Pemigatinib for adults with previously treated, locally advanced or metastatic cholangiocarcinoma with FGFR2 fusions/rearrangements

Daniel Walden, Cody Eslinger and Tanios Bekaii-Saab

Abstract: Biliary tract cancers are a diverse and aggressive malignancy that carry a poor chance for curative treatment and significant associated mortality. Current first-line treatment only extends median overall survival to roughly 1 year and is associated with a significant adverse event profile. Recently, advancements in genetic sequencing have opened new avenues of targeted treatment. In cholangiocarcinoma, FGFR2 alterations have been shown to be present in roughly 10–15% of intrahepatic cholangiocarcinoma. Pemigatinib, a FGFR1–4 inhibitor, has been shown to significantly extend survival in the second-line setting to over 20 months in patients who harbor FGFR2 fusions. Here, we outline the development and future direction of pemigatinib and other FGFR2 inhibitors in the field of advanced biliary tract cancers.

Keywords: cholangiocarcinoma, FGFR, FGFR inhibitor, fusion, pemigatinib

Background
Biliary tract cancers represent a diverse group of epithelial cancers characterized by aggressive and chemoresistant tumors with poor long-term survival.1 Surgery remains the only curative treatment; however, only roughly 35% of patients can undergo curative surgery and of surgically resected patients, 35% have clinical relapse in 2 years.2,3 Often limiting surgical resection includes the presence of vascular involvement and the presence of metastatic spread to regional lymph nodes, which are often evident at time of diagnosis given the frequent asymptomatic status of early disease. Systemic therapy for cholangiocarcinoma represents the only feasible option for patients with locally advanced or metastatic cholangiocarcinoma. Results of the multicenter ABC-02 trial showed superior results of gemcitabine-based chemotherapy combined with cisplatin when compared to gemcitabine alone. However, this regimen is associated with significant toxicity, limited to patients with adequate renal function, and achieves only limited efficacy with median overall survival (OS) of 11.7 months.4 Outside of the United States, a commonly used regimen includes gemcitabine plus S-1 (tegafur/ gimeracil/oteracil). Both gemcitabine/cisplatin and gemcitabine/S-1 showed similar results with regard to median OS (15.1 versus 13.4 months) and median PFS (6.8 versus 5.8 months) with gemcitabine plus S-1 compared to gemcitabine plus cisplatin.5

Following first-line treatment, only 15–25% of patients are candidates for salvage therapy due to morbidity of the disease and rapid decline in performance status.6 Prognostic tools to determine clinical response in second-line treatment are not established; however, three studies suggest that patients with ECOG 0–1, disease control to first-line therapy, low CA 19-9, and absence of peritoneal carcinomatosis confer the best response in the second line.7–9 Patients who progress on first-line treatment have limited treatment options with dismal OS and progression-free survival benefit compared to active symptom control

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The recently published ABC-06 trial reported an OS benefit of just 4 weeks with the addition of 5-fluorouracil, oxaliplatin, and leucovorin (FOLFOX) compared to ASC alone (6.2 months versus 5.3 months). Furthermore, the recent results from the NIFTY trial suggest added efficacy of liposomal irinotecan with fluorouracil when compared to fluorouracil and leucovorin in the second-line setting with an OS of 8.6 months versus 5.5 months ($p=0.035$), highlighting the need for additional therapies.

In recent years, advancements in gene sequencing have better highlighted the genetic landscape of BTC and have shown that molecular profiles segregate with anatomical location [perihilar/distal versus intrahepatic cholangiocarcinoma (iCCA)]. A recent analysis which reviewed next generation sequencing of 1200 patients with cholangiocarcinoma revealed that patients harbor an average of 4.6 genomic alterations with the most frequent being altered genes in p53 (40%), CDKN2A (29.0%), KRAS (22.6%), CDKN2B (19.7%), ARID1A (16.0%), SMAD4 (11.7%), IDH1 (10.2%), and BAP1 (10.2%). Mutations harboring potential actionable mutations were reported at 44% with most being IDH1 mutations (10.2%), ERBB2 mutations/amplifications (8.0%), FGFR2 mutations/rearrangements (7.1%), PIK3CA mutations (7.0%), and BRAF mutations (4.7%). Better definition of potential actionable mutations in BTC has led to numerous trials evaluating the efficacy of blockade of such driver mutations including IDH1/2, FGFR2/4, EGFR, HER2, and PIK3CA. Of these trials, the most promising has been through inhibition of the FGFR receptor.

