Review Article

Safety and efficacy of pemigatinib in patients with cholangiocarcinoma: a systematic review

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Background: Cholangiocarcinoma (CCA) is an aggressive bile duct cancer with limited therapeutic options and poor prognosis. Pemigatinib, a selective *FGFR* inhibitor, has emerged as a promising targeted therapy for CCA patients harboring *FGFR2* fusions or rearrangements. This systematic review evaluated the safety and efficacy of pemigatinib in this patient population.

Methods: A comprehensive systematic review was conducted across PubMed, Scopus, Embase, Cochrane Library, and Web of Science to identify studies investigating pemigatinib in CCA patients. Five studies involving a total of 459 patients met the inclusion criteria.

Results: Pemigatinib demonstrated an overall objective response rate (ORR) of 43.2%, with a complete response (CR) achieved in 3% of patients. Stable disease was observed in 36.9% of patients, while 14.9% experienced disease progression. Median progression-free survival (PFS) varied across studies, due to differences in patient cohorts. The most common adverse effects (AEs) included hyperphosphatemia (48%), diarrhea (28.6%), fatigue (33%), and dry eyes (20.1%).

Conclusions: This systematic review suggests that pemigatinib has modest therapeutic efficacy in CCA patients, with a considerable proportion achieving disease control. However, the ORR of less than 50% highlights the potential need for combination or sequential therapies to improve outcomes. Close monitoring and management of AEs, particularly hyperphosphatemia, are crucial for optimizing treatment. Further large-scale randomized trials and research are warranted to identify predictive biomarkers and optimize pemigatinib-based treatment strategies for CCA patients with FGFR2 alterations.

Keywords: Cholangiocarcinoma (CCA); pemigatinib; FGFR inhibitors; targeted therapy

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Introduction

Cholangiocarcinoma (CCA) is the most prevalent primary malignancy of the bile duct, accounting for approximately 3% of all gastrointestinal tumors. It represents a challenging cancer subtype with poor prognosis and limited treatment options (1). Surgical resection remains the standard of care for CCA when feasible. However, due to advanced stage of disease at diagnosis, only about one-third of patients are eligible for surgery. Even among those undergoing curative resection, approximately 60–70% have recurrence after curative resection (2). For patients with advanced disease, combined chemotherapy with cisplatin and gemcitabine (CisGem) serves as the first-line treatment (1,3,4). Unfortunately, there is no established treatment protocol following first-line therapy failure, and second-line chemotherapy provides limited benefits (5-7). The rising global incidence of CCA has fueled the search for novel therapeutic strategies (8).

Recent advancements in genomic profiling have identified several actionable oncogenic alterations in CCA. Most notably mutations in *IDH1* and *FGFR2*, particularly in patients with intrahepatic CCA (1,9).

Aberrations in *FGFR* signaling such as *FGFR2* fusions or rearrangements, promote tumorigenesis by driving cellular proliferation, migration, survival, and angiogenesis (9). *FGFR2* gene fusions or translocations, present in 10–15% of intrahepatic CCA cases, lead to continuous activation of the *FGFR* tyrosine kinase, thus playing a pivotal role in oncogenesis (10). This has led to increasing interest in the *FGFR* inhibitors as potential therapeutic options (11).

Pemigatinib, a selective *FGFR1*, *FGFR2*, and *FGFR3* inhibitors, was the first targeted therapy approved by the U.S Food and Drug Administration (FDA) for CCA patients harboring *FGFR2* fusions or rearrangements as illustrated in *Figure 1*. This potent, oral competitive inhibitor blocks receptor autophosphorylation and downstream *FGF/FGFR* signaling, effectively inhibiting tumor cell growth in *FGFR*-driven cancers (12). Pemigatinib received accelerated FDA approval in April 2020 based on the results of the FIGHT-202 study, which demonstrated its clinical efficacy and manageable safety profile (13).

Despite its promise, several questions remain regarding pemigatinib's long-term efficacy, safety, and resistance mechanisms. Therefore, this systematic review aims to consolidate evidence from existing clinical trials to provide a comprehensive understanding of therapeutic potential of pemigatinib and limitations in treating CCA patients with *FGFR2* alterations. We present this article in accordance with the PRISMA reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-2024-923/rc) (14).

