

The Evolving Role of FGFR2 Inhibitors in Intrahepatic Cholangiocarcinoma: From Molecular Biology to Clinical Targeting

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Abstract: Intrahepatic cholangiocarcinoma (iCCA) is an anatomically and biologically distinct entity with a rising incidence and a poor prognosis on conventional treatments. Surgery followed by adjuvant chemotherapy is a potentially curative option in resectable cases, while palliative-intent chemotherapy is the standard-of-care in the advanced setting. Technological advances through massive parallel sequencing have enabled a deeper understanding of disease biology with the identification of several druggable molecular vulnerabilities in nearly 50% of cases. Among them, gene fusions involving the fibroblast growth factor receptor 2 (FGFR2) are the most therapeutically exploited so far with a number of Phase II clinical trials investigating FGFR2 inhibitors showing unprecedented efficacy results in this molecular subgroup. Over the last year, these efforts have culminated in the US FDA-approval of pemigatinib and infigratinib, the first two oral selective FGFR2 targeted agents for previously treated, locally advanced or metastatic iCCA driven by FGFR2 fusion or rearrangements. While first-line Phase III trials are currently underway to test these targeted approach against standard-of-care chemotherapy, translational studies are trying to better understand primary and secondary resistance mechanisms in order to optimize FGFR2 blockade in iCCA. In this article, we extensively reviewed the current evidence on the biological rationale, as well as preclinical and clinical development of FGFR inhibitors in iCCA.

Keywords: biliary cancer, cholangiocarcinoma, intrahepatic, FGFR2, targeted therapy, precision medicine

Introduction

Cholangiocarcinoma (CCA) is a relatively rare and highly heterogenous hepatobiliary malignancy that can be anatomically subdivided into intrahepatic CCA (iCCA), perihilar CCA (pCCA), and distal CCA (dCCA).^{1,2} Among them, iCCA, arising from the small bile ducts proximal to the second-order ones, usually presents as an intrahepatic tumor mass which is an incidental finding in 20–25% of cases. In the last decades, its incidence is increasing globally both in Eastern and Western countries. Well-established risk factors for iCCA include inflammatory biliary tract diseases, cirrhosis, obesity-associated liver disease, hepatolithiasis and liver fluke infestations.^{3,4} Unfortunately, the diagnosis usually occurs late in the course of disease and the prognosis remains poor. The standard of care for the early stage disease is represented by curative-intent surgery followed by adjuvant capecitabine. Nonetheless, relapse rates are in the ranges of 60–70% and roughly two-thirds of

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cases display unresectable advanced disease at presentation. Combination chemotherapy in the form of cisplatin/gemcitabine and mFOLFOX6 (5-fluorouracil, folinic acid, oxaliplatin) regimen are evidence-based treatments for the first- and second-line setting, respectively,^{5–7} though the overall survival (OS) hardly exceeds 12 months.

Poorly studied and poorly understood for decades, CCA is now gaining momentum as a molecularly distinct entity with a variety of genetic aberrations implicated in cholangiocarcinogenesis and progression with translational relevance. The discovery that some of them can be therapeutically targeted with several compounds under clinical development has opened new avenues for precision medicine in this rare and hard-to-treat cancer. To this end, FGFR2 fusions present in 11–45% of patients affected by iCCA are being clinically validated in phase II and currently ongoing phase III trials.^{8,9} Following positive results coming from them, in the last year, the oral FGFR inhibitors pemigatinib and infigratinib have been granted United States Food and Drug Administration approval, for patients with previously treated iCCA harbouring FGFR2 gene fusions, making them the first targeted agents ever approved for biliary cancers.

In this article, we discuss the biological rationale for FGFR2 targeting, thoroughly review the preclinical and clinical development of FGFR2 inhibitors, and provide an overview of future perspectives in FGFR2-driven iCCA.

The Molecular Landscape of Cholangiocarcinoma

In the last few years, massive profiling studies enabled by the advent of next-generation sequencing technologies, have started disentangling the complex molecular landscape of CCA, thus shedding initial light on mechanisms underpinning cholangiocarcinogenesis and putative therapeutic targets.^{10–12} To this end, compelling evidence showed that the most frequently deregulated oncogenic networks in CCA comprise DNA repair (TP53), the WNT-CTNNBQ1 pathway, Notch signaling, protein kinase signaling (KRAS, BRAF, SMAD4, and FGFR2), protein tyrosine phosphatase (PTPN3), chromatin-remodeling factors (MLL3, ARID1A, PBRM1 and BAP1) and epigenetic modifiers (IDH1 and IDH2).¹³

In accordance with the clinical behaviour of CCA, substantial heterogeneity is also evident at molecular level with specific aberrations segregating with the subsite

of the tumour: KRAS mutations and erbB-2 (ERBB2) gene amplification are more common in eCCA, while FGFR2 gene fusions and IDH1 mutations occur nearly exclusively in iCCA.¹⁴

