other relevant treatment options.
- **Need for ophthalmology exams:** pERC highlighted the necessity of conducting a comprehensive ophthalmological examination, including visual acuity tests, slit-lamp examinations, fundoscopy, and optical coherence tomography, before starting pemigatinib treatment and these examinations should be repeated as per the recommendation in the product monograph. pERC also noted that pemigatinib can cause serous retinal detachment, which may manifest as blurred vision, visual floaters, or photopsia.
- **Real-world evidence (RWE):** pERC agreed with the clinical experts that, despite the limitations associated with the RWE studies submitted, the results shown were consistent with the pivotal trial and increased confidence in the results of the pivotal trial.
- **Availability of *FGFR2* testing:** pERC noted that the pharmacoeconomic reanalysis assumed that *FGFR2* testing was not publicly funded without pemigatinib. Feedback from the sponsor indicated that *FGFR2* testing is currently available and funded in Alberta and Ontario and may be provided on a case-by-case basis in Nova Scotia and New Brunswick.

Background

Gallbladder cancer and CCA are known as BTCs accounting for 10% to 15% of all primary liver cancer. In Canada and the US, respectively, there are approximately 400 to 5,000 new cases of CCA diagnosed each year. Symptoms commonly appear when a bile duct is blocked and include jaundice, itching, light-coloured greasy stools, dark urine, abdominal pain, loss of appetite and weight loss, fever, and nausea and vomiting. One of the most frequent genetic alternations in patients with intrahepatic CCA involve *FGFR2*. The *FGFR2* fusions or rearrangements are found in 10% to 20% of patients with intrahepatic CCA, while they rarely occur in extrahepatic CCA. While there is strong genetic and functional evidence that *FGFR* genetic alternations

can drive the formation of tumours, it is currently not known, if patients with *FGFR2*-positive alterations represent a distinct prognostic subgroup.

For patients with advanced-stage or unresectable CCA and with good Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1, standard of care first-line treatment is gemcitabine-platinum (cisplatin or carboplatin) in combination with immunotherapy (durvalumab or pembrolizumab). The clinical experts consulted by CDA-AMC noted that treatment options are limited for patients in second-line setting once the disease has progressed on first-line treatment. The ABC-06 trial evaluated the efficacy and safety of FOLFOX plus ASC compared with ASC alone in patients with locally advanced or metastatic BTC (including CCA and gallbladder or ampullary carcinoma) who had progressed on first-line cisplatin and gemcitabine therapy. At the median follow-up time of 21.7 months, median OS was 6.2 months in the FOLFOX group and 5.3 months in the control group (hazard ratio [HR] = 0.69; 95% CI, 0.50 to 0.97; P = 0.031); median PFS was 4 months in the FOLFOX group; and objective response was observed in 5% of patients in the FOLFOX group. In the absence of effective treatment options in the second-line setting, participation in clinical trial and best supportive care are recommended including alleviating biliary obstruction and full access to palliative care and symptom management.

Pemigatinib is a small molecule kinase inhibitor with antitumour activity by inhibiting *FGFRs*. *FGFRs* are receptor tyrosine kinases that activate signalling pathways in tumour cells. On September 17, 2021, pemigatinib was approved by Health Canada for the treatment of adults with previously treated, unresectable locally advanced or metastatic CCA with an *FGFR2* fusion or other rearrangement. Oral pemigatinib is available as 4.5 mg, 9 mg, and 13.5 mg tablets. The recommended starting dose is 13.5 mg administered orally for 14 consecutive days followed by 7 days off therapy, in 21-day cycles. The product monograph states that treatment is to be continued until disease progression or unacceptable toxicity. Furthermore, it is recommended to initiate a low phosphate diet when the phosphate level is more than 5.5 mg/dL and to consider adding a phosphate lowering therapy when the level is more than 7 mg/dL. The dose of phosphate lowering therapy is to be adjusted until the phosphate level returns to less than 7mg/dL. It is recommended to consider discontinuing phosphate lowering therapy during pemigatinib treatment breaks or if the phosphate level falls below normal.

Submission History

In 2022, pemigatinib was reviewed by CDA-AMC for the treatment of adult patients with previously treated, unresectable, locally advanced, or metastatic CCA with an *FGFR2* fusion or other rearrangement and received a do not reimburse recommendation. pERC deliberated on the evidence available from the FIGHT-202 trial as well as an ITC of pemigatinib compared to FOLFOX. While pERC acknowledged the rarity of *FGFR2*-positive CCA, ultimately the uncertainty related to the noncomparative evidence provided by the FIGHT-202 trial led to the recommendation against reimbursing pemigatinib. As part of this resubmission, the sponsor has submitted 4 additional studies that provide RWE in support of the FIGHT-202 trial data for pemigatinib.

Sources of Information Used by the Committee

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

- a review of 1 single-arm phase II trial in adult patients with previously treated, unresectable locally advanced or metastatic CCA with an *FGFR2* fusion or other rearrangement; 1 ITC; and 4 additional studies addressing gaps in the evidence
- patients' perspectives submitted via 2 patient input submissions, a joint submission from 5 patient groups: Cholangio-Hepatocellular Carcinoma Canada, Colorectal Cancer Resource & Action Network, Canadian Cancer Survivor Network, Canadian Cholangiocarcinoma Collaborative, and Gastrointestinal Society, and a separate input from the Cholangiocarcinoma Foundation (CCF)
- input from public drug plans and cancer agencies that participate in the reimbursement review process
- 2 clinical specialists with expertise diagnosing and treating patients with CCA
- input from 1 clinician group, the Canadian Gastrointestinal Oncology Evidence Network, additionally 1 individual physician submitted input
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Perspectives of Patients, Clinicians, and Drug Programs

Patient Input

Two patient group inputs were received for this review. A joint input from 5 patient groups: Cholangio-Hepatocellular Carcinoma Canada, Colorectal Cancer Resource & Action Network, Canadian Cancer Survivor Network, Canadian Cholangiocarcinoma Collaborative, and Gastrointestinal Society, and a separate input from the CCF were received for this submission. The joint input was based on telephone and Zoom interviews with a total of 12 respondents who had treatment experience with pemigatinib. Among them, 11 participants were across Canada (British Columbia, Alberta, and Ontario) and 1 from Israel.