Highlight box

Key findings

- pemigatinib achieved a 43% objective response rate in cholangiocarcinoma (CCA) patients with FGFR2 fusions or rearrangements.
- Median progression-free survival (PFS) ranged from 6.3 to 8.7 months across studies.
- Common adverse effects (AEs) included hyperphosphatemia (48%), diarrhea (28.6%), fatigue (33%), and dry eyes (20.1%).
- Low complete response rate of 3% highlights challenges in achieving significant tumor regression.

What is known and what is new?

- CCA is an aggressive bile duct cancer with limited treatment options and poor prognosis.
- FGFR2 fusions or rearrangements are actionable genetic alterations present in a subset of intrahepatic CCA cases.
- Pemigatinib, a selective FGFR inhibitor, is approved for treating CCA patients with FGFR2 fusions or rearrangements.
- This systematic review consolidates evidence from five studies involving 459 patients, providing an in-depth assessment of pemigatinib's safety and efficacy, highlighting pemigatinib's modest efficacy, variable PFS, and notable adverse events.
- Ongoing research aims to optimize treatment strategies and address resistance mechanisms.

What is the implication, and what should change now?

- The modest efficacy of pemigatinib suggests that combining it with other therapeutic agents or employing sequential treatment strategies could improve patient outcomes in CCA.
- Proactive monitoring of AEs, particularly hyperphosphatemia, is essential for optimal patient care.
- Large-scale trials and biomarker-driven approaches are needed to refine pemigatinib-based treatment strategies in CCA.

Methods

Data sources and search strategy

The Population, Intervention, Comparator, Outcome (PICO) framework was utilized to structure this systematic review, concentrating on patients diagnosed with CCA as the population of interest. The intervention examined was pemigatinib, and no comparator or control group was included in the analyzed studies. The primary outcomes assessed were: safety [defined as the incidence and severity of adverse effects (AEs), including hyperphosphatemia,

