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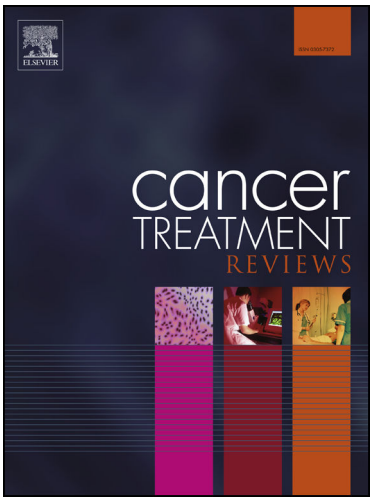

Anti-tumour Treatment

Targeting FGFR inhibition in cholangiocarcinoma

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Title: Targeting FGFR inhibition in cholangiocarcinoma

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Abstract

Cholangiocarcinomas (CCAs) are rare but aggressive tumours of the bile ducts, which are often diagnosed at an advanced stage and have poor outcomes on systemic therapy. Somatic alterations with therapeutic implications have been identified in almost half of CCAs, in particular in intrahepatic CCA (iCCA), the subtype arising from bile ducts within the liver. Among patients with CCA, fibroblast growth factor receptor 2 (*FGFR2*) fusions or rearrangements occur almost exclusively in iCCA, where they are estimated to be found in up to 10–15% of patients. Clinical trials for selective FGFR kinase inhibitors have shown consistent activity of these agents in previously treated patients with iCCA harbouring *FGFR* alterations. Current FGFR kinase inhibitors show differences in their structure, mechanisms of target engagement, and specificities for FGFR1, 2, 3 and 4 and other related kinases. These agents offer the potential to improve outcomes in FGFR-driven CCA, and the impact of variations in the molecular profiles of the FGFR inhibitors on efficacy, safety, acquired resistance mechanisms, and patients' health-related quality of life remains to be fully characterized. The most common adverse event associated with FGFR inhibitors is hyperphosphatemia, an on-target off-tumour effect of FGFR1 inhibition, and strategies to manage this include dose adjustment, chelators, and the use of a low phosphate diet. As FGFR inhibitors and other targeted agents enter the clinic for use in FGFR-driven CCA, molecular testing for actionable mutations and monitoring for the emergence of acquired resistance will be essential.

Keywords: Cholangiocarcinoma; Receptor, Fibroblast Growth Factor, Type 2; Cancer; Oncogenes; Chronic liver disease

Introduction

Cholangiocarcinomas (CCAs) are heterogeneous epithelial tumours arising from the biliary tree with features of cholangiocyte differentiation [1]. The anatomical subtypes of cholangiocarcinoma include intrahepatic cholangiocarcinoma (iCCA), which arises in the bile ducts within the liver, and extrahepatic cholangiocarcinoma (eCCA), which involves the ducts outside of the liver including the left and right hepatic ducts and the common bile duct. The prognosis of both types of CCA is poor, but is particularly poor in iCCA, where only 30–40% of patients present with surgically resectable disease [2] and unfortunately, the majority of cases recur even in apparently resectable disease. The 5-year overall survival for patients with iCCA is <10% [3], so treatments to improve survival are urgently needed. As iCCA symptoms may be non-specific, such as vague abdominal discomfort, nausea, fatigue, and weight loss, delayed diagnosis is particularly common [4]

In recent years, precision oncology has emerged as an promising approach for CCA. One of the most promising range of targets are the fibroblast growth factor receptor 2 (*FGFR2*) fusions, gene alterations present in 10–15% of iCCAs, but in almost no eCCAs. Multiple efforts to drug this target led to the first US Food and Drug Administration (FDA) approval in CCA. Pemigatinib, an oral selective FGFR inhibitor with potent activity against FGFR1–3, gained approval for treatment of patients with previously treated, locally advanced or metastatic CCA harbouring an *FGFR2* fusion or rearrangement [5]. This review focuses on the molecular biology driving biliary tract malignancies, the clinical development of FGFR inhibitors in *FGFR*-altered CCA, and future considerations as this promising new precision medicine-based option moves into the clinic.

Molecular biology of the *FGFR* gene

The FGF-FGFR signaling pathway

Fibroblast growth factors (FGFs) and their associated fibroblast growth factor receptors (FGFRs) have been studied extensively, with a focus to exploit the therapeutic potential of FGF-FGFR signaling being made over the past 10 years [6]. The FGF pathway consists of 22 human FGFs and four highly conserved transmembrane receptors with intracellular tyrosine kinase domains, FGFR 1–4 [7]. The FGFRs are expressed on multiple cell types [8]. FGF-FGFR signaling is triggered by the ligand-dependent receptor dimerization following binding of FGF at the cell surface. This leads to intracellular phosphorylation of receptor kinase domains, a cascade of intracellular signaling, and gene transcription that activates a number of intracellular survival and proliferative pathways (**Figure 1A**) [9]. The specificity of the FGF-FGFR interaction is influenced by the differing ligand binding capacities of the receptor paralogues, by alternative splicing of FGFR, and by tissue-specific expression of ligands and receptors, coupled with cell surface or secreted proteins that facilitate the FGF-FGFR interactions and increase ligand specificity [10]. Alterations in *FGFR* genes, including activating mutations, chromosomal translocations, gene fusions, and gene amplifications, can result in ligand-independent signaling which, in turn, leads to constitutive receptor activation (**Figure 1B**).

FGF-FGFR signaling has been shown to have oncogenic roles in many cancers. Key downstream signaling pathways altered by FGF-FGFR activation are the *Ras-Raf-MEK-ERK* pathway, the *PI3-AKT-mTOR* pathway, and *JAK-STAT* pathway (**Figure 1A**) [11]. In an analysis of 4,853 solid tumours, *FGFR* aberrations were found in 7.1% of all cancers, with the majority (66%) being gene amplifications, followed by mutations (26%), and rearrangements (8%) [8]. Among the CCA tumours in that study (N=115), 7% harboured *FGFR* aberrations. These aberrations were mostly in the gene encoding for *FGFR2* (6.1%),

with a small proportion in the *FGFR1* gene, and none identified in the *FGFR3* or *FGFR4* genes.

Genomic profiling of CCA

Biliary tract cancers (BTCs) arise from epithelial cells lining the bile duct and can occur at distinct anatomical locations: intrahepatic, extrahepatic and in the gallbladder [12]. Analyses of the genomic and transcriptomic landscape of the anatomical subtypes of BTC show that molecular profiles vary between iCCA, eCCA, and gallbladder cancer (GBC), with multiple small cohorts of patients having mutually exclusive or co-existent aberrations [12–15]. Given the heterogenous nature of BTCs, it is unsurprising that multiple genetic factors are implicated in CCA development, including chromosomal aberrations, and genetic and epigenetic alterations in tumour suppressor genes and oncogenes.

The most prevalent genetic alterations identified in CCA influence key networks such as DNA repair (*TP53*), the *WNT–CTNNB1* pathway, protein kinase signaling (*KRAS*, *BRAF*, *SMAD4* and *FGFR2*), protein tyrosine phosphatase (*PTPN3*), epigenetic modifiers (*IDH1* and *IDH2*), chromatin-remodeling factors (*MLL3, ARID1A*, *PBRM1* and *BAP1*) [16,17], and *Notch* signaling, which is involved in cholangiocyte differentiation and biliary duct development [18]. In patients with iCCA, the main targetable aberrations identified were *FGFR2* fusions [19–21], *IDH1* mutations [22], *NTRK* fusions [23], and microsatellite instability [24].