Moreover, CCA displays genomic diversity according to the predisposing risk factor as shown by the higher mutational burden and the enrichment for ERBB2 amplification and TP53 mutations in liver fluke-associated tumors. Contrariwise, non-liver fluke-associated CCA has been associated with high copy-number aberrations, PD-1/PD-L1 expression, epigenetic mutations involving IDH1/2 and BAP-1, and FGFR/PRKA-related gene rearrangement.¹⁵

Similarly, distinct gene expression signature and epigenetic profiles have been identified in patients with an underlying history of primary sclerosing cholangitis.¹⁶ A further level of complexity was added by the attempt to overcome this considerable molecular heterogeneity through integrative multiplatform analysis efforts. As such, the International Cancer Genome Consortium was able to molecularly subtype 489 cases from 10 different countries in four different subsets (clusters 1 to 4), each characterized by peculiar genomic, epigenomic, and clinico-pathological features and a different prognosis.¹⁷

Despite this molecular complexity, recurring driver aberrations amenable to therapeutic targeting have been identified that are mutually exclusive from one another. Most frequently occurring targetable alterations in CCA include IDH1 mutations (20–25%), FGFR2 fusions (10–16%), microsatellite instability (1%), and NTRK fusions (<1%).¹⁴ Among them, the targeting of FGFR2 inhibition, which is the focus of the current review, has been the most extensively and successfully attempted so far.

The FGFR Signalling Pathway and Its Role in Cholangiocarcinoma

The FGFRs are membrane-bound receptor tyrosine kinases (RTKs) encompassing FGFR1, FGFR2, FGFR3, FGFR4, which are encoded by *flg*, *bek*, *cek-2*, and *frek* genes, respectively.¹⁸

The receptors are composed by three domains: an extracellular, a transmembrane, and an intracellular one. The extracellular ligand-binding domain, consisting of three immunoglobulin Ig-like loops/domains (Ig-I, Ig-II and Ig-III),¹⁹ contains the specific region for binding to FGFs, heparin, heparan sulfate proteoglycans, and other extracellular matrix molecules; Ig-I has autoinhibitory capabilities, while Ig-II and Ig-III form the active ligand-

binding domain. The intracellular domain has a C-terminal tail and contains two split tyrosine kinases (tyrosine kinase 1 and tyrosine kinase 2) which interact with cytoplasmic molecules, transferring the intracellular FGFR signaling.²⁰ Multiple isoforms of FGFR are known, resulting from alternative splicing events of the region encoding for the extracellular domain²¹ that show modified affinity and sensitivity for the FGF ligands²² and have different abilities to activate intracellular signal transduction.²³ The binding with the native ligand FGF is mandatory for FGFR activation and induces the receptor dimerization by autophosphorylation in the C-terminal portion of the intracellular domain. In this form, the FGFR becomes active and phosphorylates other receptors or effector molecules involved in specific pathways of cell survival and proliferation, including RAS-MAPK, PI3K-AKT, PLC γ , and STAT (Figure 1).²⁴⁻²⁶ The regulation of the FGFR signaling pathway is ensured by receptor degradation after its internalization through different mechanisms like the autoinhibition of Ig-I domain.¹⁸ All four FGFRs share structural homology with vascular endothelial growth

factor receptors (VEGFR), platelet-derived growth factor receptors (PDGFR), and other tyrosine kinase receptors, with consequent implications for pharmacologic therapy.²⁰ The activation of the FGF/FGFR complex occurs in embryogenesis, organogenesis, and angiogenesis, taking part in the regulation of different biomolecular processes such as apoptosis, cell adhesion, cell motility, and cell differentiation.²⁷ In addition, FGFR signaling is one of the most frequently deregulated pathways in human cancers, through various molecular mechanisms such as amplification, fusions, missense mutations in FGFR genes. The dysregulation of FGFR signaling has been implicated in enhanced proliferation, survival and development of anticancer drug resistance as well as in promoting neoangiogenesis and immune evasion in the tumor microenvironment.²⁸⁻³³

As stated previously, alterations affecting the FGFR have been reported to be not only among the most frequently occurring but also to be among the most potentially druggable aberrations in iCCA.¹² Of note, overexpression of FGFRs 1 to 4 via mutations or amplifications has been reported to be