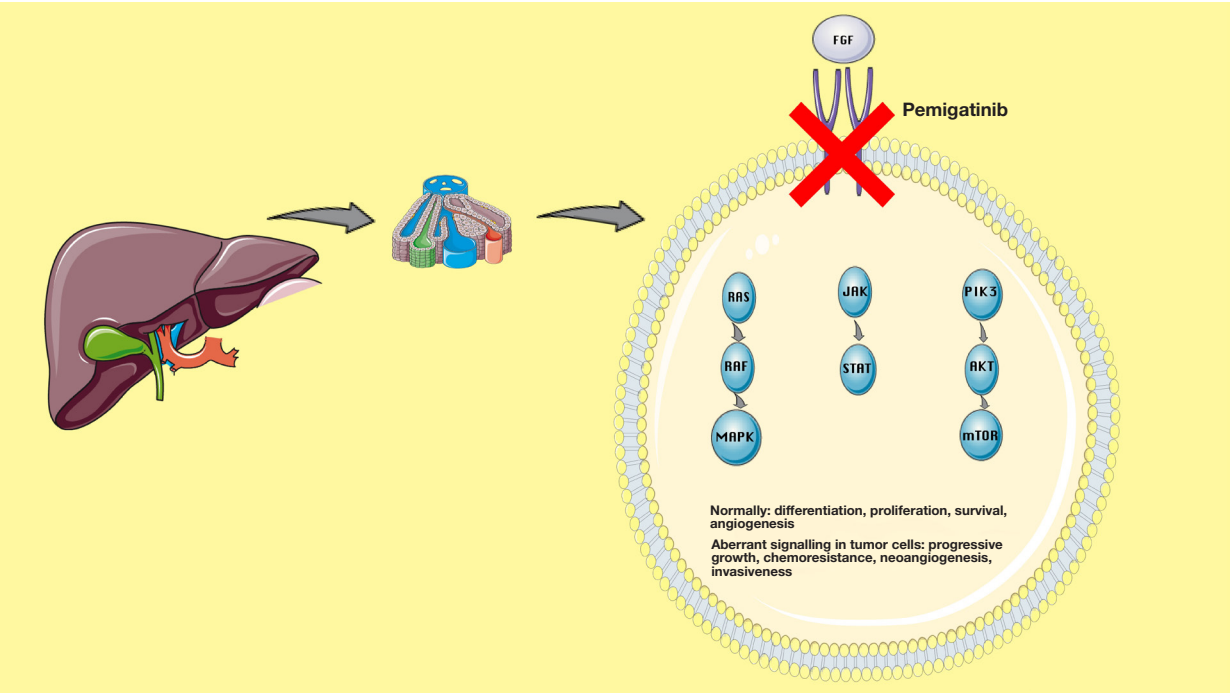

Figure 1 Mechanism of action of pemigatinib; FGFR1–4 inhibitor. This figure has been created by the authors and incorporates images from Servier Medical Art, which is licensed under a Creative Commons Attribution 4.0 Unported License by Servier (https://creativecommons.org/licenses/by/4.0/). RAS, rat sarcoma; RAF, rapidly accelerated fibrosarcoma; MAPK, mitogen-activated protein kinases; JAK, Janus kinase; STAT, signal transducer and activator of transcription; PI3K, phosphoinositide 3 kinase; AKT, protein kinase B; mTOR, mammalian target of rapamycin.

diarrhea, and fatigue] and efficacy [measured by objective response rate (ORR), progression-free survival (PFS), and complete response (CR) only].

Two independent researchers conducted a comprehensive literature review using the following keywords: ("Pemigatinib") OR ("Pemazyre") OR ("INCB054828") OR ("INCB-054828") AND ("cholangiocarcinoma") OR ("Bile duct cancer") OR ("biliary tract cancer") OR ("BTC"). Searches were performed across multiple databases, including PubMed, Embase, Scopus, Web of Science, and Cochrane, without applying any filters. The search was conducted up to September 2024.

The study is registered with PROSPERO (CRD42024603160) (15).

Study selection and eligibility criteria

A systematic search was performed for all relevant articles from inception until September 2024. The inclusion criteria were as follows: (I) randomized clinical trials (RCTs), observational studies, cohort or case controls studies, and case series involving more than five patients; (II) study participants aged 18 years of age or older; (III) articles published in English; (IV) studies with histologically or cytologically confirmed CCA; and (V) patients who have progressed after at least one prior systemic therapy. Studies were excluded if they involved (I) prior treatment with a selective FGFR inhibitor; (II) pediatric patients; or (III) a history of calcium or phosphate homeostasis disorders (IV) comparative studies involving other drugs

Search results were exported to Rayyan software for screening (16), and duplicates were removed. Two independent reviewers conducted an initial screening of titles and abstracts, followed by a full-text review. Any discrepancies between the reviewers were discussed and resolved through consensus, with a third reviewer consulted if necessary.

Data extraction and quality assessment

After finalizing the selected studies, data were extracted into

a pre-designed Excel sheet. Baseline characteristics of each study were recorded, and separate tables were created for the outcomes. In case where direct data, such as the overall mean age, were not provided, these values were calculated based on available group data from the studies.

Quality assessment of the included studies was conducted using the Methodological Index for Non-Randomized Studies (MINORS) for non-randomized trials and Newcastle-Ottawa Scale (NOS) for observational studies. All studies had good scores with no significant bias.

Results

Search and studies retrieved

The process of study selection is presented in Figure S1. A total of 1,062 studies were initially identified across five databases; PubMed (n=126), Scopus (n=308), Embase (n=461), Cochrane (n=12), and Web of Science (n=155). After removing 579 duplicates, the remaining studies were screened for relevance. Studies that did not assess the safety and efficacy of pemigatinib, as well as study protocols, case reports, case series with fewer than five patients, and animal studies, were excluded. Following full-text screening, five studies met the inclusion criteria for this review.

Out of these, four clinical trials were published in 2024, and one clinical trial was published in 2022. The final selection included two phase II clinical trials (17,18), one prospective study as part of an expanded access program (19) and two observational retrospective cohort study (20,21). The characteristics of these studies are summarized in *Table 1*.