Discovery of targetable *FGFR2* aberrations in iCCA

The earliest report of *FGFR2* fusions in CCA was in 2013 by Wu and colleagues [19]. The two fusions identified occurred in patients with iCCA, and subsequent studies have shown that *FGFR2* fusions occur nearly exclusively in iCCA compared to other BTCs and epithelial

cancers, making them a useful diagnostic marker. Across multiple tumour genotyping studies in CCA, the frequency of *FGFR2* fusions in iCCA is estimated to be approximately 10–15% [20,25–27]. Geography and etiology may impact reported frequencies in *FGFR2* fusions. Kongpetch and colleagues evaluated 193 CCA tumours from Thailand, Romania, and Singapore, and reported that rates of *FGFR2* fusions were 0.8%, 6.8%, and 15.7%, respectively [28]. These authors also reported that the rate of *FGFR2* fusions in fluke-associated and non-fluke associated CCA were 0.8% and 11.6%, respectively (p=0.0006), suggesting that *FGFR2* fusions might play a crucial role in the evolution of non-liver fluke-associated CCA, but less so in liver fluke-associated CCA. An integrated data analysis from whole-genome sequencing/targeted DNA sequencing with RNA-fusion sequencing showed mutations in *FGFR1*, *FGFR2*, *FGFR3* and *FGFR4* were present in 1.0%, 3.6%, 1.0% and 0.5% of CCAs, respectively. *FGFR2* fusions and *FGFR* mutations were mutually exclusive in this study [28].

FGFR2 fusions generally encode a functional fusion protein with *FGFR2* fused to a partner gene at the C-terminus that has strong dimerization or oligomerization capabilities [19,20]. The most common partner is *BICC1*, but various other fusion partners with *FGFR2* have subsequently been identified in iCCA [13,19–21,25,27–29] (**Table 1**), most of which fuse at a consistent breakpoint within the *FGFR2* gene on chromosome 10 [21]. *In vitro* and *in vivo* experiments show that the oncogenic ability of *FGFR2* fusion proteins can be suppressed by treatment with FGFR kinase inhibitors [19,20,30], this has been mirrored clinically.

FGFR2 fusions in iCCA have been associated with a better prognosis [27,31] and younger age at diagnosis [27,28] in some studies. They are also mutually exclusive with *KRAS* and *BRAF* [20] and *ERBB2*/*BRAF*/*NRAS* alterations [28] in some studies. *FGFR2* fusions have been found to be frequently co-altered with mutations in the chromatin-

remodeling gene *BAP1* [27], which acts as a tumour suppressor in iCCA [32]. The implications of these genetics on the therapeutic potential of combination therapy have yet to be realized.

iCCA epidemiology and current systemic treatment for iCCA

CCA epidemiology and risk factors for developing CCA

Globally, the incidence and mortality rates of CCA show substantial geographical variation, which may reflect exposure to different geographical risk factors and genetic determinants [33,34]. Multiple studies from Europe, the USA, Japan and Australia have reported rising rates of iCCA [33,35], which appear to have plateaued over the past 10 years. This increase may be due to advances in imaging, molecular diagnostics and pathology, enabling more accurate diagnosis of iCCA [34,35], however, in contrast, the incidence of both perihilar CCA and distal CCA appears to be stable or decreasing [33,35] suggesting the increase is real. However, a recent international analysis of population-based incidence rates of CCA, the Cancer Incidence in Five Continents Plus (CI5*plus*), showed that the incidence rates of both iCCA and eCCA increased in a majority of countries worldwide during the period 1993–2012, with iCCA incidence rates being higher than eCCA incidence rates in most countries between 2008 and 2012 [34].

The highest rates of CCA are in South East Asia (Northeast Thailand, Cambodia, and Laos), where the incidence is approximately 80/100,000 per year compared to 1–2/100,000 in the UK and USA, the former primarily associated with liver fluke infection [4,36]. Other risk factors include primary sclerosing cholangitis, hepatolithiasis, liver fluke infections, chronic viral hepatitis, metabolic syndrome, alcohol use, and congenital anomalies of the bile ducts, such as choledochal cysts [4,33]. Risk factors may overlap, for example, parasitic infection

often induces hepatholithiasis [37]. In Western countries about 50% of cases are still diagnosed without any identifiable risk factor despite advances in the knowledge of CCA etiology [33].

Current systemic treatment for iCCA

The standard of care for patients with unresectable or metastatic disease is combination chemotherapy with gemcitabine and cisplatin, based on the ABC-02 and BT22 trials showing an improved median overall survival (mOS) with this combination compared to gemcitabine alone [38,39]. In patients with unresectable, liver-confined disease, liver-directed therapy with external beam radiation, radioembolization, chemoembolization or ablation can be considered [40].

If the disease progresses, second-line treatment with FOLFOX is the preferred regimen based on the ABC-06 trial findings, which demonstrated a mOS of 6.2 months for modified FOLFOX plus active symptom control versus 5.3 months for active symptom control alone [41]. The response rate of 5% and disease control rate (DCR) of 33% for patients in that study underline the urgent need for improvements in therapy for refractory patients with iCCA. Although the overall survival for iCCA treated with standard chemotherapy seems to be better than that for other BTCs [42], overall, systemic chemotherapy has a low survival benefit for patients with unresectable iCCA as the majority of patients have a chemorefractory course [43].

A recently published multicenter, randomized, double-blind, placebo-controlled phase III trial demonstrated the efficacy of the IDH1 inhibitor, ivosidenib, in a majority intrahepatic CCA study population [44]. It is anticipated that this will be licensed for second line in iCCA patients with an *IDH1* mutation.

Targeting *FGFR* in iCCA

History of FGFR-targeted therapies in CCA

Several candidate drugs targeting this pathway are under development, including non-selective and selective FGFR tyrosine kinase inhibitors (TKIs), anti-FGF/FGFR monoclonal antibodies, and FGF traps [45]. Although the non-selective TKIs pazopanib and ponatinib showed anecdotal anti-tumour activity in patients with iCCA harbouring an *FGFR2* fusion [21], other preclinical and clinical trials have highlighted the pitfalls of using non-selective FGFR TKIs, including issues with off-target side effects [45]. The use of selective FGFR kinase inhibitors has therefore been a rational approach to address these issues. Several FGFR inhibitors have been evaluated in early phase clinical trials in patients with refractory iCCA harbouring *FGFR2* gene rearrangements, either in trials specifically enrolling patients with iCCA or in trials evaluating a variety of advanced solid tumours harbouring *FGFR2* gene rearrangements or other alterations (**Table 2** and **Table 3**). Derazantinib differs in that it is not a selective FGFR inhibitor, but rather a multi-kinase inhibitor with potent pan-FGFR activity [46].