Numerous agents have been developed to target FGFR inhibition in this clinical context. Initial agents acquiring FDA approval included pemigatinib in April 2020 and shortly followed by infigratinib in May 2021. Third-generation FGFR inhibitors including futibatinib (TAS-120) have recently been FDA approved which have been shown to overcome the gatekeeper mutation, V565F, that exemplifies resistance to pemigatinib and infigratinib.

**FGFR2 alterations in cholangiocarcinoma**

The prevalence of FGFR2 alterations including fusions, translocations, and rearrangements in cholangiocarcinoma ranges from 10 to 15% and are almost exclusively confined to iCCA. FGFR2 is a part of a larger FGFR family of four transmembrane receptors (FGFR1–5) and has been shown to be critical in physiologic proliferation, survival, migration, and angiogenesis. Notable downstream substrates include activation of PKC, Pi3K, MAPK as well as c-JUN and STAT. The FGFR2 gene most commonly undergoes a rearrangement/fusion with other genes resulting in dimerization and subsequent constitutive activation, promoting oncogenesis. The most common translocations include FGFR2 to periphilin 1, adenosyl-homocysteinase, and bicaudal-C family RNA-binding protein (BICC1); however, over 150 fusion partners have been identified. FGFR2 gene fusions may represent a distinct molecular subtype of iCCA with a predominance toward younger age of onset, less aggressive clinical course with female predominance. Since the discovery of these aberrant signaling domains in iCCA, numerous trials have emerged to discover mechanisms to block this constitutive signaling leading to carcinogenesis.

**Pemigatinib preclinical studies**

Pemigatinib (Pemazyre™) is a potent ATP-competitive selective inhibitor of FGFR1, FGFR2, and FGFR3 with half maximal inhibitor concentration (IC50) values of 0.4, 0.4, and 1 nmol/l, respectively, with weaker inhibition of FGFR4. Pemigatinib is highly selective for FGFR but has been shown to have mild inhibitor effects on vascular endothelial growth factor receptor 2 (IC50 182 nM and c-kit (IC50 266 nM). In vitro studies showed reduction in phosphorylation of FGFR to basal levels at a concentration of just 5 nM of pemigatinib with concurrent downstream suppression of phosho-ERK and phospho-STAT5 in concentration-dependent manner. In vivo studies revealed significant tumor suppression in mice xenograph models with oral doses of 0.3 mg/kg in AML (FGFR1), cholangiocarcinoma (FGFR2), and urothelial carcinoma (FGFR3). By sparing FGFR4, the effects on bile acid metabolism and subsequent hepatotoxicity can be mitigated.

**Phase 1 trials with pemigatinib**

FGFR inhibitor therapy in oncology and hematology trial (FIGHT)-101 was a phase I/II, open label, three-part, dose escalation trial in patients...
with pretreated advanced solid tumors with and without FGF/FGFR alterations who progressed after prior therapy with no effective standard therapy available. In part 1, FGF/FGFR mutations were not required, and patients were enrolled into cohorts 1–3 (1–4 mg QD) with escalation following a 3+3 design (6–20 mg QD). Part 2 followed a dose expansion protocol for which FGF/FGFR mutations were required and additional patients were dosed at 13.5 mg or 20 mg QD. Part 3 included pemigatinib in combination with standard therapies. The most frequent all-cause, all-grade adverse events (AEs) were hyperphosphatemia (74%) and fatigue (40%) for 9/13.5 mg QD dose. Similar AEs were noted for the 20 mg dose. No dose-limiting toxicities were observed and recommended phase 2 dose was 13.5 mg QD.