The joint patient input highlighted the absence of any reimbursable first-line targeted therapy for CCA patients in Canada with the *FGFR2* fusion mutation. The respondents interviewed in the joint input reported varying symptoms associated with chemotherapy, including nausea; loss of train of thought; inability to move; hair loss; swelling of the feet, hands, and face; and shortness of breath on exertion. Respondents also indicated that their quality of life had been impacted while they were on systemic chemotherapy. Respondents highlighted some aspects of their treatment which were more difficult to control, such as complications while taking treatments, inability to access pemigatinib due to its high cost, and difficulty in controlling side effects (i.e., nausea, shortness of breath, flu-like symptoms, fatigue, inability to move, drowsiness, constipation, and poor quality of life).

On the other hand, the CCF input highlighted that for patients with *FGFR2* fusions or rearrangements, treatment using pemigatinib represents both an alternative as well as a chance at improved outcomes. The

patients interviewed in the joint input emphasized that the side effects were worth the benefits with respect to their quality of life while on the targeted drug. The input also pointed to the drug's feasibility and convenience for patients due to its oral administration. The CCF input further noted that the inability to access pemigatinib places an undue burden on patients who are already going through a challenging phase.

Clinician Input

Input From Clinical Experts Consulted by CDA-AMC

The clinical experts consulted by CDA-AMC indicated that there are currently no effective standard funded second-line treatment options. Palliative therapy (e.g., FOLFOX, leucovorin calcium (folinic acid) + fluorouracil + irinotecan hydrochloride [FOLFIRI], fluorouracil [5-FU], and capecitabine) and best supportive care are recommended for patients in this target setting. The clinical experts identified an unmet need for effective therapies with acceptable toxicity profiles that achieve disease control, delay worsening of symptoms, maintain HRQoL, delay disease progression, and prolong survival. The clinical experts consulted by CDA-AMC stated that pemigatinib was to be used in adult patients with previously treated, unresectable locally advanced or metastatic CCA with an *FGFR2* fusion or other alterations as per the FIGHT-202 trial. Among patients enrolled in cohort A of the FIGHT-202 trial, the clinical experts did not identify any patient subgroups who would potentially be either best suited for or benefit the least from pemigatinib. The clinical experts consulted by CDA-AMC felt that it would be reasonable to generalize the results from cohort A to patients with *FGFR2* alterations, who are intolerant to first-line therapy.

The clinical experts agreed that patients would be identified as possible candidates for pemigatinib if they had an *FGFR2* alteration. Clinical assessment to evaluate the response to treatment with pemigatinib would include regular radiological imaging (i.e., CT and/or MRI) and a CA19-9 biomarker test every 2 to 3 months to determine if a patient experiences disease progression. In addition, patients would be seen by an oncologist every 3 to 4 weeks for clinical assessment (i.e., to assess disease symptoms and the patient's performance status). The clinical experts indicated that the most clinically meaningful responses to treatment include disease control (i.e., disease stability or response), improvement in disease-related symptoms, better pain control, weight gain, regaining a more active lifestyle, maintenance of HRQoL, and prolonged PFS and OS. Acceptable drug-related toxicity was also noted as a clinically meaningful outcome.

In the opinion of the clinical experts consulted by CDA-AMC, treatment with pemigatinib should be discontinued if a patient experiences disease progression, has a worsening performance status, is intolerant to or experiences unacceptable toxicity from pemigatinib (which cannot be improved with dose delays or reductions), or the patient may not be interested in continuing treatment.

Clinician Group Input

Clinician group input was received from the Canadian Gastrointestinal Oncology Evidence Network and other physicians treating CCA for this review. The clinicians noted that the treatment goals for the management of CCA are extending survival, delaying disease progression, and maintaining quality of life while in therapy. In terms of unmet needs, the clinicians suggested that new second-line treatments with a meaningful survival benefit are required for this patient population. The clinicians in this input anticipated that pemigatinib would

offer patients improved efficacy in terms of survival, PFS, response rate, and disease control. The clinicians further suggested that it would be reasonable to consider pemigatinib upfront for patients deemed unsuitable for cisplatin or gemcitabine plus durvalumab or pembrolizumab as first-line therapy. The clinicians from this input emphasized that a clinically meaningful response to treatment would be to achieve tumour control (response or disease stabilization) and to maintain or improve quality of life.

A clinician submission was received from a single community oncologist with experience treating 2 patients with CCA with pemigatinib. The first patient had been diagnosed in their 70s and responded well to first-line chemotherapy and radiation, controlling the disease for 3 years. When the tumour began to grow again, the patient received gemcitabine and cisplatin, although the disease progressed after a few months. Testing revealed *FGFR2* fusion, and the patient was able to enrol in the patient support program to receive pemigatinib. This patient has continued to respond to pemigatinib for 2.5 years. The second patient that was treated with pemigatinib was a 26-year-old female that had recently given birth. The clinician noted that while the response was brief of 4 months, the improvement in quality of life and the time she was able to spend with her child was precious. The clinician reiterated their belief that based on RWE and the status as standard second-line therapy with patients with CCA and *FGFR2* fusion or other alterations elsewhere in the world, that pemigatinib should be reimbursed in Canada.