All of the compounds discussed in the following section and shown in **Table 2** and **Table 3** bind reversibly to FGFR, with the exception of futibatinib which covalently binds to a highly conserved P-loop cysteine residue in the ATP pocket of FGFR (C492 in the FGFR2-IIIb isoform) [47]. The earliest reported data of selective FGFR inhibition in patients with CCA was with the oral agent infigratinib [48], while pemigatinib is the first FGFR-targeted agent to gain regulatory approval from the US FDA for use in previously treated patients with iCCA with *FGFR2* fusions or rearrangements [5,49]. Note that in the following section, the FGFR-targeted agents of interest are presented and discussed in alphabetical order.

Debio 1347

Debio 1347 is an ATP-competitive, oral TKI with high selectivity for FGFR1–3 [50]. In a first-in-human, open-label study in patients with advanced solid tumours harbouring *FGFR1–3* gene alterations (NCT01948297), 58 patients were treated with Debio 1347 at doses from 10 to 150 mg/day. The preliminary efficacy observed in the dose-escalation phase was encouraging, and tolerability acceptable up to 80 mg/day, so this dose was used for the expansion phase of the study [50]. In the expansion phase, 5 of the 18 patients treated with Debio 1347 had CCA (one patient had an *FGFR1* fusion; four patients had an *FGFR2* fusion). At the 80 mg once daily (QD) dose, Debio 1347 was generally well tolerated, and in the patients with *FGFR2* fusions, two patients had stable disease (SD) and two patients achieved partial response (PR). The patient with an *FGFR1* fusion did not respond to treatment and showed progressive disease (PD) [51].

The adaptive phase II, non-controlled, open-label, multicenter FUZE trial (NCT03834220) was designed to evaluate Debio 1347 (80 mg QD) in previously treated *FGFR* fusion-positive advanced solid tumours, irrespective of the tumour histology. Recruitment for this study started in February 2019 and the trial planned to enroll 125 patients made up of cohorts of patients with BTC cancer, urothelial cancer, and other solid tumour histologies [52]. At the time of writing (January 2021), the FUZE trial had completed enrolment of 63 participants and was closed for further enrolment.

Derazantanib

Derazantinib is an oral, potent, ATP-competitive, pan-FGFR inhibitor with strong activity against FGFR1–3 kinases [53]. Derazantinib also inhibits a number of other kinases, including RET, DDR2, VEGFR1, and KIT (IC_{50} values [nM]: 3, 3.6, 11, and 8.2, respectively) [53]. A phase I study (NCT01752920) in 80 patients with advanced solid tumours identified 300 mg QD as the recommended phase II dose (RP2D) for derazantinib. A

follow-on multicenter, phase I/II, open-label study (NCT01752920) enrolled 29 adult patients with unresectable iCCA with an *FGFR2* fusion, who progressed on, were intolerant to, or not eligible for first-line chemotherapy [46]. In this study, treatment with derazantinib 300 mg QD provided an overall response rate of 20.7% and the DCR was 82.8%.

Based on the results from the phase I/II study, the pivotal, open-label, single-arm, phase II FIDES-01 (NCT03230318) trial of derazantinib 300 mg QD is now ongoing in previously treated iCCA patients with one cohort for patients with *FGFR2* gene fusions and another for patients with *FGFR2* mutations or amplifications. Enrolment into the first cohort of

100 patients in FIDES-01 has been completed [54].

Erdafitinib

Erdafitinib (Balversa™) is an orally active small molecule with potent tyrosine kinase inhibitory activity against all four FGFR family members and selectivity versus other highly related kinases [55].

In an open-label phase IIa study conducted in China, Korea and Taiwan (NCT02699606), adults with advanced CCA containing *FGFR* alterations who had failed at least one prior systemic treatment, received erdafitinib 8 mg QD on a 28-day cycle with the option of pharmacodynamically-guided uptitration to 9 mg QD (the dose could be increased to 9 mg QD if a patient's serum phosphate level on cycle 1 day 14 was <5.5 mg/dL, in the absence of significant drug-related toxicity). In interim results from this ongoing study, 15 of the 17 treated Asian patients with advanced CCA and *FGFR* alterations (10 *FGFR2* fusion, 4 *FGFR2* mutation, 1 *FGFR3* fusion, and 2 *FGFR3* mutation) had an evaluable response: 7 (46.7%) achieved PR; 5 (33.3%) had SD; and PD was seen in 3 (20.0%) patients. The objective response rate (ORR) was 7/15 (47%) and the DCR was 12/15 (80%) [56].

Futibatinib

Futibatinib is an oral, highly selective, irreversible FGFR1-4 inhibitor [57,58]. A phase I dose-escalation study (FOENIX-101; NCT02052778) in 86 patients with heavily-pretreated advanced solid tumours identified 20 mg QD as the RP2D. In FOENIX-101, PRs were observed in five patients (5.8%; three patients with *FGFR2* fusion-positive iCCA, and two patients with *FGFR1*-mutated primary brain tumour), and SD in 41 (48%) of the futibatinib-treated patients. Responses were rapid (mostly occurring within 3 months) and lasted for >12 months in 2 of the 5 responders, indicating durable clinical benefit [59]. On the basis of the FOENIX-101 dose-escalation study results, futibatinib has been evaluated in the dose-expansion in 45 patients with *FGFR2* fusion- or rearrangement-positive CCA and showed an ORR of 25% [60].

This promising activity in the phase I expansion led to FOENIX-CCA2, an open-label, multicenter phase II registrational trial in patients with iCCA harbouring *FGFR2* gene fusions or other rearrangements (NCT02052778). Interim results from the FOENIX-CCA2 study (NCT02052778) were reported after enrolment of 103 patients, who had progressed on previous standard therapies, or for whom standard therapy was not tolerated [61]. Among the 67 patients having ≥6 months of follow-up included in this analysis for efficacy and safety, the ORR was 37.3% and the DCR was 82.1%. FOENIX-CCA2 has completed enrolment, and updated results from the entire cohort are anticipated in 2021.

The irreversible binding currently unique to futibatinib may confer an efficacy benefit in specific patients although the data are anecdotal (see below). There appears to be no toxicity difference.

Infigratinib

Infigratinib is an oral ATP-competitive FGFR1–3-selective TKI with weaker activity against FGFR4 [62]. In a multicenter, first-in-human dose-escalation and dose-expansion study (NCT01004224) in 132 patients with advanced solid tumours harbouring *FGFR* genetic alterations, the RP2D for infigratinib was identified as 125 mg QD given on a 3-weeks-on/1-week-off schedule [63].

Final results from an ongoing, multicenter, single-arm, phase II study (NCT02150967) of infigratinib in previously-treated patients with advanced or metastatic CCA having *FGFR* genetic alterations have been reported [64]. Among 108 patients with *FGFR2* fusion/rearrangement, the confirmed ORR was 23.1% (95% CI: 15.6–32.2%). The median duration of response was 5.0 months (range 0.9–19.1 months) and the median PFS was 7.3 months (95% CI: 5.6–7.6 months).

Pemigatinib

Pemigatinib (Pemazyre™) is an oral selective inhibitor of FGFR1–3, with weaker activity against FGFR4 [65]. In April 2020, the US FDA approved pemigatinib as the first targeted drug for patients with refractory advanced CCA with an *FGFR2* fusion or rearrangement [5].

