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CADTH 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

Final recommendation: Do not reimburse

CADTH

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Summary

CADTH

What Is the CADTH Reimbursement Recommendation for Pemigatinib?

CADTH recommends that pemigatinib should not be reimbursed by public drug plans for the treatment of adults with previously treated, unresectable, locally advanced or metastatic cholangiocarcinoma (CCA) with a fibroblast growth factor receptor 2 (FGFR2) fusion or other rearrangement

Why Did CADTH Make This Recommendation?

- The clinical evidence reviewed by CADTH was not strong enough to show whether treatment with pemigatinib benefits patients with CCA. It is not known if pemigatinib would lead to better outcomes for patients compared to treatments that are currently available.
- Patients identified a need for treatments that improve tumour response, delay disease progression, and improve quality of life. It is not clear whether pemigatinib meets these needs.

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 after 5 years.

Unmet Needs in CCA

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

How Much Does Pemigatinib Cost?

Treatment with pemigatinib 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

The pCODR Expert Review Committee (pERC) recommends that pemigatinib not be reimbursed for the treatment of adults with previously treated, unresectable locally advanced, or metastatic cholangiocarcinoma (CCA) with a FGFR2 fusion or other rearrangement.

Rationale for the Recommendation

One single-arm, open-label, phase II trial (FIGHT-202) evaluated the efficacy and safety of pemigatinib in a cohort of patients with advanced/metastatic or surgically unresectable CCA with FGFR2 fusions or rearrangements who failed previous therapy (N = 107). Although 35.5% (95% confidence interval [CI], 26.50 to 45.35) of patients exhibited an objective response (the primary end point), there was a high degree of uncertainty regarding the magnitude of clinical benefit directly attributable to pemigatinib due to the limitations associated with the study design. Further, due to the single-arm nature of the study, the potential clinical benefit of pemigatinib compared to other relevant treatment options is unknown. The sponsor submitted an indirect treatment comparison (ITC) of pemigatinib to a relevant comparator in Canada (FOLFOX), but there were significant limitations of the analysis, and no conclusions could be drawn regarding comparative efficacy with respect to survival outcomes (e.g., progression-free survival [PFS] and overall survival [OS]). Patients identified a need for treatments that improve tumour response, delay disease progression, and improve quality of life, but pERC was uncertain whether pemigatinib meets this need given the limitations associated with the evidence reviewed.

While pERC acknowledged the rarity of FGFR2 positive CCA, and the unmet need for more effective treatment options for patients with previously treated, unresectable locally advanced, or metastatic FGFR2 positive CCA, pERC concluded that there is insufficient evidence that pemigatinib meets this need.

Discussion Points

- pERC acknowledged that given the rarity of FGFR2 positive CCA, conducting a phase III randomized controlled trial in this setting with pemigatinib would likely not be feasible and that there is an unmet need for more effective treatment options for patients with previously treated, unresectable, locally advanced, or metastatic FGFR2 positive CCA. However, pERC concluded that there was insufficient evidence that pemigatinib addressed the need for effective treatment options, given the uncertainty in the results from the FIGHT-202 trial.
- Although pERC considered that pemigatinib produced antitumour activity based on tumour response observed with pemigatinib in the FIGHT-202 trial, pERC was concerned about the limitations and inherent biases of small non-comparative studies and their risk of providing unreliable efficacy estimates. pERC highlighted that the FIGHT-202 trial did not include formal statistical significance testing and therefore no robust conclusions could be drawn regarding the antitumour activity of pemigatinib.

- Given the lack of direct comparative evidence for pemigatinib to other treatments currently used for CCA, pERC considered a sponsor-provided ITC comparing the efficacy of pemigatinib to FOLFOX plus active symptom control (ASC) and ASC alone. pERC noted that the results of the ITC favoured pemigatinib for OS in comparison with FOLFOX plus ASC and ASC alone and for PFS in comparison to FOLFOX plus ASC. However, the ITC was associated with substantial limitations such as heterogeneity across the study designs and populations (including the inability to assess the comparative effects in patients with FGFR2 alterations; [redacted] and primary tumour sites), and the inability to adjust for all potential confounders and prognostic variables in the unanchored matching-adjusted indirect comparison (MAIC), which precluded drawing definitive conclusions about the comparative effectiveness of pemigatinib versus FOLFOX. The sponsor provided additional subgroup and post-hoc analyses to explore the potential impact of the heterogeneity between studies related to FGFR2 alterations, prior anti-cancer therapies, and primary tumour sites. However, several methodological limitations precluded pERC's ability to draw firm conclusions from the results of these additional analyses.
- pERC was unable to draw any firm conclusions from the exploratory patient-reported outcomes analyzed in the FIGHT-202 trial given the non-comparative, open-label design of the trial, the lack of a pre-specified analysis of the patient-reported outcomes data, [redacted].
- • pERC considered the unmet needs of patients including more treatment options, improved quality of life, control of disease progression, and long-lasting benefits or cure. Although pERC recognized that pemigatinib would provide an additional treatment option, there was insufficient evidence and uncertainty that pemigatinib addressed patients' needs for improved quality of life, reduced disease progression and long-lasting benefits.
- • Although updated results from the July 8, 2021 data cut-off date of the FIGHT-202 trial were consistent with results from previous data cut-off dates, the updated results did not address the main limitations identified for the trial, including the non-comparative design and lack of formal hypothesis testing.