Phase 2 trials with pemigatinib

The FIGHT-202 trial was a multicenter, open-label, single arm, multicohort phase 2 trial in patients aged >18 years old who developed disease progression following first-line treatment with an Eastern Cooperative Oncology Group (ECOG) of 0–2 from the United States, Europe, Middle East, and Asia. Patients were enrolled to one of three cohorts: patients with FGFR2 fusions or rearrangements, patients with other FGF/FGFR mutations including mutations, amplifications, or deletions, or patients without FGFR mutations. All patients received 13.5 mg of oral pemigatinib daily (21-day cycles, 2 weeks on, 1 week off). Treatment was continued until disease progression or intolerable side effects. Tumor response was assessed by independent review according to RECIST 1.1. The primary end point was overall response rate (ORR). A total of 146 patients were included, 107 with FGFR2 fusions or rearrangements, 20 with other FGF/FGFR mutations, and 18 without FGFR alterations. The most common FGFR2 partner was BICC1 (29%). Overall median follow-up was 17.8 months with a median duration of treatment of 7.2 months (3.9–10.9) in patients with FGFR2 fusions or rearrangements and only 1.4 months (1.0–6.0) in patients with other FGF/FGFR fusions or rearrangements and 1.3 months (0.7–1.9) in patients without FGF/FGFR alterations. Across all cohorts, 57 patients (39%) had received two or more previous systemic therapies, representing a relatively heavily pretreated population. Of the 107 patients with FGFR2 fusions or rearrangements, 105 (98%) had ICCA. This cohort represented a greater proportion of women, patients aged younger than 65 years, and patients with disease confined to the liver and included a smaller proportion of patients with an ECOG performance status of 2 than patients in the other cohorts.

Thirty eight (35.5%) of the 107 patients with confirmed FGFR2 fusions/rearrangements achieved a centrally confirmed objective response with 3 patients (2.8%) achieving a complete response. Eighty eight (82%) patients achieved disease control. The median time to first response was 2.7 months (IQR 1.4–3.9) with a median duration of response of responders was 7.5 months (95% CI 5.7–14.5). The median progression-free survival (PFS) was 6.9 months (95% CI 6.2–9.6) and median OS reported at 21.1 months (95% CI 14.8–NR). None of the patients with other FGF/FGFR alterations or without FGF/FGFR alterations had an objective response. Median PFS of patients with other FGF/FGFR fusions or rearrangements and without FGF/FGFR mutations was 2.1 and 1.7 months with OS of 6.7 and 4.0 months, respectively.

The most common AE across all three cohorts was hyperphosphatemia (60%); however, no grade 3–4 hyperphosphatemia was reported. Grade 3 hypophosphatemia was noted in 7% of patients. Additional common grade 1–2 AE included alopecia (46%), dysgeusia (38%), diarrhea (34%), fatigue (31%), stomatitis (27%), nausea (23%), arthralgia (11%), and palmar-plantar erythrodysesthesia (11%).

Future directions of pemigatinib in cholangiocarcinoma

Based on the results of the FIGHT-202, pemigatinib was granted accelerated FDA approval for the treatment of adults with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with a FGFR2 fusion or rearrangement in April 2020. This further led to the development of the phase III FIGHT-302 trial which is currently actively recruiting patients to evaluate the efficacy of pemigatinib versus standard chemotherapy in the first-line setting in unresectable or metastatic cholangiocarcinoma (NCT03656536). The trial is estimated to complete accrual in 2023 with estimated completion in 2026. The phase 1 trial, “A Phase I, Multi-Center, Open Label, Dose De-Escalation and Expansion
Numerous other phase 2 and phase 3 studies are actively recruiting patients and are set to determine the efficacy of pemigatinib in conjunction with gemcitabine and cisplatin in the first-line setting with an estimated completion date of 2025 (NCT04088188).

A subset of patients in both the FIGHT 101 and FIGHT 202 trials had rapid disease progression shortly after initiation of pemigatinib, suggesting the development of resistance to FGFR inhibition. Numerous mechanisms of acquired resistance have been demonstrated including activation of MET, PI3K/AKT/mTOR, Ephrin 3B, or EGFR.31–33 A study evaluating genomic alterations in cell-free circulating DNA (ctDNA) in patients who recently progressed on FGFR2 inhibitor, infigratinib, revealed V565F gatekeeper point mutations. Given the predictability in the development of these mutations in response to FGFR blockade, the use of ctDNA to monitor for the development of such mutations and subsequent adjustment in treatment may become mainstay. These resistant mutations have also been shown to be present in de novo disease, which would direct treatment decisions, further highlighting the need for genomic monitoring. In the landmark paper by Goyal, we observed the profound inter and intraleisonal genetic mutational heterogeneity that develops in response to FGFR inhibition, so direct biopsy of one metastatic lesion is likely inadequate for mutational monitoring.36