The dose-escalation part of the multicenter, open-label phase I/II, FIGHT-101 study (NCT02393248) of pemigatinib in patients with refractory advanced malignancies with or without *FGF*/*FGFR* alteration identified 13.5 mg QD on days 1 to 14 of each 21-day cycle as the RP2D for pemigatinib [66]. This dose was used in the pivotal, multicenter, open-label, single-arm, multicohort, phase II FIGHT-202 (NCT02924376) study [67].

In FIGHT-202, 146 enrolled patients were assigned to one of three cohorts: patients with *FGFR2* fusions or rearrangements (N=107), patients with other *FGF/FGFR* alterations (N=20), or patients with no *FGF/FGFR* alterations (N=18) [67]. The primary endpoint was centrally-assessed ORR among those with *FGFR2* fusions or rearrangements. After a median

follow-up of 17.8 months, 38 (35.5%) of patients with *FGFR2* fusions or rearrangements achieved an objective response (3 had complete responses, 35 had PRs). The median duration of response was 7.5 months, with responses lasting ≥6 months in 68% of responding patients and ≥12 months in 37% of patients.

Recognized toxicities of FGFR inhibitors

Toxicities of FGFR inhibitors are very similar, with little to differentiate between them. They are, as a class, very well tolerated and although there are no direct comparisons, are likely to confer a significant improvement in quality of life compared to systemic chemotherapy.

Hyperphosphatemia: Increased phosphate levels are a pharmacodynamic effect of all FGFR inhibitors, with hyperphosphatemia reported in 55%–81% of patients with CCA and *FGFR* alterations in clinical trials [48,49,61]. Fibroblast growth factor 23 (FGF23) plays an important role in phosphate homeostasis [68,69] and FGFR1 is the predominant receptor for the hypophosphatemic action of FGF23 *in vivo* [70]. If FGFR inhibitors disrupt interactions between FGF23 and FGFR1, this may impair the phosphate-lowering activities of FGF23, which include inhibiting phosphate absorption in the intestine and reducing phosphate reabsorption in the kidney [71].

For patients who develop hyperphosphatemia while being treated with an FGFR inhibitor, phosphate-lowering therapy using phosphate binding agents and a low phosphate diet should be considered (**Table 4).**

Ophthalmologic toxicity: Retinal toxicities such as retinal pigment epithelial detachment (RPED) and central serous retinopathy (CSR) may cause symptoms such as blurred vision, visual floaters, or photopsia, and CSR is often asymptomatic. RPED and CSR occur in ~4%

[67] and ~9% [61], respectively, in patients with CCA treated with FGFR inhibitors, and these are generally grade 1 or 2. Comprehensive ophthalmological examination including optical coherence tomography (OCT) is therefore recommended before initiating all FGFR inhibitors and regularly during treatment. If visual symptoms are significant, patients should modify the dose, or discontinue the FGFR inhibitor as recommended; if mild or asymptomatic, patients can often be rechallenged with the same dose with a plan for dose modification if the symptoms recur. In clinical studies, dry eye occurred in 19–21% of patients with CCA treated with FGFR inhibitors [48,49,61]. Other eye toxicities reported with FGFR inhibitors include blepharitis, cataract development, increased lacrimation, trichiasis, trichomegaly, and blurred vision.

Nail toxicity: Nail toxicities also occur on FGFR inhibitors, especially with increased duration on treatment; most are grade 1 and 2, and grade 3 nail toxicity rarely occurs. Onycholysis, the painless detachment of the nail from the nail bed, occurs in 5–7% of patients [48,49]. Paronychia, an often tender bacterial or fungal infection that develops at the nailbed, occurs in 5–7% of patients [48,49]. Other nail toxicities reported with FGFR inhibitors include nail discoloration, nail disorder, nail dystrophy, nail hypertrophy, nail infection, onychalgia, and paronychia [48,49,61].

Future directions in targeting FGFR in iCCA

Resistance to FGFR kinase inhibitors in iCCA treatment

Primary and acquired resistance limits the efficacy of FGFR inhibitors, similar to other TKIs in oncogene-driven cancers [72].

With respect to primary resistance, Silverman and colleagues describe a tendency towards a shorter progression-free survival amongst *FGFR* fusion patients with co-occurring

tumour suppressor gene alterations including *BAP1*, *CDKN2A/B*, *PBRM1* and *TP53*, although the numbers of patients do not allow any significant conclusions [73]. Assembly of datasets as we have greater clinical experience will be critical in describing the optimal genomic environment to predict benefit from treatment.

With respect to acquired resistance, Goyal and colleagues reported the first evidence of clinically-acquired resistance to a selective FGFR inhibitor in three patients with *FGFR2* fusion-positive iCCA treated with infigratinib [74]. All three patients developed the *FGFR2* V565F gatekeeper mutation, and two patients developed polyclonal secondary mutations in the *FGFR2* kinase domain with a total of 5 *FGFR2* mutations each. This study also demonstrated, as have other studies [75], that circulating tumour DNA (ctDNA) analysis captured more putative resistance mechanisms than single tumour biopsy alone, suggesting that tumour heterogeneity may play a role in resistance and the commonly seen mixed responses on FGFR inhibitors. Rapid autopsy studies in patients with *FGFR2* fusion-positive iCCA treated with selective ATP-competitive FGFR inhibitors have confirmed that different resistant subclones evolve in different metastatic nodules [74,76], including the finding of two *FGFR2* mutant subclones in the same nodule. It is clear that single tumour sampling by biopsy or even multi-tumour sampling by autopsy may not capture the full spectrum of *FGFR2* kinase domain mutations identified on ctDNA analysis, and thus serial ctDNA analysis can provide useful complementary information about FGFR resistance mechanisms. Additionally, the success of next generation FGFR inhibitors depends on their ability to overcome multiple *FGFR2* mutations in the kinase domain.

Unlike other extant inhibitors, futibatinib binds covalently to FGFR, and preclinical studies demonstrate that it has strong potency against multiple *FGFR2* kinase domain mutations. Goyal and colleagues showed in a proof-of-concept study in four patients with *FGFR2* fusion-positive iCCA that sequential treatment with futibatinib after progression on

the ATP-competitive inhibitors infigratinib or Debio 1347 led to prolonged clinical benefit from FGFR inhibition [30]. Among these four patients, two patients had a PR on futibatinib, and they stayed on drug for 16 and 17 additional months beyond their first FGFR inhibitor. Furthermore, *in silico* structural modelling suggested that futibatinib retained activity against several mutations that conferred infigratinib or Debio 1347 resistance by altering conformational dynamics of FGFR2, rather than directly interacting with mutated residues. In iCCA cell line models, each containing one of nine clinically observed secondary *FGFR2* kinase domain mutations, several of these mutations conferred resistance to infigratinib and Debio 1347, whereas futibatinib remained active against all mutations, except the *FGFR2* V565F gatekeeper mutation. Additionally, Debio 1347 showed reduced potency against most mutants, but remained relatively active against V565F compared to infigratinib and futibatinib. These results highlight the critical role of serial biopsy and ctDNA analysis to identify resistance mechanisms; this can guide selection of the next FGFR inhibitor for patients currently in the clinic, and also guide the development of the next generation of FGFR inhibitors beyond futibatinib. This study also showed that such a guided approach is feasible and effective in prolonging benefit for patients from FGFR inhibition in these FGFR-dependent tumours [30].