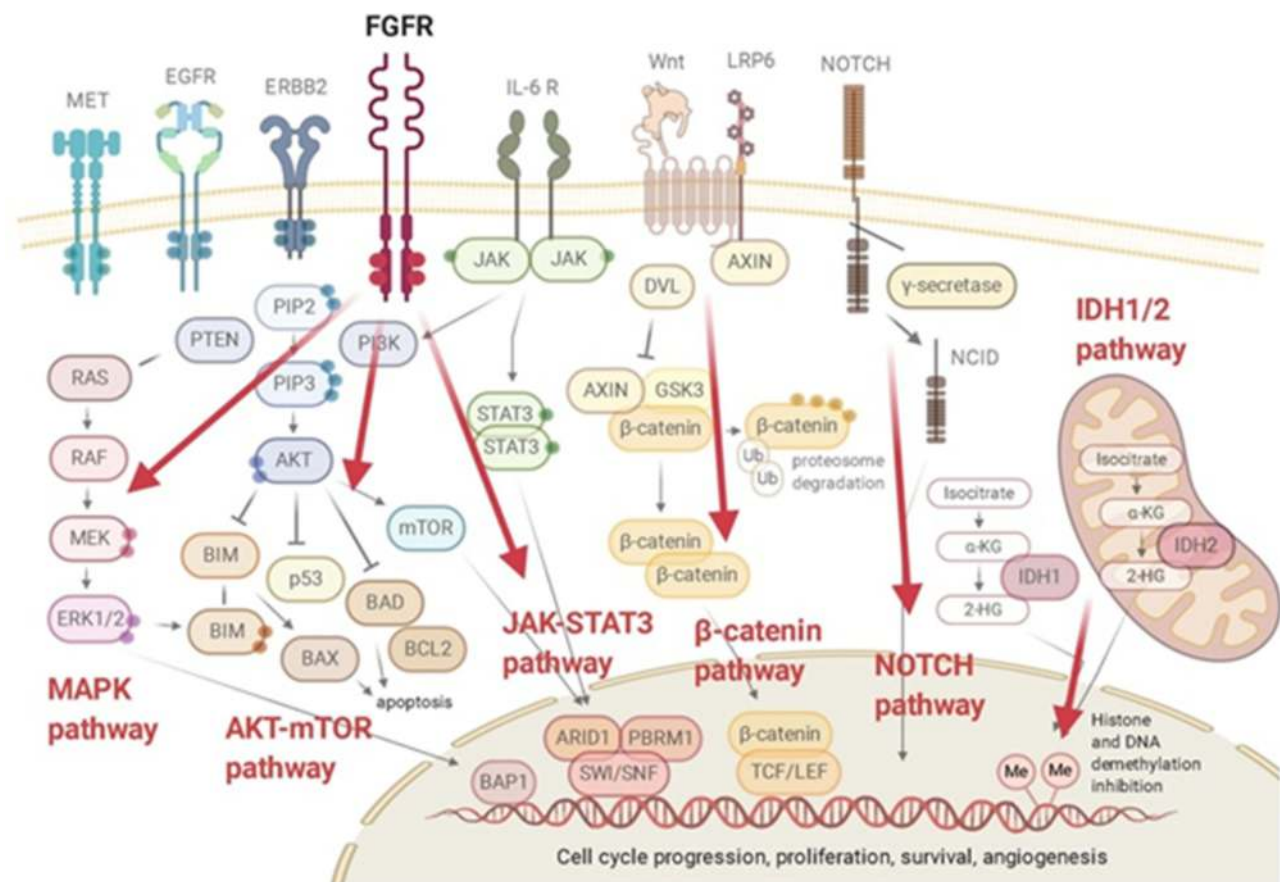


Figure 1 Schematic representation of the FGFR signalling and other relevant oncogenic pathways in iCCA.

a fundamental oncogenic boost in iCCA.³⁴ In particular, FGFR4 activation is able to induce proliferation, invasion, and epithelial–mesenchymal transition of tumor cells;^{36,37} moreover, high expression of FGFR4 is closely associated with poor prognosis and CCA progression.³⁵ However, from both a diagnostic and therapeutic standpoint, the most relevant FGFR aberration in CCA is represented by FGFR2 fusions or rearrangements. As reported by several studies, these FGFR2 molecular aberrations occur in 15% to 20% of cases, are enriched almost exclusively in the iCCA subsite and are mutually exclusive with other oncogenic mutations such as KRAS.^{13,39} The FGFR2 fusions have been reported to occur in early stage iCCA, driving the initiation and the progression of the disease, and are associated with female predilection, younger age at onset, and a more favourable prognosis compared to wild-type patients. The most common FGFR chromosomal aberration in iCCA is FGFR2–BICC1 fusion arising from t(10;10) (q21;q26), which is constitutively active and is involved in the activation of MAPK and PIK3CA/mammalian target of rapamycin (mTOR) pathways.^{38,43} Several authors reported the most common FGFR2 fusions, including FGFR2–PPHLN1 (Periophilin 1), FGFR2–AHCYL1 (Adenosylhomocysteinase Like 1), FGFR2–BICC1 (Bicaudal family RNA binding protein 1), FGFR2–PARK2 (Parkin RBR E3 ubiquitin protein ligase), FGFR2–MGEA5 (Meningioma Expressed Antigen 5), FGFR2–TACC3 (Transforming Acidic Coiled-Coil Containing Protein 3), FGFR2–CCDC186 (Coiled-Coil Domain Containing 186), FGFR2–NOL4 (Nucleolar Protein 4) and FGFR2–KIAA1598 (Shootin 1).^{42,43} In iCCA, chromosomal translocations of FGFR2 result in the formation of oncogenic fusion proteins containing an intact tyrosine kinase domain fused to a C-terminal portion of a partner protein that exhibits a strong dimerization/oligomerization capability.^{40,41} These FGFR fusions play a role in the regulation of different biomolecular mechanisms, such as the migration, the anchorage, and the aggregation of the tumor cells forming the tumor mass, given to the activation of specific molecular pathways.²³ Interestingly, the overexpression of FGFR2 fusion proteins results in increased sensitivity to FGFR inhibitors both *in vitro* and *in vivo*.³⁸