Background

Pemigatinib has a Health Canada indication for the treatment of adults with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or other rearrangement. Pemigatinib is a molecule kinase inhibitor with antitumour activity that inhibits fibroblast growth factor receptors (FGFR). FGFRs are receptor tyrosine kinases that activate signalling pathways in tumour cells. Pemigatinib is a selective, potent, oral inhibitor of FGFR 1, 2, and 3. 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 once daily 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 > 5.5 mg/dL and to consider adding a phosphate lowering therapy when the level is > 7 mg/ dL. The dose of phosphate lowering therapy is to

be adjusted until the phosphate level returns to < 7 mg/ dL. It is recommended to consider discontinuing phosphate lowering therapy during pemigatinib treatment breaks or if the phosphate level falls below normal.

Sources of Information Used by the Committee

To make their recommendation, pERC 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 a FGFR2 fusion or other rearrangement.
- Patients' perspectives gathered by 3 patient groups, the Canadian Liver Foundation (CLF), the Canadian Organization for Rare Disorders (CORD), and the Cholangiocarcinoma Foundation (CCF) which co-created 1 patient input for this review.
- Input from public drug plans and cancer agencies that participate in the CADTH review process.
- Two clinical specialists with expertise diagnosing and treating patients with cholangiocarcinoma.
- Input from 2 clinician groups, including 1 from the Ontario Health (Cancer Care Ontario) Gastrointestinal Cancer Drug Advisory Committee (GI DAC) and 1 from the Canadian Gastrointestinal Oncology Evidence Network (CGOEN) and other cholangiocarcinoma-treating physicians.
- A review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

Patient Input

Three patient groups, the CLF, the CORD and the CCF co-created 1 patient input for this review. The input was based on an online survey and a virtual focus group with a total of 27 respondents (15 patients diagnosed with CCA [out of which 4 patients had CCA with FGFR2 fusions], 2 patients with symptoms of CCA but without a diagnosis, and 10 caregivers or family members of patients with CCA) were included in the patient input.

Respondents indicated a varying range of CCA symptoms affecting patients' daily activities (including their social, work, and school lives and their relationships) causing detrimental effects on patients' quality of life. Respondents highlighted problems with intimacy or sexual desire, fatigue, and anxiety. Other commonly experienced symptoms indicated by respondents included unintended weight loss, insomnia, gastrointestinal problems, abdominal pain, constipation, depression, and neuropathy. According to the 3 patient groups, delayed diagnosis, misdiagnosis, and a lack of specialists and treatment options available for this rare cancer significantly contributed to patients' feelings of stress and anxiety and may delay or eliminate treatment options.

According to the patient input received, respondents reported that they expect the following key outcomes to be improved from any new drug or treatment: quality of life, tumour

response, delay in disease progression and it provides an additional treatment choice. Additionally, it was highlighted by the 3 patient groups that the identification of gene mutations and the development of targeted therapies was perceived to be very important by respondents and would spur the hope for curable options. Four respondents indicated that they had direct experience with taking pemigatinib. Respondents indicated overall little challenge dealing with the side effects from pemigatinib.

Clinician Input

Input From Clinical Experts Consulted by CADTH

The clinical experts consulted by CADTH indicated that there currently are no standard funded second-line treatment options. Palliative therapy (e.g., FOLFOX, FOLFIRI, 5-FU, and capecitabine) and best supportive care are recommended for patients in the present 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 health-related quality of life (HRQoL), delay disease progression, and prolong survival. The clinical experts consulted by CADTH stated that pemigatinib was to be used in adult patients with previously treated, unresectable locally advanced or metastatic CCA with a FGFR2 fusion or other rearrangement 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 CADTH 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 the FGFR2 alteration. Clinical assessment to evaluate the response to treatment with pemigatinib would include regular radiological imaging (i.e., CT/ 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 patients' 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 CADTH, 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 to continue treatment.