Across the five included studies, a total of 459 patients were included. However, treatment response data were reported for 370 patients across four studies, comprising 280 females and 179 males. In all the studies included, pemigatinib was administered orally, most commonly at 13.5 mg once daily on a 3-week cycle (2 weeks on, 1 week off), although some patients either initially received or had their dose lowered to 9.0 mg or 4.5 mg. Overall, 86% (n=395) of the participants had undergone at least one prior therapy, primarily chemotherapy. Vogel *et al.* reported the highest adverse-event related dropout rate, at 8.2% (18).

The mean patient age across all studies ranged from 52 to 62.5 years. All included studies were assessed being of good quality, with no significant bias identified, see *Tables 2,3*.

Treatment response

In the first clinical trial conducted by Shi *et al.* [2023], a small cohort of 31 patients (thirty-one for safety analysis while thirty for efficacy analysis) with a mean age of 52 years was included. All participants had previously received systemic therapies before initiating pemigatinib treatment, administered in a 2 weeks on, 1 week off regimen (3-week cycle). Among these patients, 50% (n=15) achieved a partial response (PR), while another 50% (n=15) exhibited stable disease with no further progression. The median PFS was 6.3 months, and the median time to response was 1.4 months (17).

In a phase II single-arm study by Vogel *et al.* [2024], 147 patients (62 males and 85 females) from 146 global sites were treated with the same pemigatinib regimen as the Shi *et al.* cohort. The population was stratified into three groups based on FGFR status: fusions/rearrangements, other alterations, or no alterations, with data reported separately for each subgroup. Overall, 41.4% of patients achieved stable disease, 25.5% had a PR, and 23.4% experienced disease progression, while 2.06% achieved a CR. The median PFS varied by subgroup, reported as 7 months for FGFR fusions and rearrangements, 2.1 months for other alterations, and 1.5 months for no alterations; the median time to response was 2.7 months in FGFR mutations group (18). Due to the study's global nature, stratification by specific racial or cultural groups was not feasible.

Parisi *et al.* reported findings from two cohort studies: the French PEMI-BIL (n=49) and the Italian PEMI-REAL (n=23), totaling 72 patients (55 females and 17 males). In this cohort, 2.7% of patients achieved a CR, 43.1% achieved a PR, and 38.8% had stable disease post-treatment. Notably, 12.5% of patients continued to experience disease progression. The median PFS was 8.7 months; however, the time to response was not reported (20).

Saverno *et al.* examined data from the Cardinal Health Oncology Provider Extended Network in the United States, encompassing 120 patients with unresectable, advanced, or metastatic CCA. The majority of patients achieved a PR (54.2%), while 5% had a CR. Additionally, 27.5% of patients maintained stable disease, while 10% experienced disease progression. Overall survival at 3 months was 95.8% with data presented as point estimate with 95% confidence interval (CI), and the median PFS observed in this cohort was 7.4 months (21).

Overall, across all studies involving 368 patients, 3%

Table 1 Characteristics of included studies

Characteristics	Shi 2023, (17)	Lindley 2024, (19)	Vogel 2024, (18)	Parisi 2024, (20)	Saverno 2025, (21)
Country	China	USA, Austria, Germany	Multinational	France and Italy	USA
Study design	Single arm, phase II trial	Prospective cohort study	Single arm, phase II trial	Retrospective cohort study	Retrospective cohort study
Sample size	31	89	147	72	120
Intervention	13.5 mg OD in 3-week cycles (2 weeks on/1 week off)	13.5 mg OD in 3-week cycles (2 weeks on/1 week off)	13.5 mg OD in 3-week cycles (2 weeks on/1 week off)	–	13.5 mg OD in 3-week cycles (2 weeks on/1 week off)
Mean age (years)	52[a]	58.67[a]	55.5[a]	56.9	62.5[a]
Males, n (%)	10 (32.3)	31 (34.8)	62 (42.2)	17 (24.0)	59 (49.2)
ECOG status, n (%)					
0	16 (51.6)	–	60 (40.8)	28 (38.0)	–
1	15 (48.4)	–	76 (51.7)	31 (43.0)	94 (78.3)
2	0 (0)	–	11 (7.5)	12 (16.0)	26 (21.7)
Previous therapies, n (%)					
1	16 (51.6)	52 (58.4)	89 (60.5)	43 (59.7)	113 (94.2)
2	8 (25.8)	10 (11.2)	39 (26.5)	15 (20.8)	7 (5.8)
≥3	7 (22.6)	2 (2.2)	19 (12.9)	14 (19.4)	–
Major outcomes	1. ORR [(CR) or (PR)]	TEAEs	1. Duration of follow-up	1. Best overall response	1. Best overall response
	2. DOR		2. Best overall response	2. SD	2. SD
	3. DCR (CR, PR, or SD)		3. DOR	3. PD	3. PD
	4. OS		4. DCR	4. ORR [(CR) or (PR)]	4. ORR [(CR) or (PR)]
	5. TTR		5. Best overall response	5. DCR	5. PFS
	6. Tolerability		6. OS	6. Median DOR	9. OS
	7. Tumor response		7. PFS	7. Mean DOR (months)	
			8. TEAEs	8. PFS	
				9. OS	