Drug Program Input

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

- considerations of relevant comparators
- considerations for initiation of therapy
- care provision issues
- system and economic issues.

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

Table 2: Responses to Questions from the Drug Programs

Implementation issues	Response
Relevant comparators	
There is no established standard of care. IV chemotherapy (e.g., mFOLFOX, FOLFIRI, capecitabine, or best supportive care) may be used. New evidence submitted for this review is not comparative data.	This is a comment from the drug programs to inform pERC deliberations.
Considerations for initiation of therapy	
Patients with an ECOG PS of 0 to 2 were eligible for the FIGHT-202 trial as well as the RWE evidence submitted. Can patients with ECOG PS > 2 be eligible for treatment?	The clinical experts agreed that patients with an ECOG PS of 3 were not included in the available evidence for pemigatinib, as well as being unlikely to be offered treatment with

Implementation issues	Response
	pemigatinib due to being too unwell. pERC recommended that only patients with good performance status should be eligible to receive pemigatinib.
Standard first-line treatment is typically cisplatin and gemcitabine. Should patients who have experienced disease progression while on cisplatin and gemcitabine be eligible for pemigatinib?	pERC agreed with the clinical experts that patients that received cisplatin with gemcitabine based first-line therapy and then progressed should be eligible for pemigatinib.
Care provision issues	
Oral medication is available in 4.5 mg, 9 mg, and 13.5 mg tablets in a 14-day blister pack (not unit dose format). Recommended starting dose is 13.5 mg orally once daily for 14 consecutive days followed by 7 days off therapy, in 21-day cycles. Wastage is not considered in economic analysis but is likely to occur when dose adjustment is needed or when patients are admitted to hospital.	This is a comment from the drug programs to inform pERC deliberations.
Serous retinal detachment with symptoms of blurred vision, visual floaters, or photopsia (estimated in 11%; 1.3% grade 3 to 4). The product monograph suggested to have comprehensive ophthalmological examination including optical coherence tomography before initiation and every 2 months for the first 6 months then every 3 months thereafter. For onset of visual symptoms refer patient for urgent ophthalmologic evaluation then every 3 weeks until resolution or discontinuation of pemigatinib. Cost of ophthalmological exams should be considered in economic analysis.	This is a comment from the drug programs to inform pERC deliberations.
Review for drug interactions needed; interacts with CYP3A inhibitors and inducers.	This is a comment from the drug programs to inform pERC deliberations.
Genetic testing (*FGFR2*) for CCA is not always funded routinely, this testing needs to be funded in conjunction with this treatment.	This is a comment from the drug programs to inform pERC deliberations.
System and economic issues	
Costs associated with *FGFR2* testing should be considered and incorporated into economic analysis.	This is a comment from the drug programs to inform pERC deliberations.

CCA = cholangiocarcinoma; ECOG PS = Eastern Cooperative Oncology Group Performance Status; FOLFIRI = leucovorin calcium (folinic acid) + fluorouracil + irinotecan hydrochloride; FOLFOX = leucovorin calcium (folinic acid) + fluorouracil + oxaliplatin; mFOLFOX = modified leucovorin calcium (folinic acid) + fluorouracil + oxaliplatin; pERC = pan-Canadian Oncology Drug Review Expert Review Committee; RWE = real-world evidence.

Clinical Evidence

Systematic Review

Description of Studies

The FIGHT-202 trial is a multicentre, open-label, single-arm phase II trial that evaluated the efficacy and safety of pemigatinib in patients with advanced, metastatic, or surgically unresectable CCA with *FGFR2* alterations, other *FGF-FGFR* alterations, or no *FGF-FGFR* alterations, and who was unsuccessful with previous therapy. Patients were assigned to 3 cohorts depending on the patient's *FGF-FGFR* status (cohort A: *FGFR2* fusions or rearrangements; cohort B: *FGF-FGFR* alterations other than *FGFR2* fusions or rearrangements; or cohort C: negative for *FGF-FGFR* alterations). This review focuses on cohort A, as cohorts B and C were not part of the requested reimbursement criteria to CDA-AMC and not submitted for approval to Health Canada and are therefore beyond the scope of this review. A total of 147 patients were enrolled to receive oral pemigatinib (13.5 mg orally once daily on a 2-weeks-on and 1-week-off schedule for each 21-day cycle). The primary outcome was ORR in cohort A and secondary outcomes included ORR in cohorts B, A plus B, and C, PFS, DOR, disease control rate (DCR), OS, and safety assessed in all 3 cohorts, respectively. Exploratory end points included HRQoL and symptom severity.

Adults, diagnosed with advanced, metastatic, or surgically unresectable CCA that is *FGFR2*-positive, who had documented disease progression after at least 1 line of prior systemic therapy were enrolled into cohort A of the FIGHT-202 trial. At baseline, 107 patients were identified as having *FGFR2* fusions or rearrangements and were grouped into cohort A. Cohort B included 20 patients with other *FGF-FGFR* alterations than *FGFR2*, and cohort C included 18 patients with no identified *FGF-FGFR* alterations. One patient grouped into an "undetermined" group, was not assigned to any of the 3 cohorts as the local *FGF-FGFR* status results could not be confirmed by the central genomics laboratory. For patients in cohort A, the mean age was 55.3 years (standard deviation = 12.02 years), most patients were female (60.7%) and enrolled in trial sites in North America (59.8%) or Europe (29.9%). Almost all patients (89% of patients overall and 98.1% of patients in cohort A) had intrahepatic CCA. The majority of patients in cohort A had metastatic disease (82.2%) with lung and lymph nodes being the most common extrahepatic metastatic site (54.4% and 53.1%, respectively). Median time since diagnosis was 1.28 years (range, 0.03 to 11.1 years) in patients in cohort A. The majority of patients in cohort A had an ECOG performance status of 1 (53.3%) and all patients had received at least 1 line of prior systemic therapy for advanced or metastatic disease (60.7%, 27.1%, and 12.1% of patients received 1, 2, and ≥ 3 prior lines, respectively). Renal and hepatic impairment grades were normal or mild for most patients in cohort A (39.3% and 43.9% normal and mild renal impairment grades, respectively; 44.9% and 48.6% normal and mild hepatic grades, respectively).