Highly selective and irreversible FGFR inhibitors are slowly coming to market. Most notably, futibatinib, a pan-FGFR irreversible antagonist, has been shown to produce clinical and radiographic responses in patients who had progression on prior FGFR inhibitors pemigatinib and infirgratinib.29 Pemigatinib and infigratinib are not irreversible inhibitors and thus mutations in the FGFR binding site can lead to allosteric hindrance, preventing drug interaction and efficacy. The phase 2 FOENIX-CCA2 trial recently reported their updated results at the 2022 ASCO conference and report an ORR of 41.7% with a median OS of 20.0 months with hyperphosphatemia being the most common treatment-related AE at 85%. Data presented at ASCO 2022 suggest that futibatinib continues to have efficacy against gatekeeper mutations V565L; however, preliminary data may suggest that the V565F may continue to confer resistance. We anticipate the phase 3 FOENIX-CCA3 trial comparing futibatinib versus cisplatin plus gemcitabine in the first-line setting (NCT04093362). The most recent development in FGFR inhibitors comes out of the phase 1 data presented on drug RLY-4008, an oral, highly selective FGFR2 inhibitor to target both FGFR2 driver and resistance mutations. Most interestingly their preliminary data revealed that 100% of the previous FGFR inhibitor treated patients had stable disease with 9/16 patients with tumor reduction from −12 to −35%. Furthermore, 78% of the patients with detectable FGFR2 resistance mutation on ctDNA at baseline became undetected after one cycle of treatment.37 Furthermore, given RLY-4008’s highly specific target of FGFR2, the common side effects of hyperphosphatemia are mitigated significantly.

Expert opinion
Over the past 5 years, there has been tremendous growth in the area of FGFR inhibition in cholangiocarcinoma. We have seen the development of highly specific agents which has allowed for ongoing clinical efficacy despite the development of resistance through gatekeeper (V565) and molecular break (N550) mutations. Given the predictability in the development of these mutations in response to FGFR blockade, the use of ctDNA to monitor for the development of such mutations and subsequent adjustment in treatment may become mainstay. These resistant mutations have also been shown to be present in de novo disease, which would direct treatment decisions, further highlighting the need for genomic monitoring. In the landmark paper by Goyal, we observed the profound inter and intraleisonal genetic mutational heterogeneity that develops in response to FGFR inhibition, so direct biopsy of one metastatic lesion is likely inadequate for mutational monitoring.36

Study of Gemcitabine and Cisplatin with AG120 or pemigatinib for Advanced Cholangiocarcinoma,” is actively recruiting patients and is set to determine the efficacy of pemigatinib in conjunction with gemcitabine and cisplatin in the first-line setting with an estimated completion date of 2025 (NCT04088188).
Given the existing evidence to suggest that targeted FGFR inhibitor therapy may be superior to chemotherapy in cholangiocarcinoma harboring FGFR2 fusions (median overall survival [mOS] 6.2 months with FOLFOX versus 17.5 months with pemigatinib in second line), ongoing studies evaluating the efficacy of adjuvant or neoadjuvant FGFR inhibition in stages I–III cholangiocarcinoma is warranted. Clinical data to suggest benefit of adjuvant capcitabine is uncertain, given the absence of statistical significance of capcitabine in the intention to treat population of the BILCAP trial when compared to placebo (51.1 months versus 35.4 months), thus additional adjuvant treatments are needed.38 Evaluating the use of targeted therapy in the adjuvant and neoadjuvant space is undoubtedly an area of growing interest and clinical need.

Declarations

Ethics approval and consent to participate
None.

Consent for publication
Not applicable.

Author contributions

Daniel Walden: Conceptualization; Investigation; Methodology; Writing – original draft; Writing – review & editing.

Cody Eslinger: Visualization; Writing – original draft; Writing – review & editing.

Tanios Bekaii-Saab: Conceptualization; Methodology; Supervision.

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