Clinician Group Input

Two clinician group inputs were provided, 1 from the Ontario Health (Cancer Care Ontario) GI DAC and 1 from the CGOEN and other cholangiocarcinoma-treating physicians. The views of the clinician groups overall were consistent with the clinical experts consulted by CADTH indicating that the most important treatment goals are achievement of disease control, delaying worsening of symptoms, maintaining HRQoL, delaying disease progression, prolongation of survival, and an acceptable safety profile. The clinicians from the CGOEN also highlighted that the convenient oral route of administration of pemigatinib would contribute

to improvements in quality of life for patients as fewer visits to a cancer centre and less chair time would be required compared to alternative treatment options. The clinicians from CGOEN further suggested that it would be reasonable to consider pemigatinib upfront for patients deemed unsuitable for standard first-line chemotherapy. This clinician group also noted that patients with compromised hepatic function or significant hyperbilirubinemia would be least suitable for treatment with pemigatinib. The clinicians from both inputs anticipated that pemigatinib would offer clinically meaningful benefit and improved efficacy to patients with the potential for improved quality of life.

Drug Program Input

The drug programs provide input on each drug being reviewed through CADTH's reimbursement review processes by identifying issues that may impact their ability to implement a recommendation. The drug plans noted that standard first-line treatment for advanced or metastatic CCA is gemcitabine and cisplatin and that there is currently no standard of care for patients with CCA after failure of first-line treatment. Oral pemigatinib would allow for outpatient dispensing and administration of this drug. It was noted by the drug programs that FGFR2 testing is not routinely available nor funded in jurisdictions. The clinical experts consulted by CADTH were asked questions related to the implementation of pemigatinib. Overall, most implementation questions were related to the eligible patient population (i.e., prior lines of systemic therapy and Eastern Cooperative Oncology Group Performance Status [ECOG PS]), treatment of patients who are currently on second-line therapy, and FGFR2 testing.

Clinical Evidence

The FIGHT-202 trial is a multi-centre, 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, who failed 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 CADTH review focused on Cohort A since cohorts B and C were not part of the requested reimbursement criteria to CADTH and not approved in the Health Canada Notification of Compliance with Conditions 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 objective response rate (ORR) in Cohort A and secondary outcomes included ORR in Cohorts B, A plus B, and C; PFS, duration of response (DOR), disease control rate (DCR), OS, and safety, assessed in all 3 cohorts, respectively. Exploratory end points included HRQoL and symptom severity.

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 (standard deviation [SD]: 12.02),

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 the lung and lymph nodes being the most common metastatic sites (54.2% and 53.3%, 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 at least 3 prior lines, respectively). Renal and hepatic impairment grades were normal or mild for most patients in Cohort A (39.3% and 43.9% had normal and mild renal impairment grades, respectively; 44.9% and 48.6% had normal and mild hepatic grades, respectively).

A futility analysis was performed as pre-specified 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 pre-specified 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. Two additional updated analyses occurred at the August 2019 and April 2020 data cut-off dates, the former was a 4-month safety update required for the FDA New Drug Application, the latter was performed to support the safety data summaries for another indication outside of Canada. Since the April 7, 2020 data cut-off date included 1 additional patient in Cohort A who had been enrolled after the August 30, 2019 data cut-off date, some efficacy analyses (i.e., survival and response outcomes) were performed in addition to safety analyses and provided to the relevant regulatory authorities.

Efficacy Results

The FIGHT-202 trial achieved the predetermined threshold for a positive outcome (lower limit of the 95% CI for ORR > 15%) in Cohort A. As of the March 22, 2019 data cut-off date, after a median follow-up time of 15.44 months, the proportion of patients with an objective response, (primary end point in Cohort A) was 35.5% (95% CI, 26.50 to 45.35). A total of 3 patients had achieved a complete response (CR), 35 patients had a partial response (PR), and 50 patients had stable disease (SD) as the best response; DCR was 82.2%. The ORR results based on investigator assessment showed generally consistent results with those based on an independent review committee. As of the April 7, 2020 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 4 (3.7%) patients with CR and 36 (33.3%) patients with PR. Forty-nine (45.4%) patients had SD as the best response. The ORR results for the subgroup of interest suggested that the treatment effects on ORR for the subgroups with ECOG performance status of 0 and 1 plus 2 were generally consistent with the overall population in Cohort A. Among the 40 patients who achieved an objective response, median DOR was 8.08 (95% CI, 5.65 to 13.14) months. The probabilities of maintaining a response for at least [redacted] were [redacted] respectively.