The futility analysis, which was performed on October 12, 2017, was prespecified a priori in the statistical analysis plan. The timing of the subsequent analysis (March 22, 2019) at which point the predetermined threshold (i.e., lower limit of the 95% CI for ORR > 15%) would be assessed was not prespecified a priori in the statistical analysis plan; however, the sponsor's proposed timing was agreed upon by the FDA during their review process of pemigatinib.

Efficacy Results

At the July 8, 2021, data cut-off, the median duration of follow-up was 42.9 months (19.9 to 52.2 months) in cohort A. Median OS was 17.48 months (95% CI, 14.36 to 22.93 months). The survival probabilities of patients surviving to 6 months and 12 months were 88.7% (95% CI, 81.0% to 93.4%) and 67.6% (95% CI, 57.7% to 75.6%), respectively. Median PFS was 7.03 months (95% CI, 6.08 to 10.48 months). The PFS probabilities at 6 months and 12 months were 61.1% (95% CI, 51.0% to 69.8%) and 32.3% (95% CI, 22.9% to 42.1%).

As of the July 8, 2021, data cut-off date, the proportion of patients who achieved an objective response was 37.0% (N = 40) (95% CI, 27.94% to 46.86%), including 3 patients (2.8%) with CR and 37 patients (34.3%) with PR. Among the 40 patients who achieved an objective response, median DOR was 9.13 months (95% CI, 6.01 to 14.49 months). The probabilities of maintaining a response for at least 6 months and 12 months were 67.8% (95% CI, 50.4% to 80.3%) and 41.2% (95% CI, 24.8% to 56.8%), respectively.

The proportion of patients with best response of CR, PR, or stable disease was 82.4% (N = 89) (95% CI, 73.9% to 89.1%), including 3 patients (2.8%) with CR, 37 patients (34.3%) with PR, and 49 patients (45.4%) with stable disease for 39 or more days from the first pemigatinib dose. [redacted]

The descriptive summary statistics of observed scores for the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and the EORTC QLQ Cholangiocarcinomas and EORTC QLQ Gallbladder Cancer Module 21 (BIL21) from baseline to cycle 33 (March 22, 2019, data cut-off date) or to cycle 42 (April 7, 2020, data cut-off date) were reported to be variable with no consistent trend. A definition for what constituted a clinically meaningful change from baseline in the present target population was not provided. A post-hoc analysis assessed observed mean changes from baseline to week 16 by subgroups of patients (i.e., patients with CR or PR, stable disease, or progressive disease). Results suggested that changes from baseline appeared directionally more favourable in patients with CR or PR, or stable disease than in patients with progressive disease.

Harms Results

All patients in cohort A experienced at least 1 treatment emergent adverse event (TEAE) (100.0%). The most reported TEAEs were alopecia (59.3%), hyperphosphatemia (55.6%), diarrhea (53.7%), fatigue (46.3%), and nausea (42.6%). The percentage of patients experiencing serious TEAEs was [redacted] in cohort A. The most serious TEAEs were [redacted]. Adverse events led to discontinuation of study treatment in [redacted] of patients in cohort A. None of the patients withdrew from the FIGHT-202 study due to an adverse event as the primary reason. TEAEs leading to treatment discontinuation included [redacted]

[redacted] TEAEs leading to death occurred relatively rarely in cohort A ([redacted].

The percentage of patients experiencing nail toxicity TEAEs was [redacted] in patients in cohort A. The most commonly reported nail toxicity included [redacted]. No serious nail toxicity TEAE occurred in cohort A.

The percentage of patients experiencing serous retinal detachment TEAEs in cohort A was [redacted]. The most commonly reported serous retinal detachment was [redacted]

The percentage of patients experiencing hyperphosphatemia TEAEs in cohort A was [redacted] The most reported hyperphosphatemia events were [redacted]. No serious hyperphosphatemia TEAE occurred in cohort A.

The percentage of patients experiencing hypophosphatemia TEAEs in cohort A was [redacted]. The most reported hypophosphatemia events were [redacted]. No serious hypophosphatemia TEAE occurred in cohort A.