Preclinical Development of FGFR2 Inhibitors in Cholangiocarcinoma

Given the biological relevance of FGFR2 genetic alterations in iCCA, the therapeutic targeting of FGFR signaling has rapidly become a promising treatment approach, with various molecularly targeted agents undergoing preclinical

and clinical drug development process in this disease. Experimentally determined structures of FGFR in conjunction with both their ligands, FGF and heparin, provided the structural basis to understand ligand-receptor specificity, receptor dimerization and signaling cascade activation. This in turn constituted the structural information facilitating the design of FGFR inhibitors to be used to interfere with cell signaling derived from tyrosine kinase (TK) activation.⁴⁴ Based on the mechanism of action and their target specificities,^{45,46} the FGFR inhibitors can be classified into four groups of molecules:^{28,29} 1) Non-selective Tyrosine Kinase Inhibitors (TKIs); 2) TKIs selectively targeting FGFRs; 3) FGF ligand traps; 4) FGFR-directed monoclonal antibodies. Several compounds belonging to these groups are currently under investigation in preclinical and clinical trials involving patients with advanced malignancies, including biliary cancers.

The most widely used therapeutic approach for FGFR blockade in iCCA is represented by TKIs, which are small molecules that directly inhibit receptor kinase activity by interfering with the binding of ATP or substrates of the tyrosine kinase domain. Most TKIs were initially identified by random screening of compound libraries for specific protein kinase inhibitory activities. Recently, the molecular modelling and structure-based design of ATP-site directed protein kinase inhibitors has been reviewed, thus leading to the development of more potent compounds, with a selective activity against each tyrosine kinase receptor.

Non-selective TKIs (eg, lenvatinib, dovitinib, famitinib, and erdafitinib)^{47,48} were the first compounds developed with a prominent activity against various RTKs including, FGFRs, VEGFRs, PDGFRs, FLT3, RET, KIT, and BCR-ABL. Although the multi-target simultaneous inhibition may enhance their efficacy, it results in an impaired safety profile. Furthermore, the relative bioactivity of multikinase inhibitors against FGFRs is weak. Taken together, these drawbacks have limited their further development of non-selective TKIs as single-agent in tumors driven by aberrant FGFR signaling. However, several trials are underway to investigate the clinical efficacy of their combination with immunotherapy in biliary cancer and other solid tumours.⁴⁹

Notably, the development of selective FGFR TKIs (including pemigatinib, derazantinib, JNJ-42756493, AZD4547, BGJ398, and TAS-120)⁵⁰ has represented a turning point in the therapeutic targeting of FGFR2-dependent tumours. As such, bearing a different chemical