[a], values converted from median to mean using meta-analysis accelerator (https://bmcmedresmethodol.biomedcentral.com/articles/10.1186/s12874-024-02356-6#citeas). CR, complete response; DCR, disease control rate; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; OD, once daily; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; TEAE, treatment-emergent adverse effects; TTR, time to response.

Table 2 MINORS quality assessment (methodological index for non-randomized studies)

Criteria	Score	
	Shi 2023, (17)	Vogel 2024, (18)
A clearly stated aim	2	2
Inclusion of consecutive patients	2	2
Prospective collection of data	2	2
Endpoints appropriate to the aim of the study	2	2
Unbiased assessment of the study endpoints	1[a]	1[a]
Follow-up period appropriate to the aim of the study	2	2
Lost to follow-up less than 5%	2	1[b]
Prospective calculation of the study size	2	2
Score out of 16	15	14

[a], either difference from methods or not mentioned; [b], more than 5% patients were lost due to either adverse events or discontinuation of treatment.

Table 3 NOS for cohort studies

Criteria	Score		
	Parisi 2024, (20)	Lindley 2024, (19)	Saverno 2025, (21)
Selection (max score =1)			
1. Representativeness of the exposed cohort	1	1	1
2. Selection of the non-exposed cohort	1	1	1
3. Ascertainment of exposure	1	1	1
4. Demonstration that outcome of interest was not present at start of study	0[a]	0[a]	1
Comparability (max score =2)			
1. Comparability of cohorts on the basis of the design or analysis	2	2	2
Outcome (max score =1)			
1. Assessment of outcome	1	1	1
2. Was follow-up long enough for outcomes to occur	1	1	1
3. Adequacy of follow up of cohorts	1	1	1
Score (out of 9)	8	8	9

[a], not specified in methodology. NOS, Newcastle-Ottawa Scale.

(n=11) achieved a CR, 40.2% (n=148) achieved a PR, making the ORR 43.2%. Moreover, 36.9% (n=136) maintained stable disease post-therapy. Disease progression occurred in 14.9% (n=55) of patients. A summary of individual study outcomes is provided in *Table 4*.

Treatment-related AEs

Four studies reported treatment-related AEs across all 339 patients treated with pemigatinib. Major AEs reported were hyperphosphatemia, diarrhea, alopecia and fatigue.

Table 4 Outcomes of included studies

Variables	Shi 2023, (17)	Vogel 2024, (18)[d]	Parisi 2024, (20)	Saverno 2025, (21)
OR, n (%)				
CR	0	3 (2.06)	2 (2.7)	6 (5.0)[e]
PR	15 (50.0)	37 (25.5)	31 (43.1)	65 (54.2)[e]
SD	15 (50.0)	60 (41.4)	28 (38.8)	33 (27.5)[e]
PD	0	34 (23.4)	9 (12.5)	12 (10.0)[e]
Overall survival (months), median (95% CI)			17.1 (12.7–NA)	
3 months	96.0 (74.8–99.4)	–	–	95.8 (90.3–98.2)[a]
6 months	96.0 (74.8–99.4)	3 cohorts[b]: 88.7 (81.0–93.4); 50.8 (26.6–70.7); 26.7 (8.3–49.6)	–	88.4 (80.3–93.3)[a]
Progression-free survival (months), median (95% CI)	6.3 (4.9–NE)	3 cohorts: 7.0 (6.1–10.5); 2.1 (1.2–4.9); 1.5 (1.4–1.8)[b]	8.7 (7.3–11.8)	7.4 (6.4–8.6)
3 months	95.8 (73.9–99.4)	–	–	95.8 (90.3–98.2)
6 months	65.1 (33.2–84.7)	–	–	71.5 (61.4–79.4)[a]
Time to response (months), median (95% CI)	1.4 (1.3–1.4)	2.7 (0.7–16.6)[c]	–	–