Critical Appraisal

The primary objective of phase II (randomized or nonrandomized) trials is to document the safety outcomes and investigate if the estimate of effect for a new drug is large enough to use it in confirmatory phase III trials. Phase II trials may not accurately predict harm and/or effectiveness of treatments. The clinical experts consulted by CDA-AMC noted that, despite the high unmet need, conducting an RCT in this small patient population with a targeted therapy, such as pemigatinib, compared to currently available second-line therapies in clinical practice in Canada would not be feasible. The FIGHT-202 trial included no formal statistical significance and hypotheses testing and point estimates with 95% CIs were reported to estimate the magnitude of treatment effect. A greater than 95% probability to have a 95% CI for ORR in cohort A with a lower limit larger than 15% was the basis for the sample size determination and was regarded as the threshold for a positive study outcome. The subgroup analyses were noninferential, wide CIs reflected uncertainty in the effect estimates, and small sample sizes limited the generalizability to a broader population. Interpretation of time□to□event end points such as OS or PFS is limited in single□arm studies; as all patients in cohort A received the same treatment the extent to which the observed survival is due to the natural history of the tumour, or the intervention remains unclear. While there is strong genetic and functional evidence that *FGFR* genetic alternations can drive the formation of tumours, it is currently not known, if patients with *FGFR2*-positive alterations represent a distinct prognostic subgroup. The clinical experts agreed that progression in prior systematic therapy is a major prognostic factor in this target population and the experts did not anticipate that patients would derive any substantial benefit from their underlying disease

biology at the time they enrolled into the FIGHT-202 trial. The results for patient-reported outcomes were inconclusive given the noncomparative, open-label design of the trial, the lack of a prespecified analysis of the patient-reported outcomes data, the substantial decline in patients available to provide assessments over time, and the lack of a definition for what constituted a clinically meaningful change from baseline in the target population.

Indirect Comparisons

Description of Studies

Two studies, the FIGHT-202 trial and the ABC-06 study, were included in the sponsor's ITC. The sponsor submitted an ITC in the form of an unanchored MAIC between cohort A of the FIGHT-202 study and each of the 2 treatment groups in the ABC-06 study. The ABC-06 study compared an mFOLFOX regimen plus ASC versus ASC alone in patients with locally advanced or metastatic BTC. Cohort A of the FIGHT-202 trial only included patients with unresectable, locally advanced or metastatic CCA who had the *FGFR2* mutation.

Efficacy Results

OS Pemigatinib Versus mFOLFOX Plus ASC

The results of the ITC favoured pemigatinib for PFS and OS in comparison with mFOLFOX plus ASC as well as with ASC alone. Median OS was [redacted]) for the pemigatinib group versus [redacted] for the mFOLFOX plus ASC group, based on the March 22, 2019, data cut-off for the FIGHT-202 study. The corresponding HR was 0.209 (95% CI, 0.127 to 0.313), the HR using the results from the April 7, 2020, data cut-off was [redacted], and the HR using the results from the July 8, 2021, study close was [redacted]. Supplemental OS analyses were provided from the July 8, 2021, data cut-off comparing pemigatinib to mFOLFOX plus ASC in patients that received only 1 prior therapy. The number of patients and effective sample size for this subgroup was [redacted] and [redacted], and resulted in an HR of [redacted].

OS Pemigatinib Versus ASC Alone

Median OS was [redacted] for the pemigatinib group versus [redacted] months for the ASC group, based on the March 22, 2019, data cut-off for the FIGHT-202 study. The corresponding HR was 0.163 (95% CI, 0.099 to 0.249), the HR using the results from the April 7, 2020, data cut-off was [redacted], and the HR using the results from the July 8, 2021, study close was [redacted]. Supplemental OS analyses were provided from the July 8, 2021, data cut-off comparing pemigatinib to ASC alone in patients that received only 1 prior therapy. The number of patients and effective sample size for this subgroup was [redacted] and [redacted], and resulted in an HR of [redacted]

The median PFS for pemigatinib versus mFOLFOX plus ASC was [redacted] months versus [redacted] months for the pemigatinib versus mFOLFOX plus ASC groups, based on the March 22, 2019, data cut-off for the FIGHT-202 study. The corresponding

HR was 0.436 (95% CI, 0.319 to 0.599), the HR using the results from the April 7, 2020, data cut-off was [redacted], and remained unchanged at the July 8, 2021, study close. Supplemental PFS analyses were provided from the July 8, 2021, data cut-off comparing the pemigatinib to mFOLFOX plus ASC in patients that received only 1 prior therapy. The number of patients and effective sample size for this subgroup was [redacted] and [redacted], and resulted in an HR [redacted]).

For PFS, pemigatinib versus ASC alone was not assessed.

Harms Results

No comparisons for harms or safety were incorporated in the sponsor's ITC.

Critical Appraisal

There were potentially important underlying differences between the FIGHT-202 and ABC-06 studies. In particular, the *FGFR2* alterations were not reported in the ABC-06 trial. Given that *FGFR2* alterations occur almost exclusively in intrahepatic CCA and that the prevalence of *FGFR2* alterations is less than 20% of patients with intrahepatic CCA, there is likely a large disparity in *FGFR2* mutation status between the study populations. While the FIGHT-202 study only included patients with CCA, the ABC-06 study included patients with BTC which encompasses gallbladder cancer and ampullary cancer in addition to CCA. Ninety-nine percent of patients in cohort A of the FIGHT-202 study had intrahepatic CCA compared with 42% and 47% in the mFOLFOX plus ASC and ASC groups, respectively. Since disease type and *FGFR2* status were more restricted in the FIGHT-202 study, these differences could not be addressed through the weighting of patients in the pemigatinib group.

The covariates chosen for adjustment were based on age, sex, ECOG PS, and serum albumin. The following baseline characteristics were also available for both studies and did not appear to be considered: disease stage, percentage of patients with prior surgery for cancer, and number of lines of prior systemic therapy for advanced or metastatic cancer. The clinical experts consulted by CDA-AMC for this review believed the number of lines of previous therapy was of key importance in terms of prognosis. The clinical experts were not aware of any additional prognostic factors and/or effect modifiers that were not reported in both studies and should have been considered.