scaffold, pyrido-pyrimidine derivatives represent one of the most important classes of compounds characterized by high affinity toward FGFR and selectivity with respect to some other split TK, such as VEGFR, PDGFR, and EGFR. To this end, HMPL-453 is an orally bioavailable inhibitor of FGFR1, FGFR2, and FGFR3. In pre-clinical studies, HMPL-453 demonstrated superior potency and better kinase selectivity as compared to other drugs of the same class, as well as a favorable safety profile (NCT02966171). Belonging to the third generation of irreversible FGFR inhibitors, TAS-120 (later called futibatinib) covalently binds to a highly conserved P-loop in the ATP pocket of FGFR tyrosine kinase domain.^{41–51} Preclinical data in cell lines with constitutive activation of FGFR2 showed that TAS-120 is mainly characterized by a high in vitro potency and high specificity against wild-type FGFR1–4 as well as against some FGFR2 kinase domain mutations. Pemigatinib (INCB054828) is a pyrido(4,3-d)pyrimidin-2-one derivative, with a selective inhibitor activity against FGFR1, FGFR2, and FGFR.⁵² In in vitro studies, pemigatinib demonstrated specific pharmacologic effects against cancer cells with FGFR genetic alterations. Derazantinib (ARQ087) is a recently developed, orally bioavailable, ATP-competitive multikinase inhibitor of FGFR1, FGFR2, and FGFR3. In vitro and in vivo, this TKI has potent inhibitory effects on a variety of FGFR-dependent human cancer cell lines and xenografted tumor models.^{53–55} Preclinical pharmacologic analysis of a novel selective FGFR inhibitor reported also that E7090, a novel available tyrosine kinase inhibitor with a higher selectivity against FGFR1, exhibited an efficient antitumor activity in both in vitro and in vivo models.⁵⁶ Data retrieved from the analysis of more than 500 cancer cell lines bearing FGF/FGFR genetic alterations across various cancer types showed that the novel anticancer drug BGJ398,⁵⁷ an orally bioavailable pan-FGFR kinase inhibitor (subsequently denominated infigratinib), significantly inhibits cell proliferation. Again, INCB062079 is a potent and selective irreversible inhibitor of FGFR4 reported to suppress the tumor growth in mouse models and in cell lines with amplification and overexpression of the FGFR4 cognate-binding factor FGF19.⁵³ Finally, RLY-4008 is showing to be a highly selective FGFR2 inhibitor administered orally in patients with iCCA and other advanced solid tumors (NCT04526106).

Another therapeutic strategy for target FGFR inhibition is represented by the anti-FGFs or FGFRs monoclonal

antibodies that can block FGFR signaling by interfering with ligand-binding or receptor dimerization. FPA144 is a monoclonal antibody developed against the mutated FGFR2b isoform currently under investigation in patients with malignant tumors harbouring overexpression or amplification of this epithelial isoform. Similarly, the anti-FGFR3 monoclonal antibody MFGR1877S showed anti-tumor activity in preclinical models of bladder cancer with FGFR3 overexpression. Furthermore, the FGF ligand trap approach represents an interesting strategy to target the FGFR signalling. The FGF ligand traps sequester FGF ligands, blocking their ability to bind to and activate FGFRs. To this end, FP-1039 is a soluble fusion protein consisting of the extracellular domain FGFR1 fused with the Fc region of human immunoglobulin G1 (IgG1). It can selectively block mitogenic FGFs, though it does not recognize FGF19, FGF21, and FGF23. Still, Pentraxin-3 (PTX3) acts as a multi-FGF ligand trap capable of recognize and bind various FGFs, including FGF2, FGF6, FGF8, FGF10, and FGF17. The binding with the ligand causes the inhibition of cell proliferation and tumor growth in cancer cells both in vitro and in vivo.⁵⁸

Clinical Development of FGFR2 Inhibitors in Cholangiocarcinoma

Targeting FGFR alterations in iCCA has shown clinically meaningful benefits in recent prospective Phase I–II clinical trials evaluating several TKI inhibitors, among which are Infigratinib (BGJ398), derazantinib (ARQ087), erdafitinib, pemigatinib (INCB054828) and futibatinib (TAS-120). [Table 1](#) reports a summary of FGFR inhibitors currently investigated in clinical trials.

A multicenter, open-label, phase II trial evaluated the activity of infigratinib (BGJ398) in 61 patients with advanced or metastatic chemorefractory iCCA or eCCA harbouring FGFR2 alterations.⁵⁷ FGFR genetic status was required for eligibility confirmation to identify FGFR2 fusion (n = 48), mutation (n = 8) or amplification (n = 3) in the participants. The primary end point was the overall response rate (ORR). In this study, all responsive tumors displayed FGFR2 fusions. The ORR was 14.8% and disease control rate (DCR) was 75.4% with a median duration of disease control (mDOR) of 7.5 months.⁵⁹ At data cut-off, the median progression-free survival (mPFS) was 5.8 months. Regarding the toxicity profile, most frequent treatment-related adverse events (AEs) were fatigue, stomatitis, alopecia and nail disorders. Hyperphosphatemia emerged

Table I Published Clinical Trials of FGFR Inhibitors in Advanced Cholangiocarcinoma

| Experimental Agent | N | Study Phase | Setting | ORR % | mPFS Months | mOS Months |
|--|-----|------------------|--|-------|-------------|------------|
| Infigratinib (BGJ398) ⁵¹ | 61 | II | Previously treated advanced CCA | 14.8 | 5.8 | – |
| Derazantinib (ARQ087) ⁶² | 29 | I/II | Previously treated advanced CCA | 20.7 | 5.7 | – |
| Futibatinib (TAS-120) ⁵⁸ | 67 | II (FOENIX-CCA2) | Previously treated advanced CCA | 34.3 | – | – |
| Erdafitinib ⁵⁹ | 17 | II | Previously treated advanced solid tumors and CCA | 27.3 | 5.6 | – |
| Pemigatinib (INCB054828) ⁶⁰ | 107 | II (FIGHT-202) | Previously treated advanced CCA | 35.5 | 6.9 | 21.1 |
| Debio 1347 ⁶⁵ | 9 | I (FIH) | Previously treated solid tumors and CCA | 22 | – | – |