[a], data given as point estimate (% and CI rather than median and CI); [b], Vogel *et al*., had patients divided in three groups based on FGFR status: fusions/rearrangements, other alterations or no alterations. The values listed are in respective order; [c], values given only for FGFR2 fusions/rearrangements; [d], in the Vogel study, the overall total included two patients who did not have confirmed FGF/FGFR status by central laboratory testing and were not assigned to any cohort; therefore, the efficacy percentages were calculated using a final patient count of 145 (this adjustment does not apply to *Table 1*); [e], among the four clinical trials included here, only one reported real-world (rw) response data. For this study, we extracted the response values (rwCR, rwPR, rwSD, and rwPD) as provided without the accompanying 95% confidence intervals, and these are presented in the table for brevity. CI, confidence interval; CR, complete response; NE, not evaluable; NR, not reached; OR, overall response; PD, progressive disease; PR, partial response; SD, stable disease.

Hyperphosphatemia was the most prevalent, affecting 48% (n=163) of patients, while 13.2% (n=45) experienced hypophosphatemia. Diarrhea was observed in 28.6% (n=97) of patients, and alopecia was observed in 32.7% (n=111). Additionally, 33% (n=112) of patients reported fatigue. The most frequently documented ocular toxicity was dry eyes, noted in 20.1% (n=68), while keratitis (4.1%, n=14), retinal detachment (2.4%, n=8), corneal abrasion (1.5%, n=5), trichiasis (1.5%, n=5), blurred vision (1.8%, n=6), and conjunctivitis (1.2%, n=4) were less common but warrant caution. A summary of the most common AEs (those reported by three or more studies) is provided in the *Table 5*.

Discussion

The results of this systematic review highlight the potential of pemigatinib as a targeted therapy for CCA patients with *FGFR2* fusions or rearrangements. Our analysis, which included multiple studies and hundreds of patients, demonstrated that pemigatinib offers modest therapeutic efficacy, with a considerable proportion of patients achieving PRs and stable disease. However, the therapy also showed a low CR rate, indicating the difficulty in achieving significant tumor regression in this patient population.

Variability in treatment outcomes was evident across the included studies, with median PFS ranging from 6.3 to 8.7 months. This variability may reflect differences in patient demographics, study design, and prior therapies, as most patients had undergone at least one prior systemic therapy. For instance, Shi *et al.* (17) observed a shorter PFS of 6.3 months in a smaller cohort of 31 patients, whereas Vogel *et al.* (18) examining a larger, more diverse population of 147 patients, reported three distinct median PFS values (7.0, 2.1 and 1.5 months). The broader geographic representation in Vogel *et al.*'s study likely contributed to these observed differences in treatment outcomes.