While there are retrospective studies suggesting that the presence of *FGFR2* mutations in CCA may be associated with better prognosis the clinical experts consulted by CDA-AMC believed *FGFR2* mutation status was not an important prognostic factor in the indicated patient population. The clinical experts considered that patients in both the FIGHT-202 and ABC-06 trials had progressed on prior systemic therapy to be of greater importance in terms of prognosis. The clinical experts expected patients in the FIGHT-202 study to have more advanced disease than patients in the ABC-06 study because the FIGHT-202 study population was more heavily pretreated overall. It is unclear whether the pemigatinib group was more or less similar to the ABC-06 groups following weighting as the weighting process did not take the number of prior lines of systemic therapy into account. If substantial differences remained, these differences could have led to bias against pemigatinib in all of the comparisons.

The effective sample size of the pemigatinib group was reduced by approximately 50% after weighting to the mFOLFOX plus ASC and ASC alone groups and it is unclear how representative the postweighting pemigatinib groups are of cohort A of the FIGHT-202 study.

Comparisons of pemigatinib with other relevant comparators (FOLFIRI, 5-FU alone or in combination with cisplatin or oxaliplatin, and capecitabine alone or in combination with cisplatin or oxaliplatin) were not available. Given that mFOLFOX plus ASC is the only therapy beyond the first-line setting with RCT evidence of an OS benefit, the clinical experts consulted by CDA-AMC expected that mFOLFOX plus ASC would have the greatest efficacy of all the relevant comparators.

In summary, for the unanchored MAIC to produce unbiased treatment effect estimates, all effect modifiers and prognostic variables need to be adjusted for in the analysis. Residual confounding remains the major limitation of the MAIC despite adjusting for age, sex, ECOG PS, and serum albumin in the comparisons of pemigatinib with mFOLFOX plus ASC and ASC alone. While any bias introduced by the differences between the FIGHT-202 and ABC-06 studies in the number of prior lines of systemic therapy may have been against pemigatinib, the substantial differences in *FGFR2* mutation status and tumour site between trials introduce a high degree of uncertainty in the OS and PFS results. Furthermore, MAICs cannot account for unknown cross-trial differences; thus, the MAIC estimates are susceptible to bias from unknown sources of confounding. An evaluation of potential bias from residual confounding was not reported; therefore, the magnitude of this bias in the relative treatment effect estimates is unclear. Overall, uncertainty remains around the magnitude of the additional benefit that pemigatinib provides for OS or PFS versus mFOLFOX plus ASC or ASC alone.

Studies Addressing Gaps in the Evidence From the Systematic Review

Description of Studies

Parisi et al. (2024) conducted a multicentre, observational, retrospective study that assessed the effectiveness and safety of pemigatinib in patients with previously treated locally advanced or metastatic CCA with *FGFR2* fusion or rearrangements. Patients referred to 14 Italian centres and 25 French centres from July 2020 to September 2022 were evaluated (N = 72). These patients were initially included in 2 separate cohort studies and were pooled into a single dataset for analysis. An exploratory analysis compared PFS among patients in the cohort who had received pemigatinib in second line to those who had received chemotherapy in second line (and pemigatinib in a later line).

The study by Saverno et al. (2024) was a retrospective, observational, multisite chart review study based within the US. Physicians within the Cardinal Health Oncology Provider Extended Network were instructed to randomly select up to 10 patients that met eligibility criteria during the index period. Between February 3, 2021, and February 22, 2023, physicians abstracted details relating to demographics, clinical characteristics, biomarker testing patterns, treatment patterns, and clinical outcomes (N = 120).

The Ding et al. (2024) study was a retrospective, multisite physician survey to assess the demographic, clinical characteristics, *FGFR2* testing, and real-world treatment patterns and outcomes of patients with unresectable locally advanced or metastatic CCA treated with pemigatinib (N = [redacted]).

Post-hoc analyses were conducted to compare patients from the FIGHT-202 trial that received pemigatinib as second-line therapy and patients from the FIGHT-202 trial that received second-line systemic therapy before enrolling in the FIGHT-202 trial. In total there were 65 patients that received pemigatinib as second-line therapy within the FIGHT-202 study and 41 patients received second-line systemic therapy before enrolling in the FIGHT-202 study, 39 were evaluable for PFS. Thirty-eight of 41 patients that received second-line systemic therapy received chemotherapy (gemcitabine plus cisplatin, fluorouracil plus leucovorin calcium plus oxaliplatin, or fluorouracil plus oxaliplatin) and 3 of the 41 patients received anti-PD1 immunotherapy.

Efficacy Results

In the Parisi et al. (2024) study, median follow-up for the overall cohort was 19.5 months (95% CI, 15.0 to 30.5 months). Of the overall cohort of 72 patients, 2 patients recorded a CR, and 31 patients recorded a PR, for an ORR of 45.8%. The median DOR was 7 months (95% CI, 5.8 to 9.3 months). Patients that received pemigatinib in the second-line setting had a median PFS of 8.6 months (95% CI, 6.6 months to not applicable) while patients that received chemotherapy in the second-line setting (and received pemigatinib in a later line) had a median PFS of 3.4 months (95% CI, 2.1 months to not applicable), with an HR of 3.88 (95% CI, 1.81 to 8.31, P < 0.001).

In the Saverno et al. (2024) study, the median duration of treatment in the first-line setting was 4.9 months (95% CI, 4.4 to 5.7 months), among these patients, 94.7% received chemotherapy as their first-line treatment. Most patients received pemigatinib in the second-line setting (94.2%), while 5.8% received pemigatinib in the third-line setting. The median duration of treatment with pemigatinib was 7.4 months (95% CI, 6.2 to 8.8 months). ORR in the 116 patients with disease response data available was 59.2% (95% CI, 50.0% to 68.4%). The proportion of patients reporting a best response of CR was 5.0%, best response of PR was 54.2%, and best response of stable disease was 27.5%, for a DCR of 86.7%. The median PFS was 7.4 months (95% CI, 6.4 to 8.6 months). The PFS probability was 95.8% (95% CI, 90.3% to 98.2%) at 3 months and 71.5% (95% CI, 61.4% to 79.4%) at 6 months. The median OS was not reported; the OS probability was 95.8% (95% CI, 90.3% to 98.2%) at 3 months and 88.4% (95% CI, 80.3% to 93.3%) at 6 months.