Abbreviations: ORR, overall response rate; mPFS, median progression free survival; mOS, median overall survival; CCA, cholangiocarcinoma.

as class-specific AE (72.1% any grade), reaching grade 3–4 in 16.4% and requiring study drug adjustment or temporary interruption in 42.6% of patients. Another phase II study evaluating infigratinib in pretreated advanced biliary cancers with FGFR2 gene fusions or translocations is currently ongoing (NCT02150967).^{58,60,61}

In a phase I/II trial appraising the action of derazantinib, 29 patients with unresectable iCCA with FGFR2 fusion progressing after at least one prior systemic therapy received the targeted treatment in continuous daily doses.⁶² The primary endpoint was ORR according to RECIST 1.1 assessed every 8 weeks. The ORR was 20.7% with 4.6 months mDOR and 82.8% DCR. At 20 months follow-up mPFS was 5.7 months and mOS not reached. Grade 3–4 AEs were observed in 8 patients (27.6%) leading to 13.8% treatment discontinuation. An ongoing phase II study is further evaluating derazantinib in pretreated iCCA patients (NCT03230318).

In a phase I/II trial on futibatinib enrolling 45 pretreated iCCA with FGFR alterations (n = 28 FGFR2 gene fusions; n = 17 other aberrations), the treatment was associated with 25% ORR and 75% DCR.⁶³ Among 13 patients progressing to previous treatment with another FGFR inhibitor, 4 partial responses were detected. Grade ≥3 AEs were reported in 51% of patients, the most common was hyperphosphataemia (22%). Preliminary data from the FOENIX-CCA2 single-arm phase II trial enrolling 67 advanced/metastatic iCCA patients with FGFR2 alterations treated with futibatenib, confirmed 34.4% ORR, 76.1% DCR and 6.2 months mDOR.⁶⁴ Treatment-

related AEs were in line with those previously described and no new safety concerns were recorded.

In a Phase I trial, 187 patients with solid tumors progressing after standard chemotherapy were treated with the pan-FGFR inhibitor erdafitinib.⁶⁵ The molecular screening for FGFR alterations was provided. In the cohort of cholangiocarcinoma patients with FGFR fusions or mutations (n = 11), ORR was 27.3% with 11.4 months mDOR. Other trials are currently evaluating safety and efficacy of erdafitinib in previously treated solid tumors comprising biliary cancers (NCT02699606, NCT04083976).

Safety and activity of the oral inhibitor pemigatinib (INCB054828) were investigated in the multicentre FIGHT-202 phase II trial.⁶⁶ Before assessment for eligibility patients were centrally prescreened for FGF/FGFR status using massively parallel DNA sequencing. Among 1206 screened patients with advanced and pretreated iCCA, 146 were eligible and divided into three cohorts: FGFR2 fusions (n = 107), other FGF/FGFR alterations (n = 20) and no FGF/FGFR alterations (n = 18). The primary end point was ORR in the FGFR2 fusion group. At a median follow-up of 17.8 months ORR was 35.5% (2.8% complete response and 32.7% partial response) in the FGFR2 fusion group while none of the patients with other or without any FGF/FGFR alteration responded; mDOR was 7.5 months with 68% and 37% of subjects free of progression respectively at 6 and 12 months. The median overall survival (OS) was 21.1 months in patients with FGFR2 fusions (68% still alive at 12 months) compared to 6.7 and 4.0 months respectively in patients with other or without any FGF/FGFR mutation. Overall,

hyperphosphatemia was the most common all-grade adverse event (60%). Sixty-four per cent of patients experienced grade ≥ 3 AEs being the most frequent hypophosphatemia (12%), arthralgia (6%), stomatitis (5%), hyponatremia (5%) and abdominal pain (5%). Following these data, in April 2020 and later in May 2021, the FDA approved pemigatinib and infigratinib as the first targeted therapy for second- and later-line treatment of locally advanced/metastatic iCCA having FGFR2 fusions or rearrangements.⁶⁷

Several ongoing phase II and III trials are currently evaluating FGFR inhibitors activity in FGFR-positive iCCA either in first or later lines (Table 2).