As of the latest data cut-off date (April 7, 2020), the median duration of follow up was 27.9 months in Cohort A. Median OS was 17.48 (95% CI, 14.42 to 22.93) months. The survival probabilities of patients surviving to 9- and 12- months were 76.1% (95% CI, 66.7 to 83.2) and 67.3% (95% CI, 57.4 to 75.4), respectively. Median PFS was 7.03 (95% CI, 6.08 to 10.48) months. The PFS probabilities at [redacted] months were [redacted] and [redacted].

At the March 22, 2019 data cut-off date, the proportion of patients with best response of CR, PR, or SD was 82.2% (N = 88) (95% CI, 73.7 to 89.0), including 3 (2.8%) patients with CR, 35 (32.7%) patients with PR, and 50 (46.7%) patients with SD for 39 or more days since the first pemigatinib dose. The DCR results based on investigator assessment showed generally consistent results with those based on independent review committee (IRC); [redacted].

The descriptive summary statistics of observed scores for the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ) Core 30 (C30) and the EORTC QLQ-Cholangiocarcinomas and Gallbladder Cancer Module 21 (BIL21) from baseline to [redacted]. A post-hoc analysis assessed observed mean changes from baseline to week 16 by subgroups of patients (i.e., patients with CR or PR, SD, or progressive disease[PD]). Results suggested that changes from baseline appeared directionally more favourable in patients with CR or PR, or SD than in patients with PD.

Harms Results

As of the March 22, 2019 data cut-off date, all patients in Cohort A experienced at least 1 treatment emergent adverse event (TEAE) (100.0%). The most commonly reported TEAEs were alopecia (58.9%), hyperphosphatemia (55.1%), diarrhea (52.3%), dysgeusia (47.7%), fatigue (44.9%), and nausea (40.2%). The percentage of patients experiencing serious TEAEs was 40.2% in Cohort A. The most common serious TEAEs included pyrexia (4.7%), cholangitis (3.7%), and cholangitis infective (2.8%). Adverse events led to discontinuation of study treatment in 4.7% of patients in Cohort A.

As of the March 22, 2019 data cut-off date, the most commonly reported nail toxicity in Cohort A included onychomadesis (12.1%), nail discolouration (11.2%), nail dystrophy (9.3%), onycholysis (9.3%), paronychia, and onychoclasis, occurring in 8.4% of patients each. No serious nail toxicity TEAE occurred in Cohort A. The percentage of patients experiencing serous retinal detachment TEAEs in Cohort A was 3.7%. The percentage of patients experiencing hyperphosphatemia TEAEs in Cohort A was 57.9%. No serious hyperphosphatemia TEAE occurred in Cohort A. The percentage of patients experiencing hypophosphatemia TEAEs in Cohort A was (25.2%). No serious hypophosphatemia TEAE occurred in Cohort A.

Critical Appraisal

The primary objective of phase II (randomized or non-randomized) 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 CADTH 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. 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 non-inferential, 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; since 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 FGFR2 alteration-positive patients represent a distinct prognostic subgroup. The results for patient-reported outcomes were inconclusive given the non-comparative, open-label design of the trial, the lack of a pre-specified analysis of the patient-reported outcomes data, [redacted].

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 a 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 (oxaliplatin, L-folinic acid (also known as leucovorin), and fluorouracil) plus ASC versus ASC alone in patients with locally advanced or metastatic biliary tract cancer. Cohort A of the FIGHT-202 trial only included patients with unresectable, locally advanced or metastatic CCA who had the FGFR2 mutation.

Efficacy Results

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] months (lower limit of [redacted]) for the pemigatinib group versus [redacted] months for the mFOLFOX plus ASC group, based on the March 22, 2019 data cut-off for the FIGHT-202 study. The corresponding hazard ratio was 0.209 (95% CI, 0.127 to 0.313) and the hazard ratio using the results from the April 7, 2020 data cut-off was [redacted].

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 hazard ratio was 0.163 (95% CI, 0.099 to 0.249) and the hazard ratio using the results from the April 7, 2020 data cut-off was [redacted].

Median PFS 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 hazard ratio was 0.436 (95% CI, 0.319 to 0.599) and the hazard ratio using the results from the April 7, 2020 data cut-off was [redacted].