In the Ding et al. (2024) study, ORR in the [redacted] patients with survey responses was [redacted]. No patients included in the survey results achieved a CR. The proportion of patients reporting a best response of PR was [redacted] and the proportion of patients achieving a best response of stable disease was [redacted], for a DCR of [redacted]. The median PFS was [redacted]. PFS probability was [redacted] at 6 months and [redacted] at 12 months.

In the Bibeau et al. (2022) study, the median PFS in patients receiving second-line pemigatinib therapy was 7.0 months (95% CI, 4.9 to 11.1 months) while the median PFS for patients that received second-line therapy before enrolling in FIGHT-202 was 4.2 months (95% CI, 3.0 to 5.3 months). Median PFS for the 102 patients with evaluable results for first-line systemic therapy was 5.5 months (95% CI, 4.0 to 8.0 months).

Harms Results

In the Parisi et al. (2024) study, the proportion of patients that reported at least 1 TEAE was 97.2% with the most common being fatigue (69.4%), nail toxicities (61.1%), and hyperphosphatemia (55.6%).

Harms were not reported in the Saverno et al. (2024) study.

Harms were not reported in the Ding et al. (2024) study.

Harms were not reported in the Bibeau et al. (2022) study.

Critical Appraisal

The clinical experts consulted considered the reported baseline characteristics in all 3 RWE studies to be representative of the expected patient population of Canada. The quality and completeness of the real-world data source was not reported. All 3 RWE studies were observational studies with no comparator arm, as such it is difficult to assign with the certainty causation of the effects seen to the study drug. It is not possible to determine the extent to which observed effects can be attributed to pemigatinib as compared to placebo effects and natural history of the disease in the absence of a frame of reference for comparison. Due to the retrospective nature of the study designs, ORR and progression assessments were conducted by the treating physician, potentially introducing bias, in contrast to assessments conducted by central review commonly done in phase II and phase III trials. Timing of assessments in observational retrospective studies can also make interpretation of time to progression outcomes challenging if patients are not being assessed at standardized time points.

Patient selection methodology within the Saverno et al. (2024) study potentially introduced selection bias, as the physicians were instructed to select, at random, 10 patients that fit the inclusion criteria during the index period. As there was no methodology reported that indicated the selecting physicians were blinded to the clinical outcomes of patients when making selections, it is possible that selection bias was introduced. Additionally, patients required at least 4 months of follow-up to be included (unless they died). It is not clear how many patients were excluded for lacking adequate follow-up, nor whether these patients might have differed in an important way in their prognosis.

Patient selection methodology within the Ding et al. (2024) study potentially introduced selection bias as only [redacted] of a total [redacted] potential patients were included in the analysis. It is unknown how representative the [redacted] selected patients are of the larger group as there was no response from the associated physicians, although the sponsor did provide supplemental analysis showing that the total [redacted] patient population had a slightly longer mean duration of treatment ([redacted]) suggesting that the reduced patient population was not biased toward longer treatment duration.

The study by Parisi et al. (2024) attempted to provide a comparative assessment of PFS for patients that received pemigatinib as second-line therapy within the study and the records of patients that received other systemic therapy as second-line therapy before their inclusion in the Parisi et al. (2024) study. Similar analyses were conducted in the Bibeau et al. (2022) study drawing from patients in the FIGHT-202 study. Unadjusted comparisons were presented with no attempt to balance prognostic and confounding variables across groups and no assessment of the extent nor direction of residual confounding. The comparison was

also affected by selection bias; patients in the comparator group needed to survive long enough to have received pemigatinib in a later line of therapy (this particular bias would favour the comparator) and those following different treatment trajectories (i.e., no pemigatinib in a later line) were excluded. The small sample size in each group introduced further uncertainty.

Economic Evidence

Cost and Cost-Effectiveness

Table 3: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-effectiveness analysis Partitioned survival model
Target population	Adult patients with previously treated, unresectable, locally advanced, or metastatic CCA with an *FGFR2* fusion or rearrangement, aligned with proposed Health Canada indication.
Treatment	Pemigatinib
Dose regimen	13.5 mg orally once daily for 14 consecutive days followed by 7 days off therapy, in 21-day cycles
Submitted price	Pemigatinib, $830.30 per 4.5 mg, 9 mg, or 13.5 mg tablets
Treatment cost	At the sponsor's submitted price of $830.30 per 13.5 mg tablet, the average 28-day cost of pemigatinib is $15,499 (assuming 13.5 mg administered orally once daily for 14 consecutive days followed by 7 days off therapy, in 21-day cycles).
Comparators	ASC alone, consisting of treatments including biliary drainage, antibiotics, analgesia, steroids, and anti-emetics as well as palliative radiotherapy and blood transfusions mFOLFOX + ASC
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (20 years)
Key data sources	FIGHT-202 trial, a phase II, open-label, single-arm, multinational trial (pemigatinib) and sponsor's conducted MAIC (mFOLFOX + ASC and ASC alone)
Key limitations	• The comparative efficacy estimates derived from the MAIC assume that all known and unknown prognostic factors had been accounted for. As a randomized control trial was not conducted, residual confounders exist, meaning that the comparative efficacy between pemigatinib vs. mFOLFOX and ASC and pemigatinib vs. ASC alone is highly uncertain. • A sequential analysis was performed which is not appropriate when using data from the MAIC. As the sponsor matched pemigatinib data to the ASC and FOLFOX arms of the ABC-06 trial separately, the efficacy of pemigatinib was dependent on which arm of the trial the data were matched to. • The sponsor's parametric survival extrapolations resulted in a substantial postprogression survival benefit that would not be expected in clinical practice. • Time on treatment was lower for pemigatinib than other comparators, which was deemed to be inappropriate by clinical experts consulted for this review. • Given that genetic testing for *FGFR2* mutations to determine pemigatinib eligibility is not currently covered by the publicly funded health care system, these costs are uncertain.