Beyond the development of more effective FGFR inhibitors, combination strategies may also improve outcomes for patients with FGFR resistance in the setting of upregulation of alternative pathways in FGFR. Krook and colleagues showed via proteomic analysis of *FGFR2* pE565A mutant cells that the *PI3K/AKT* pathway was potentiated compared to non-mutant cells and that the *mTOR* pathway was activated [75]. Combination treatment combining an FGFR inhibitor with an mTOR inhibitor showed synergistic effects in mutant cells. These types of preclinical studies are key to understanding FGFR biology and

evaluating therapeutic strategies in models to aid in designing combination clinical trials for patients.

Confirmatory trials and evaluation of FGFR targeting in first-line in iCCA

Several large phase III randomized controlled trials are now underway or being planned to evaluate the efficacy of FGFR kinase inhibitors compared to gemcitabine plus cisplatin in the first-line treatment of *FGFR2* fusion- or rearrangement-positive CCA. For example, the phase III PROOF trial (NCT03773302) for infigratinib, and the phase III FIGHT-302 (NCT03656536) trial for pemigatinib are currently recruiting, while a similar study for futibatinib, FOENIX-CCA3 (NCT04093362) is preparing to open for enrolment. Accrual to these trials has been slow given this is a biomarker-driven frontline strategy in a subgroup of an uncommon cancer.

Incorporation of molecular testing within iCCA algorithm

The approval of FGFR kinase inhibitors and the emergence of first line trials with these agents require the wider and potentially earlier ordering of molecular testing in iCCA. As discussed previously, the number of potentially actionable targets in iCCA is growing (e.g. *FGFR* fusions, *IDH1/2* mutations, *NTRK* fusions), so the National Comprehensive Cancer Network (NCCN) recommends consideration of molecular testing for patients with unresectable and metastatic CCA [40].

The European Society for Medical Oncology (ESMO) Precision Medicine Working Group has recommended that tumour multigene next generation sequencing (NGS) could be used to assess level I actionable alterations in advanced CCAs based on the ESMO Scale for Actionability of molecular Targets (ESCAT) criteria. Larger panels can be used only on the basis of specific agreements with payers taking into account the overall cost of the strategy

(drug included), and if they report accurate ranking of alterations. RNA-based NGS can be used [77].

In the UK, genomic testing in the National Health Service (NHS) will be incorporated into the Genomic Laboratory Hubs of which there will be seven in the country. As targeted therapies, specifically FGFR inhibitors for iCCA, requiring genomic description become approved for standard of care, these centres will undertake standard of care profiling.

Combining FGFR inhibition with other therapy approaches

Although the clinical use of FGFR kinase inhibitors as monotherapy is still in an early stage, future trial results may support combination strategies using FGFRis with standard of care drug therapy options in solid tumours (see Supplemental information online, Table S1 for a listing of current studies). For example, Debio 1347 (NCT03344536), erdafitinib (NCT03238196), futibatinib (NCT04024436), and infigratinib (NCT04504331) are each being evaluated in combination with the hormonal therapy drug fulvestrant for hormone receptor positive, HER-2 negative metastatic breast cancer having *FGFR* genetic alterations.

Combinations of FGFRis with immune checkpoint inhibitors of programmed death ligand 1 (PD-L1) are being evaluated in patients with urothelial cancer having *FGFR2* genetic alterations (derazantinib plus atezolizumab: FIDES02 study, NCT04045613; futibatinib plus pembrolizumab, NCT04601857; and pemigatinib plus pembrolizumab, FIGHT-205 study, NCT04003610). Such trials will provide insights on whether targeting non-FGFR pathways involved in tumour growth and/or immune evasion in combination with FGFRi treatment improves outcomes over FGFRi monotherapy.

Patient and Provider Education

Given the demonstrated promise of FGFR inhibitors in clinical trials, patients and their caregivers are also closely following developments in this area. **Figure 2** illustrates the multiple issues that physicians and patients must address when considering targeted therapy. Various barriers remain, for instance the availability of material, the accuracy and funding of the test, the availability and funding of the therapy, and finally, the toxicity and efficacy of the treatment. Despite these obstacles, the potential advantages of oral therapies are evident. In addition to being an option a non-fusion patient would not receive, there would appear to be clear advantages of the FGFR inhibitors over chemotherapy with respect to toxicity, efficacy and quality of life, although data have yet to be generated. The increased complexity consequent on testing for FGFR alterations and treating with FGFR inhibitors does have resource implications that need to be addressed and acknowledged.

Conclusions

After a decade of chemotherapy being the only standard option for patients with advanced CCA, 2020 saw the first approval of a targeted therapy for this disease, ushering in the era of precision medicine in BTC. Since the discovery of *FGFR2* fusions in iCCA in 2013, multiple selective FGFR TKIs have been evaluated in clinical trials for patients with advanced refractory CCA harbouring an *FGFR2* fusion or rearrangement, and pemigatinib was the first to gain regulatory approval in April 2020. The response rate to the FGFR inhibitors is 20–37% and the mPFS is 6 to 8 months in this population, and this is welcome efficacy compared to the efficacy of chemotherapy in an unselected population. This discovery highlights the importance of molecular profiling for all patients with iCCA and also shows that understanding the biological underpinnings of cholangiocarcinogenesis can successfully lead to therapeutic breakthroughs. While the efficacy of FGFR inhibitors is encouraging, the response rates and durations of response fall short of those traditionally seen in other oncogene-addicted tumours such as *EGFR*- or *ALK*-driven lung cancer. We have learned that acquired resistance in the form of polyclonal *FGFR2* kinase domain mutations shortens the duration of benefit and that serial biopsy and ctDNA analysis can help identify mechanisms of resistance and guide the sequential use of FGFR inhibitors. Ultimately, to expand and prolong the benefit of FGFR inhibition for patients, we need to better understand both primary and secondary resistance and develop combination and next generation inhibitors that can delay or overcome resistance. In a historically difficult-to-treat disease, the approval of a targeted therapy represents an important milestone that paves the way for additional personalized medicine approaches in CCA.

Declaration of Competing Interest

Dr. Bridgewater reports personal fees from Taiho, Merck-Serono, BMS, Roche, Bayer, and Servier outside the submitted work.

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Dr. Crolley declares no conflicts of interest that pertain to this work.

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Authors' contributions

Drafting of the manuscript, revision of the manuscript, and approval of the final version of the manuscript: JB, LG, SK and VEC.