Table 5 Treatment-related adverse events

Variables	Shi 2023, (17)	Lindley 2024, (19)	Vogel 2024, (18)	Parisi 2024, (20)
Hyperphosphatemia	24 (77.4)	20 (22.5)	79 (53.7)	40 (55.6)
Hypophosphatemia	6 (19.4)	4 (4.5)	19 (12.9)	16 (22.2)
Stomatitis	–	6 (6.7)	51 (34.7)	35 (48.6)
Dry mouth	17 (54.8)	5(5.6)	43 (29.3)	–
Nausea	–	2 (2.2)	38 (25.9)	11 (15.3)
Vomiting	1 (3.2)	–	17 (11.6)	11 (15.3)
Diarrhea	13 (41.9)	5 (5.6)	53 (36.1)	26 (36.1)
Alopecia	17 (54.8)	3 (3.4)	68 (46.3)	23 (31.9)
Dysgeusia	10 (32.3)	–	50 (34.0)	18 (25.0)
Fatigue	11 (35.5)	3 (3.4)	48 (32.7)	50 (69.4)
Dry eyes	5 (16.1)	–	34 (23.1)	29 (40.3)
Palmar-plantar erythrodysesthesia	4 (12.9)	–	23 (15.6)	24 (33.3)
Retinal pigment epithelial detachment	–	2 (2.2)	–	6 (8.3)
Blurred vision	6 (19.4)	–	–	–
Trichiasis	5 (16.1)	–	–	–
Corneal abrasion	5 (16.1)	–	–	–
Conjunctivitis	4 (12.9)	–	–	–
Keratitis	–	–	–	14 (19.4)

Data are presented as n (%).

Moreover, the relatively longer PFS in some subgroups underscores the potential value of identifying predictive biomarkers to optimize patient selection and enhance therapeutic efficacy.

The consistently low CR rate across studies indicates that while pemigatinib can stabilize the disease in a large portion of patients, its ability to induce complete remission remains limited, which reflects the poor prognosis and aggressiveness nature of CCA. Given these limitations, these findings suggest that combining pemigatinib with other therapeutic agents or implanting sequential treatment strategies may offer a more comprehensive approach to improving outcomes.

The safety profile of pemigatinib shows that AEs are both common and consistent with those observed in other *FGFR* inhibitors. Hyperphosphatemia, affecting nearly half of patients, emerged as the most frequently reported side effect, highlighting the importance of careful monitoring of serum phosphate levels throughout treatment. Managing this side effect may require dietary modifications and the use of phosphate binders to maintain phosphate homeostasis and optimize therapeutic outcomes. Further research is warranted to explore the underlying mechanisms driving these AEs and to develop mitigation strategies that can improve patient tolerance and safety.

Incorporating pemigatinib into clinical practice represents a significant step towards personalized medicine for CCA patients, particularly those with *FGFR2* fusions or rearrangements. This approach has the potential to improve both survival rates and quality of life for patients who have limited treatment options.

Our findings align with those of the FIGHT-202 trial (18), which reported an ORR of 37% and four cases of CRs. However, the efficacy observed in our study appears slightly lower, which may be attributed to differences in treatment protocols and patient populations. While the FIGHT-202 trial reported a median PFS of 7 months, our review highlights variability in PFS across studies, potentially influenced by factors such as patient demographics, the number of prior therapies received, and

the study designs (9). This variability reinforces the need for individualized treatment strategies to maximize therapeutic benefits.

Regarding adverse events, our findings are consistent with existing literature, which highlights hyperphosphatemia as the most common side effect of pemigatinib (9,22,23). The safety profile observed in this review aligns well with other studies, emphasizing the importance of proactive side-effect management. Many of these adverse events reflect on-target FGFR inhibition, including hyperphosphatemia, ocular toxicities, and skin toxicities (24). Consequently, close monitoring protocols are recommended, such as baseline and periodic ophthalmologic evaluations to promptly detect any vision changes, as well as regular serum phosphate checks with timely intervention (e.g., phosphate binders or dose adjustments) if levels become elevated. These measures would be essential for optimizing patient safety, minimizing toxicity-related treatment interruptions, and ensuring the best possible outcomes for patients receiving pemigatinib.

When comparing pemigatinib's efficacy with other *FGFR* inhibitors, such as futibatinib, previous studies indicate that futibatinib demonstrated a higher ORR and PFS. Although numerical trends favor futibatinib, the differences in efficacy outcomes between the two drugs were not statistically significant (25).

When interpreting these findings, it is important to consider the limitations of this systematic review. First, the generalizability of the results might be constrained by the relatively small sample size in each study. Furthermore, most of these studies were single-arm trials lacking control groups, making it difficult to draw definitive conclusions regarding the comparative efficacy of pemigatinib versus standard therapies. Another notable concern is the influence of prior therapies on the observed efficacy and safety outcomes, as most patients had received previous treatments. Additionally, the absence of long-term follow-up data limits our understanding of the durability of treatment effects and long-term safety profile of pemigatinib.