Component	Description
	• The health state utility values used by the sponsor assumed that a patient who is progression-free off treatment has a lower utility than in any progressed disease health state, which is not clinically expected. • Costs and consequences of subsequent therapies — which may differ depending on whether patients receive pemigatinib, ASC, or mFOLFOX — were not incorporated in the sponsor's analysis. • Some relevant off-label comparators were not included in the analysis, as such the cost-effectiveness of pemigatinib relative to these is unknown.
CDA-AMC reanalysis results	• Due to the highly uncertain nature of data derived from the MAIC, CDA-AMC was unable to perform a base-case analysis. Instead, a reanalysis was conducted that used more appropriate assumptions, though CDA-AMC notes the magnitude of benefit seen from pemigatinib estimated in this analysis may be overestimated. • CDA-AMC undertook reanalyses to address limitations relating to: the incorporation of MAIC-derived comparative efficacy estimates into the sponsor's analysis; long-term extrapolations for pemigatinib PFS and OS; selecting comparator extrapolations for PFS and OS; assuming that utility values do not vary by whether patients are on or off treatment; increasing genetic testing costs and assuming 0% of ASC and mFOLFOX patients will have publicly covered testing; changing the relative dose intensity to 100%; and using costs for mFOLFOX sourced from DeltaPA. • Compared to ASC, the ICER for pemigatinib is $252,718 per QALY. For pemigatinib to be considered cost-effective at a willingness-to-pay threshold of $50,000 per QALY, a price reduction close to 100% is needed. If no testing costs are incurred by the public payer, then cost-effectiveness can be achieved with a 77% price reduction. • Compared to mFOLFOX, the ICER for pemigatinib is $261,226 per QALY. For pemigatinib to be considered cost-effective at a willingness-to-pay threshold of $50,000 per QALY compared to mFOLFOX, a 95% price reduction is needed. If no testing costs are incurred by the public payer, then cost-effectiveness can be achieved with a 72% price reduction.

ASC = active symptom control; CCA = cholangiocarcinoma; CDA-AMC = Canada's Drug Agency; ICER = incremental cost-effectiveness ratio; LY = life-year; MAIC = matching-adjusted indirect comparison; mFOLFOX = modified leucovorin calcium (folinic acid) + fluorouracil + oxaliplatin; OS = overall survival; PFS = progression-free survival; QALY = quality-adjusted life-year; vs. = versus.

Budget Impact

CDA-AMC identified the following key limitations with the sponsor's analysis:

- uptake of pemigatinib is expected to be higher than what was estimated by the sponsor
- the relative dose intensity used by the sponsor could not be validated (compliance with treatment in the FIGHT-202 trial was observed to be high)
- the sponsor used the mean growth rate between extrahepatic CCA and intrahepatic CCA, whereas the majority of patients in the FIGHT-202 trial have intrahepatic CCA
- clinical trials were given a 10% market share in the reference and new-drug scenario which was considered unlikely
- the percentage of patients who are diagnosed and unresectable was higher in clinical practice in Canada than what was estimated by the sponsor
- rates of public coverage in the sponsor's analysis were based on assumptions
- more appropriate costs for the components of mFOLFOX could have been used

- exploration of broader health care system costs was not transparently incorporated into the sponsor's analysis.

CDA-AMC conducted a reanalysis that included: increasing pemigatinib uptake, changing the relative dose intensity to 100%, using the growth rate associated with intrahepatic CCA, removing market shares for clinical trials, assuming 85% of patients were diagnosed and unresectable and using component mFOLFOX prices sourced from DeltaPA. Based on the CDA-AMC reanalyses, the budget impact from the introduction of pemigatinib is expected to be $18,571,801 in year 1, $21,113,817 in year 2, and $23,920,712 in year 3 for a 3-year total of $63,606,331. This is likely an underestimation of the true budget impact, as costs for patients who remain on pemigatinib for more than 1 year are not captured.

If 100% of patients have public coverage for pemigatinib, the expected 3-year budget impact will increase to $79,507,913. If pemigatinib was available at a 95% price reduction, the expected budget impact will be much lower at $979,163 over 3 years.

pERC Information

Members of the Committee

Dr. Catherine Moltzan (Chair), Dr. Phillip Blanchette, Dr. Kelvin Chan, Dr. Matthew Cheung, Dr. Michael Crump, Annette Cyr, Dr. Jennifer Fishman, Dr. Jason Hart, Terry Hawrysh, Dr. Yoo-Joung Ko, Dr. Aly-Khan Lalani, Amy Peasgood, Dr. Anca Prica, Dr. Adam Raymakers, Dr. Patricia Tang, Dr. Pierre Villeneuve, and Danica Wasney.

Meeting date: March 5, 2025

Regrets: Three expert committee members did not attend.

Conflicts of interest: None

Canada's Drug Agency
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Questions or requests for information about this report can be directed to Requests@CDA-AMC.ca.