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Tables

Table 1 *FGFR* fusions identified in iCCA

***FGFR* fusion**	**Frequency**	**References**
Recurrent *FGFR2* fusions		
• FGFR2-BICC1	2 cases	Wu 2013 [19]
	3.0% (2/66)	Arai 2014 [78]
	12.7% (8/63)	Jain 2018 [27]
	28.9% (31/107)	Abou-Alfa 2020 [67]
• FGFR2-*AHCYL1*	10.6% (7/66)	Arai 2014 [78]
• FGFR2-PPHLN1	16.8% (18/107)	Sia 2015 [29]
Less frequently observed *FGFR* fusions		**References**
• FGFR2-AFF4 • FGFR2-AFF4, R678G • FGFR2-AMPD2 • FGFR2-ARHGAP24 • FGFR2-C10 • FGFR2-CCDC6 • FGFR2-CELF2 • FGFR2-CGNL1 • FGFR2-CTNNA3 • FGFR2-DCTN2 • FGFR2-DNAJC12 • FGFR2-DZIP1 • FGFR2-f118 • FGFR2-FOXP1 • FGFR2-INA • FGFR2-KCTD1 • FGFR2-KIAA1217 • FGFR2-KIAA1598 • FGFR2-KIF7 • FGFR2-LGSN • FGFR2-LPXN	• FGFR2-MGEA5 • FGFR2-MYPN • FGFR2-NOL4 • FGFR2-NRAP • FGFR2-PARK2 • FGFR2-PCMI • FGFR2-Rearrangement intron 17 • FGFR2-RNF41 • FGFR2-SH3GLB1 • FGFR2-SLMAP • FGFR2-SORBS1 • FGFR2-STK26 • FGFR2-STK3 • FGFR2-TACC3 • FGFR2-TBC1D1 • FGFR2-UBQLN1 • FGFR2-WAC • FGFR2-ZMYM4 • FGFR3-TACC3	Abou-Alfa 2020 [67]; Borad 2014 [21]; Ross 2014 [25]; Jusakul 2017 [13]; Jain 2018 [27]; Javle 2017 [48]; Goyal 2019 [30]; Kongpetch 2020 [28]

Table 2 Current status of FGFRi in clinical development for iCCA harbouring FGFR gene rearrangements

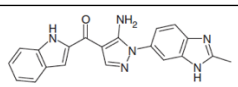
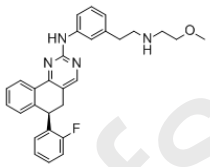
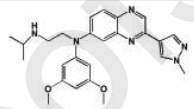
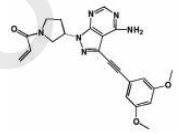
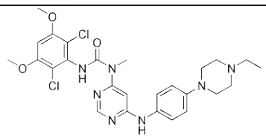
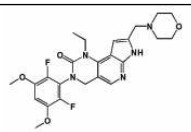
Compound	Current development status in CCA	CCA population studied	Dosage regimen	Efficacy results	Treatment-emergent adverse events
Debio 1347	Phase II basket trial ongoing in pts with solid tumors with FGFR1, FGFR2 or FGFR3 fusions after ≥1 line of ST (FUZE, NCT03834220)	5 of 18 pts in a phase I expansion cohort had CCA (FGFR2 fusions, n=4; FGFR1 fusion, n=1); all had prior ST (NCT01948297) [1]	80 mg QD (used in phase I and in ongoing phase II)	From 4 CCA pts with FGFR2 fusions in phase I: 2 (50%) achieved PR 2 (50%) had SD; [PD was seen in the CCA pt with an FGFR1 fusion]	In phase I safety analysis cohort (n=18), the most common TEAEs reported were: Fatigue (n=9; 50.0%); Hyperphosphatemia (n=8; 44.4%); Anemia (n=7; 38.9%); No grade ≥3 AEs related to study drug One pt needed dose reduction due to grade 2 nails toxicity Ocular toxicity: none reported, and no findings on ocular exams were compatible with retinal detachment
Derazantinib	Pivotal phase II study ongoing in pts with iCCA with FGFR2 alterations after ≥1 line of ST (FIDES-01; NCT03230318)	29 pts with FGFR2-fusion positive iCCA in an open-label phase I/II study; 27 (93%) had prior ST (NCT01752920) [2]	300 mg QD	From 29 iCCA pts in phase I/II study: 20.7% ORR, with 6 confirmed PR from 29 evaluable pts; 82.8% DCR; estimated mPFS 5.7 months (95% CI:4.04–9.2 months)	In the phase I/II study iCCA pts (n=29), the most common TEAEs reported were: Hyperphosphatemia (n=22; 75.9%) Dry mouth and nausea (n=13; 44.8%) Asthenia, fatigue (n=10; 34.5%) Dysgeusia, vomiting (n=9; 31.0%) Grade 3/4 TRAEs observed in 8 pts (27.6%) Ocular toxicity: reported in 12 pts (41%), this included dry eye (5 pts; 17.2%), conjunctivitis (4 pts; 13.8%) blurred vision (3 pts; 10.3%), and photophobia (2 pts; 6.9%); two events were grade 3 (1 each for dry eye and blurred vision)
Erdafitinib	Phase IIb study ongoing as tumour agnostic therapy for advanced solid tumours with FGFR alterations after ≥1 line of ST (NCT04083976)	Interim results from ongoing phase IIa open-label study in which 17 Asian pts with CCA with FGFR alterations were treated (all had prior ST) (NCT02699606) [3]	8 mg QD (could be uptitrated to 9 mg QD in phase IIa study)	From 17 treated pts, 15 were response evaluable: 7 (46.7%) achieved PR; 5 (33.3%) had SD; PD was seen in 3 (20.0%) pts; ORR was 7/15 (47%) and DCR was 12/15 (80%)	In the phase IIa study safety analysis cohort (n=17), the most common TEAEs reported were: Hyperphosphatemia (n=17; 100%); Stomatitis (n=11; 64.7%); Dry mouth (n=10; 58.8%); Elevated AST, elevated ALT (n=7; 41.2%); TEAEs led to dose interruption in 16 (94%) and to dose reduction in 8 (47.0%) of the 17 pts Ocular toxicity: dry eye (n=3; 17.6%), no cases were grade ≥3
Futibatinib	Pivotal phase II study ongoing in iCCA with FGFR2 alterations after ≥1 line of ST (FOENIX-CCA2, NCT02052778), interim data reported [4]; Phase III study versus chemotherapy as 1L in	Interim analysis from phase II open-label FOENIX-CCA2 study in 67 pts with iCCA with FGFR2 fusions/other rearrangements (all had prior ST)[4]	20 mg QD (dose reduction to 16 or 12 mg was permitted to manage TEAEs)	From interim analysis of 67 pts with ≥6 months of follow-up in FOENIX-CCA2: 1 (1.5%) achieved CR; 24 (35.8% achieved PR; 30 (44.8%) had SD ORR was 25/67 (37.3%) and DCR was 55/67 (82.1%) mPFS was 7.2 months (95% CI: 4.9	In the FOENIX-CCA2 interim analysis cohort (n=67), the most common TEAEs reported were: Hyperphosphatemia (n=54; 80.6%); Diarrhoea (n=25; 37.3%); Dry mouth (n=22; 32.8%); TEAEs led to dose interruption in 37 (55.2%) and to dose reduction in 34 (50.7%) of the 67 pts; 1 pt discontinued because of TEAEs Ocular toxicity: Central serious retinopathy (n=6; 9.0%), no