PFS for pemigatinib versus ASC alone was not assessed.

Harms Results

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

Critical Appraisal

The CADTH critical assessment identified limitations with the sponsor's submitted unanchored MAIC, including heterogeneity across study designs and populations and the inability to adjust for all potential confounders and prognostic variables, which limited the ability to interpret the relative treatments effects observed between pemigatinib and other treatments. There were 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 cholangiocarcinoma and that the prevalence of FGFR2 alterations is less than 20% of patients with intrahepatic cholangiocarcinoma, there is likely a large disparity in FGFR2 mutation status between the study populations. While the FIGHT-202 study only included patients with cholangiocarcinoma, the ABC-06 study included patients with biliary tract cancer which encompasses gallbladder cancer and ampullary cancer in addition to cholangiocarcinoma. Ninety-eight percent of patients in Cohort A of the FIGHT-202 study had intrahepatic cholangiocarcinoma 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.

It is unclear whether the pemigatinib group was more or less similar to the ASC-06 groups with respect to lines of prior treatment following weighting as the weighting process did not take the number of prior lines of systemic therapy into account.

The effective sample size of the pemigatinib group was reduced by approximately [redacted] after weighting to the mFOLFOX plus ASC and ASC alone groups, and it is unclear how representative the post-weighting 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. mFOLFOX plus ASC is the only therapy beyond the first-line setting with phase III RCT evidence.

MAICs cannot account for unknown cross-trial differences; thus, the MAIC estimates are susceptible to bias from unknown confounding. [redacted].

Other Relevant Evidence

One additional relevant report was summarized that was included in the sponsor's submission to CADTH. FIGHT-101 is an ongoing, open-label phase I/II dose-escalation and expansion study of pemigatinib among participants with previously treated advanced malignancies with and without FGF/FGFR alteration. As of February 2019, FIGHT-101 enrolled 160 participants from 14 study sites in the US and Denmark, 116 of which received at least 1 dose of pemigatinib monotherapy. Sixteen participants who were treated with pemigatinib monotherapy had cholangiocarcinoma, [redacted] of whom had FGFR2 rearrangements or fusions and received pemigatinib 13.5 mg orally once daily on a 2-weeks-on and 1-week-off schedule for each 21-day cycle. [redacted]. The best overall response of PR was observed in [redacted]. In terms of safety outcomes, [redacted]. However, due to the open-label design and the

limited data on the efficacy of pemigatinib on CCA within the report, the ability to interpret these results is considerably limited.

Economic Evidence

Table 1: Cost and Cost-Effectiveness

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 a FGFR2 fusion or rearrangement, aligned with proposed Health Canada indication
Treatment	Pemigatinib
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 was matched to. • The sponsor's parametric survival extrapolations resulted in a substantial post-progression 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. • 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

Component	Description
	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.
CADTH reanalysis results	• Due to the highly uncertain nature of data derived from the MAIC, CADTH was unable to perform a base-case analysis. Instead, a reanalysis was conducted that used more appropriate assumptions, though CADTH notes the magnitude of benefit seen from pemigatinib estimated in this analysis may be overestimated. • CADTH 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; ICER = incremental cost-effectiveness ratio; FGFR2 = fibroblast growth factor receptor 2; LY = life-year; OS = overall survival; PFS = progression-free survival; QALY = quality-adjusted life-year.

Budget Impact

CADTH conducted a reanalysis that included: increasing pemigatinib uptake, changing the relative dose intensity to 100%, using the growth rate associated with intrahepatic cholangiocarcinoma (iCCA), 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 CADTH 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. Note that this is likely an underestimation of the true budget impact, since costs for patients who remain on pemigatinib for more than 1 year are not captured.

pERC Information

Members of the Committee

Dr. Maureen Trudeau (Chair), Mr. Daryl Bell, Dr. Jennifer Bell, Dr. Matthew Cheung; Dr. Winson Cheung, Dr. Michael Crump, Dr. Leela John, Dr. Christian Kollmannsberger, Mr. Cameron Lane, Dr. Christopher Longo, Dr. Catherine Moltzan, Ms. Amy Peasgood, Dr. Anca Prica, Dr. Adam Raymakers, Dr. Patricia Tang, Dr. Marianne Taylor, and Dr. W. Dominika Wranik.

Initial meeting date: November 10, 2021

Regrets: None

Conflicts of interest: None

Reconsideration meeting date: March 8, 2022

Regrets: One expert committee member did not attend

Conflicts of interest: None