Moreover, the incorporation of both real-world and clinical trial data introduces heterogeneity in disease assessment. Although most studies used RECIST 1.1 there were varying independent review committees in each study, also one study did not specify its criteria, this can potentially lead to under- or overestimation of response and PFS outcomes, despite overall alignment with the FIGHT-202 trial.

Finally, conducting larger studies in this relatively rare subset of CCA patients with FGFR2 alterations poses significant challenges, and many trials of FGFR inhibitors had to halt recruitment due to slow accrual.

These limitations emphasize the need for further research, particularly larger, randomized controlled trials and multicenter studies, to validate the current findings and fully assess pemigatinib's full therapeutic potential in CCA. Such studies are critical for drawing robust conclusions regarding long-term efficacy and safety. Additionally, a deeper understanding of resistance mechanisms is essential for developing new therapeutic strategies. Comprehensive genomic profiling has identified several targetable alterations in CCA, making it critical to identify biomarkers for both response and resistance to pemigatinib to optimize personalized treatment and improve patient outcomes. For instance, Wu *et al.* demonstrated that resistance mechanisms can emerge in patients taking *FGFR* inhibitors for *FGFR2*-altered CCA, particularly the N550 molecular brake and V565 gatekeeper mutations in the *FGFR2* kinase domain (26). Furthermore, recent findings have shown that *PTPN9* interacts with *FGFR2* and negatively regulates *FGFR2* pY656/657, enhancing the effectiveness of pemigatinib. Coexpression of *PTPN9* and *ACAP1* has been associated with a favorable prognosis in CCA, and mutations such as *FGFR2* I654V that reduce *PTPN9*-*FGFR2* interaction may limit pemigatinib efficacy (27). Identifying such biomarkers could aid in selecting patients who are more likely to benefit from pemigatinib therapy and in developing strategies to overcome resistance.

Considering this, future research should explore combination therapies involving pemigatinib with other treatment modalities, such as immunotherapy or chemotherapy, which could enhance its effectiveness. Numerous studies are underway, including phase II clinical trials like NCT05913661, NCT06530823, and NCT06439485, which are exploring the combination of pemigatinib with sintilimab, durvalumab, and atezolizumab + durvalumab, respectively. Additionally, a phase I trial investigated combining pemigatinib or ivosidenib with gemcitabine and cisplatin, but was terminated due to low accrual, with only one patient in the pemigatinib arm which reflects the paucity of patients eligible for clinical trials due to how uncommon the disease is and the wide range of genetic mutations involved (28).

Table 6 gives a summary of the ongoing and future clinical trials using pemigatinib for CCA.

Conclusions

This systematic review underscores the critical need for healthcare providers to remain abreast of advancements

Table 6 Ongoing and future clinical trials using pemigatinib for CCA

Intervention	CT phase	CT number	Previous treatment	Status
Pemigatinib	II	NCT05565794	Surgery/SBRT or ablation	Recruiting
Pemigatinib + sintilimab	II	NCT05913661	No	Recruiting
Pemigatinib *vs*. gemcitabine + cisplatin	III	NCT03656536	No	Active, not recruiting
Pemigatinib + durvalumab	II	NCT06530823	Yes	Not yet recruiting
Pemigatinib + atezolizumab + bevacizumab	II	NCT06439485	Yes	Not yet recruiting

CCA, cholangiocarcinoma; CT, computed tomography; SBRT, stereotactic body radiation therapy.

in targeted therapies to ensure that patients receive the most effective and up-to-date treatments. Pemigatinib shows promise as a targeted therapy for CCA patients with *FGFR2* fusions or rearrangements. However, its modest efficacy and notable AEs necessitate a cautious approach in clinical practice. The variability in response rates and PFS highlights the importance of personalized treatment strategies tailored to the unique biology of each patient's tumor.

As our understanding of CCA, particularly *FGFR2*-driven tumors, deepens, there is hope for optimizing the use of pemigatinib within treatment regimens. Continuous research and clinical trials are essential for refining these therapies, improving patient outcomes, and ultimately enhancing the quality of life for those facing this challenging cancer.

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