	iCCA planned (FOENIX-CCA3, NCT04093362)			to 15.2)	cases were Grade ≥3
Infigratinib	Phase II study ongoing (NCT02150967), initial results reported [5], QED Therapeutics planning to submit NDA for 2L use of infigratinib in CCA to the US FDA; Phase III study versus chemotherapy as 1L in CCA ongoing (PROOF, NCT03773302)	Final results from an ongoing open-label phase II study were reported for 108 pts with iCCA having FGFR2 alterations (all had prior ST)[5]	125 mg QD for 3w Q4W	From final analysis of 108 iCCA pts with FGFR2 alterations in phase II study: Confirmed ORR was 23.0% (95% CI: 15.6–32.2%); Median duration of response was 5.0 months (range 0.9–19.1 months) mPFS was 7.3 months (95% CI: 5.6–7.6); mOS was 12.2 months (95% CI: 10.7–14.9)	In the phase II final analysis cohort (n=108), the most common TEAEs reported were: Hyperphosphatemia (n=83; 76.9%) Eye disorders excluding CSR/RPED (n=73; 67.6%) Stomatitis (n=59; 54.6%) Fatigue (n=43; 39.8%) Ocular toxicity:CSR/RPED (n=18, 16.7%), 1 case was grade 3, no cases were grade 4.
Pemigatinib	US FDA approved for previously treated unresectable advanced/metastatic CCA with FGFR2 alterations based on phase II FIGHT-202 results [6]; Phase III study versus chemotherapy as 1L in CCA ongoing (FIGHT-302, NCT03656536)	Open-label phase II FIGHT-202 study evaluated pemigatinib in 146 pts with CCA, including 107 with FGFR2 fusions or rearrangements (all had prior ST)[6]	13.5 mg QD for 2w Q3W	From 107 pts with FGFR2 fusions or rearrangements in FIGHT-202: 3 (2.8%) achieved CR; 35 (32.7%) achieved PR; 50 (46.7%) achieved SD; PD seen in 16 (14.9%) pts; ORR was 35.5% (95% CI: 26.5–45.4); mPFS was 6.9 months (95% CI: 6.2–9.6); mOS was 21.1 months (95% CI: 14.8–Not estimable)	In FIGHT-202, across all 146 pts enrolled, the most common TEAEs reported were: Hyperphosphatemia (n=88; 60.3%) Alopecia (n=72; 49.3%) Diarrhoea (n=69; 47.2%) Fatigue (n=61; 41.8%) Dysgeusia (n=58; 39.7%) 13 (8.9%) of pts discontinued treatment due to a TEAE; 20 (13.7%) of pts had TEAEs leading to dose reductions Ocular toxicity: dry eye (n=30, 20.5%), 1 case (0.7%) was grade 3, all others were grade 1 or 2; serious retinal detachment due to subretinal fluid accumulation occurred in 6 pts (4.1%), all events were grade 1 or 2, except for one grade 3 event that was classified as of rhegmatogenous origin and unrelated to treatment

1L, first-line; 2L, second-line; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CCA, Cholangiocarcinoma; CI, confidence interval; CSR/RPED, central serious retinopathy/retinal pigment epithelial detachment; DCR, disease control rate; mOS, median overall survival; mPFS, median progression-free survival; N.R., not reported; ORR, objective response rate; PD, progressive disease; PR, partial response; Pt/Pts, patient(s); SD, stable disease; ST, systemic therapy; TEAE, treatment-emergent adverse events; US FDA, United States Food and Drug Administration

Compiled from: 1. Cleary 2020 [51]; 2. Mazzaferro 2019 [46]; 3. Park 2019 [56]; 4. Goyal 2020 [61]; 5. Javle 2021 [64]; 6. Abou-Alfa 2020 [67]

Table 3 Target selectivity and binding features of FGFRi

Compound	Binding features	IC_{50} (nM)	Structure
Debio 1347 (CHF5183284; FF284)	Selective FGFR1–3 inhibitor, reversible	FGFR1: 9.3 FGFR2: 7.6 FGFR3: 22 FGFR4: 290	
Derazantinib (ARQ 087)	Multikinase inhibitor, reversible	FGFR1: 4.5 FGFR2: 1.8 FGFR3: 4.5 FGFR4: 34	
Erdafitinib (JNJ-42756493)	Selective FGFR1–4 inhibitor, reversible	FGFR1: 1.2 FGFR2: 2.5 FGFR3: 3.0 FGFR4: 5.7	
Futibatinib (TAS-120)	Selective FGFR1–4 inhibitor, irreversible	FGFR1: 3.9 FGFR2: 1.3 FGFR3: 1.6 FGFR4: 8.3	
Infigratinib (BGJ398)	Selective FGFR1–3 inhibitor, reversible	FGFR1: 0.9 FGFR2: 1.4 FGFR3: 1.0 FGFR4: 60.0	
Pemigatinib (INCB054828)	Selective FGFR1–3 inhibitor, reversible	FGFR1: 0.4 FGFR2: 0.5 FGFR3: 1 FGFR4: 30	

Adapted from: Dai 2019 [79]; Guagnano 2011 [62]; Hall 2016 [53]; Liu 2020 [65]; Nakanishi 2014 [80]; Perera 2017 [55]

Table 4. Recommendations for hyperphosphatemia management during FGFR inhibitor therapy

Serum phosphorus result	Grade	Action
ULN < P <1.78 mmol/L [ULN < P <5.51 mg/dL]	1	Low phosphate diet
1.78 ≤ P ≤2.26 (mmol/L) [5.51 ≤ P ≤ 7.00 (mg/dL)]	2	Low phosphate diet Sevelamer monotherapy (range from 800 mg TID to 2400 mg TID) Acetazolamide 250 mg QD or TID Lanthanum carbonate 1.0 g QD or TID
2.26 < P ≤3.23 (mmol/L) [7.00 < P ≤ 10.00 (mg/dL)]	3	Interrupt dosing until grade 2 Dose reduction (1-2 levels) until grade 2
P >3.23 mmol/L [P >10 mg/dL]	4	Interrupt dosing until grade 2 Dose reduction (1-2 levels) until grade 2

P, serum phosphorus; TID, three times daily; QD, once daily; ULN, upper limit of normal;

Figure legends

Figure 1A and 1B. FGF-FGFR signaling pathway

A) FGF-FGFR signaling under physiologic conditions: Binding of FGF ligands to FGFRs at the cell surface causes the receptors to dimerize, leading to intracellular phosphorylation of receptor kinase domains, a cascade of intracellular signaling, and gene transcription. Through this signaling cascade, the FGF ligands activate intracellular survival and proliferative pathways.