Toxicity Profile of FGFR2 Inhibitors and Its Management

The safety profile of FGFR2 inhibitors has been reported to be largely manageable in clinical trials, with the occurrence of mostly mild to moderate treatment-related adverse events. FGFR-inhibitor-related toxicities can be classified into class-specific (due to the class effect of FGFR blockade) and non-specific and are superimposable between different FGFR2 inhibitors.⁶⁸ The most

frequently reported class-specific side effect is hyperphosphatemia, defined as serum phosphate levels >5.5 mg. This is an on-target off-tumour effect of FGFR1 inhibition, occurring in 55–81% of cases, caused by disruption of the FGF23/FGFR1 signaling, an important player in the phosphate homeostasis. For patients developing hyperphosphatemia while on FGFR-directed therapy, strategies to manage it span from the use of dietary modifications (low phosphate diet) to phosphorous-lowering agents (including both phosphate binders Sevelamer, Lanthanum and phosphaturic agents such Acetazolamide) depending on its severity. Rarely, dose reductions or interruptions are recommended for G3-G4 hyperphosphatemia (>7 mg/dL), until return to \leq G2. Other recognized class-specific adverse events of FGFR inhibitors include ophthalmologic toxicity, among which dry eye (19–21%) is the most frequently occurring, followed by peculiar retinal toxicities including pigment epithelial detachment (4%) and central serous retinopathy (9%). Although these are usually mild or asymptomatic, a comprehensive ophthalmologic examination is advisable before initiating FGFR2-directed therapies and on demand in the event of vision changes in order to avoid permanent sequelae for the patient.

Table 2 Selected Ongoing Trials Evaluating FGFR Inhibitors in Advanced Cholangiocarcinoma

| Treatment Arms | Study Phase | Setting | Primary End Point | Clinical Trials.gov Identifier |
|---------------------------------------|-------------|---|-------------------------|--------------------------------|
| Pemigatinib vs gemcitabine+cisplatin | III | First Line | PFS | NCT03656536 (FIGHT-302) |
| Infigratinib vs gemcitabine+cisplatin | III | First Line | PFS | NCT03773302 (PROOF) |
| Futibatinib vs gemcitabine+cisplatin | III | First Line | PFS | NCT04093362 (FOENIX) |
| Derazantinib | II | After at least one prior systemic therapy | ORR and PFS at 3 months | NCT03230318 |
| Derazantinib | II | After at least one prior systemic therapy | ORR | NCT03230318 (FIDES-01) |
| BGJ398 (Infigratinib) | II | After at least one prior regimen containing gemcitabine with or without cisplatin | ORR | NCT02150967 |
| Futibatinib | II | After at least one prior systemic gemcitabine and platinum-based chemotherapy | ORR | NCT02052778 |
| Erdafitinib | II | After at least one prior systemic therapy | ORR | NCT02699606 |
| Erdafitinib | II | After at least one prior systemic therapy | ORR | NCT04083976 |
| Pemigatinib | II | After at least one prior systemic therapy | ORR | NCT04256980 |

Abbreviations: ORR, overall response rate; PFS, progression free survival.

Regarding their management, the FGFR inhibitor should be withheld immediately in case of grade ≥ 3 toxicity and for resolved after 4 weeks following onset, the FGFR inhibitor can be restarted at a lower dose under the close supervision of a specialist. Of note, persistent grade ≥ 2 ocular side effect despite a reduced dose or any grade ≥ 4 ocular side effect should lead to permanently discontinue the FGFR inhibitor.⁶⁹ FGFR-inhibitor-associated dermatologic toxicities: stomatitis (20–40%), alopecia (24–46%), nail toxicity (5–17%), and diarrhea (15% to 60%) have been reported in clinical trials.^{62–66}

Finally, fatigue is the most commonly described non-specific adverse event during FGFR2 blockade (32–71%). Importantly, a thorough knowledge of the unique safety profile of this drug class and patient education are key to avoid unnecessary dose reductions and interruptions which can jeopardize treatment intensity. In fact, prevention, prompt recognition and early treatment of these adverse events, better if within a multidisciplinary team, may result in prolonged exposure to FGFR inhibition and a better treatment efficacy.

Discussion

Less than a decade from the discovery of FGFR2 fusions in iCCA,⁴⁵ over the last few years various highly potent and selective FGFR2 tyrosine kinase inhibitors have displayed a clinical meaningful and consistent antitumour activity across phase II trials of previously treated, unresectable advanced, FGFR2 fusion or rearranged iCCA. Very recently, in May 2021, infigratinib has become the second FGFR2 inhibitor after pemigatinib to grant regulatory approval for this indication in the US.⁷⁰ The drug development process of FGFR2 targeting has proceeded at a surprisingly brisk pace, fostered by the unprecedented results seen in a molecularly selected subset of iCCA without convincingly available therapeutic options after failing cisplatin/gemcitabine combination. In pretreated patients, FGFR inhibitors produced objective responses in the range of 21% to 41%, disease control rates of 82–83% and an estimated mPFS in the range of 5.7 to 6.9 months. More interestingly, preliminary assessments have reported an impressive median OS above 20 months.^{62–66} These results compare very favourably with the daunting data of chemotherapy trials, where objective responses were uncommon (around 5%) and overall survival hardly exceeded 6 months in all comers.⁷¹ Moreover, anti-FGFR2 agents seem to be better tolerated than cytotoxics, with predictable and manageable side effects that

do not adversely impact on response and a quality of life maintained during treatment.^{68,72}

Of great interest, the earlier use of FGFR2 inhibitors in the therapeutic path of iCCA, has resulted in a higher activity compared to later lines (ORR of 34% for second line vs 13.8% for third and fourth line).⁷³ Collectively, these data have laid the foundation for the design and the conduct of large first-line phase III randomized controlled trials that are currently underway to evaluate FGFR2-directed therapy against standard-of-care chemotherapy in the molecularly selected population of fusion-positive iCCA. Such ongoing trials included the PROOF trial (NCT03773302) with infigratinib, the FIGHT-302 trial (NCT03656536) with pemigatinib, and the FOENIX-CCA3 trial (NCT04093362) with futibatinib and these results are eagerly awaited within the oncology community. Although the targeting of FGFR2 has emerged as a milestone in the advancement of precision oncology in iCCA, several challenges remain to be addressed to advance further its development in the next future. Among them, as one could expect for oncogene-addicted tumours under the selective pressure of a targeted inhibition, both primary and acquired resistances invariably occur that led to treatment failure with transitory responses followed by disease progression. Regarding the former, a clinico-genomic analysis has reported initial data showing that FGFR2-fusion patients with specific co-occurring alterations, particularly in tumor-suppressor genes, such as BAP1, PBRM1, CDKN2A/B, and TP53, experience worse outcomes when treated with pemigatinib.⁷⁴ As concerns the latter, intriguing translational findings using serial ctDNA analysis and on-treatment tissue biopsies have identified polyclonal FGFR2 kinase domain gatekeeper mutations as acquired resistance mechanisms to pemigatinib and infigratinib, that act by impairing their binding affinity to the target receptor.⁷⁵ Interestingly, the same research group also showed that the third-generation, irreversible, FGFR inhibitor futibatinib (TAS-120), may be active in patients who developed secondary resistance to ATP-competitive inhibitors, thanks to its capability of covalently binding the FGFR2.³³ To this end, ctDNA analysis represents a useful tool not only to track emerging resistance mechanisms to targeted inhibition but also to strategically guide the sequencing of FGFR inhibitors that could in turn extend the duration of its clinical benefit in FGFR2-dependent tumours.

Another avenue which deserves investigation in patients developing resistance to FGFR2 is to combine

FGFR2 inhibitors with other compounds aimed at blocking alternative oncogenic pathways. To this end, preclinical evidence from Krook et al⁷⁶ demonstrated that the PI3K/AKT/mTOR signaling is upregulated in FGFR2 pE565A mutant iCCA cells, and the addition of an mTOR inhibitor to FGFR2-directed therapy has synergistic effect in the same in vitro model.

Although the field of precision oncology is just in its infancy in iCCA, the FGFR2 blockade has been representing a successful story for a cancer type until recently regarded as an orphan disease. However, the molecular heterogeneity and the clonal evolution of FGFR2-fusion positive iCCA under FGFR2 blockade represent a barrier to the full accomplishment of its potential. The application of next-generation technologies such as NGS and ctDNA analysis will give more insights into molecular vulnerabilities and together with the development of both next-generation FGFR2 inhibitors and innovative treatment combinations could represent the key for tackling a historically hard-to-treat cancer type.

Conclusions

iCCA still poses a great clinical challenge since its incidence is steadily rising and the conventional treatment options produced disappointing outcomes, making it one of the deadliest cancer worldwide. In recent years, thanks to the improved knowledge of disease biology, CCA has emerged as a multifaced disease characterized by distinct molecular subset each with peculiar clinicopathologic and therapeutic implications. Among them, the FGFR2 gene fusions hallmarked a specific iCCA subgroup which are increasingly being validated as therapeutic targets with various FGFR inhibitors in advanced-phase clinical development. When compared with historical controls, efficacy data of anti-FGFR2 agents are unprecedented and their tolerability is good. Despite this, some research questions remain to be addressed in the near future, mainly concerning the ways to circumvent resistance mechanisms as well as the need for more selective and potent anti-FGFR agents. The results of ongoing trials evaluating FGFR-directed therapy versus standard-of-care chemotherapy will ascertain the role of targeted agents in the front-line setting of this molecular subset of CCA. Over the last few years, we are witnessing a paradigm change in the management of iCCA towards a more personalized and precise treatments approach that can improve reshape the outcome of patients affecting by this burdensome disease.

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Disclosure

Prof. Dr. Massimo Dominici reports personal fees from Rigenrand srl and is Founder and Stockholder of Rigenrand srl, outside the submitted work. The authors have no other conflicts of interest to declare.

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