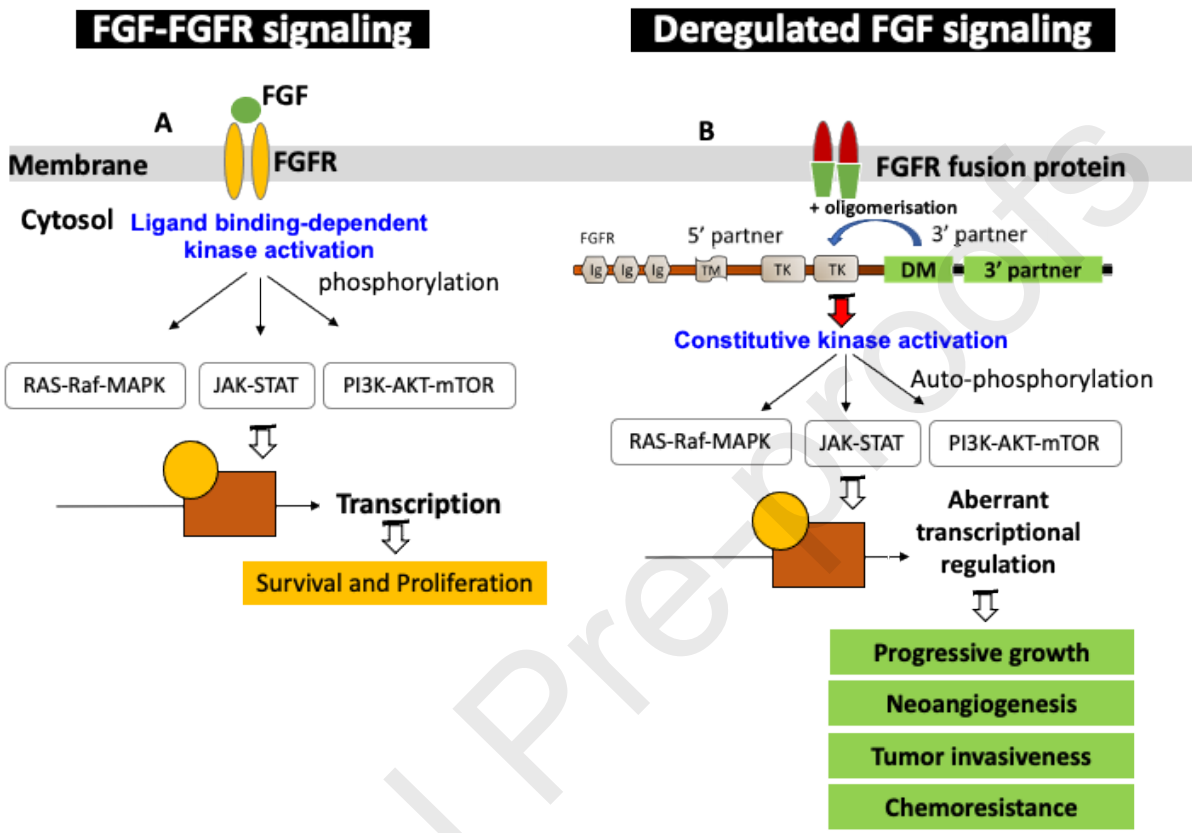
B) Deregulated FGF signaling: Chromosomal translocation can result in fusion of the kinase domain of an FGFR to a dimerisation domain (DM) from another protein that promotes oligomerization, leading to constitutive kinase activation. The aberrant signaling cascades then activate oncogenesis through progressive growth and invasiveness, neoangiogenesis as well as promote chemoresistance.

FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptor; RAS: Rat Sarcoma; RAF: Serine/Threonine Kinase; MAPK, mitogen activated protein kinase; JAK: Janus kinase; STAT: signal transducer and activator of transcription; PI3K: Phosphatidylinositol-4,5-Bisphosphate 3-Kinase; AKT: Protein kinase B (PKB); mTOR: mammalian target of rapamycin.

Figure 2. Managing patients' expectations

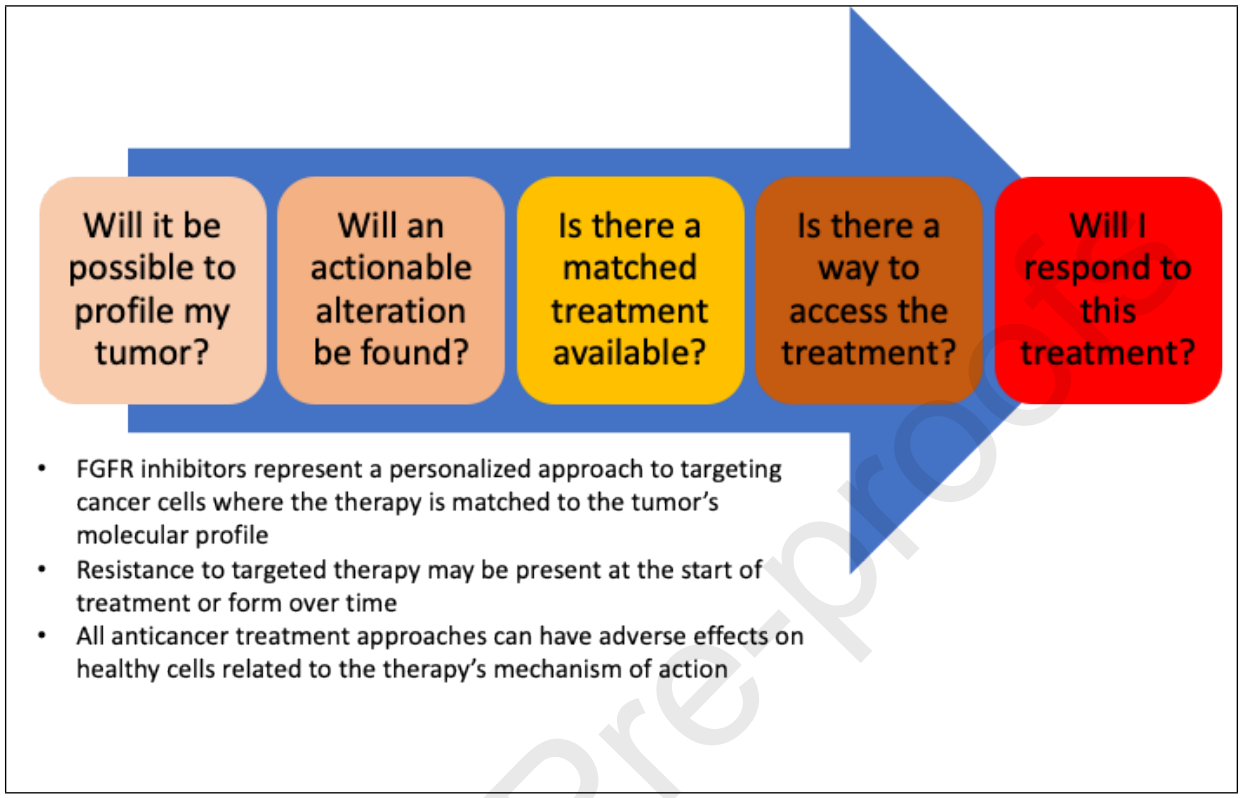
Figures

Figure 1.



AKT, Protein kinase B (PKB); DM, dimerization domain; FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptor; Ig, extracellular immunoglobulin-like domain; JAK, Janus kinase; MAPK, mitogen activated protein kinase; mTOR, mammalian target of rapamycin; PI3K, Phosphatidylinositol-4,5-Bisphosphate 3-Kinase; RAS, Rat Sarcoma; RAF, Serine/Threonine Kinase; STAT, signal transducer and activator of transcription; TK, tyrosine kinase subdomain

Figure 2.



Highlights for CTR-D-20-00799L: Targeting FGFR inhibition in cholangiocarcinoma

- Cholangiocarcinomas (CCAs) are rare but aggressive tumours of the bile ducts
- Almost half of CCAs harbour potentially targetable somatic alterations
- Fibroblast growth factor receptor 2 (*FGFR2*) alterations occur in up 15% of iCCAs
- Selective FGFR inhibitors show promise to improve outcomes in FGFR-driven CCA
- Research to further optimise the use of new and emerging FGFR inhibitors is ongoing