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REVIEW

Fibroblast Growth Factor Receptor (FGFR) Inhibitors for the Treatment of Cholangiocarcinoma: Key Therapeutic Developments and Knowledge Gaps

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Abstract: Fibroblast growth factor receptor 2 (FGFR2) alterations have emerged as an important targetable oncogenic driver in a biologically distinct subset of biliary tract cancers (BTCs), particularly intrahepatic cholangiocarcinoma (iCCA), alongside other actionable genomic events such as IDH1 mutations, BRAF V600E, HER2 amplification and MSI-H. FGFR2 fusions and mutations define a distinct molecular subgroup whose prevalence varies across geographic regions and etiologic backgrounds such as liver fluke–associated disease. Clinical studies of both reversible and irreversible FGFR inhibitors have demonstrated meaningful activity in FGFR2-rearranged iCCA, while also highlighting a characteristic toxicity profile dominated by on-target hyperphosphataemia. Parallel translational work using cfDNA-based liquid biopsy has mapped a spectrum of secondary kinase-domain mutations that underlie acquired resistance, informing the development of next-generation FGFR2-selective inhibitors (eg, lirafugratinib) and combination strategies with EGFR/ERBB blockade. Collectively, these data underscore the need for comprehensive molecular profiling and innovative umbrella trial designs to optimise targeted therapy in this rare, biologically heterogeneous malignancy.

Keywords: intrahepatic cholangiocarcinoma, FGFR2 alterations, biliary tract cancer, FGFR inhibitors, acquired resistance, liquid biopsy

Introduction

Cholangiocarcinoma (CCA) constitutes a heterogeneous group of aggressive malignancies arising from the biliary tree epithelium. Anatomically, these tumors are classified into intrahepatic (iCCA), perihilar (pCCA), and distal (dCCA) subtypes, with iCCA comprising 10–20% of cases, while perihilar and distal lesions account for approximately 50% and 30–40%, respectively.[1,2] Although CCA represents only about 3% of all gastrointestinal malignancies worldwide, its clinical burden is disproportionately high due to late-stage diagnosis and limited therapeutic options.[1]

The epidemiology of CCA exhibits marked geographic variation. In high-income Western countries, age-adjusted incidence rates range from 0.35 to 2 cases per 100,000.[1] In contrast, rates soar to 80–100 per 100,000 in endemic regions of East Asia, particularly Thailand, driven by the prevalence of liver fluke infections (Opisthorchis viverrini and Clonorchis sinensis).[3] Notably, the incidence of iCCA has risen alarmingly in Western populations over the past four decades, with a reported 165% increase in the United States alone.[4] Despite advances in oncology, the prognosis remains

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dismal: the 5-year overall survival rate for iCCA is less than 8%, and patients with advanced disease typically have a median overall survival of approximately one year.[1,5]

Historically, systemic treatment for advanced biliary tract cancer (BTC) has relied on gemcitabine–cisplatin–based chemotherapy, with median overall survival rarely exceeding one year. The addition of immune checkpoint inhibitors to this backbone has yielded statistically significant, but overall modest, gains in survival, and most patients still experience relapse within a relatively short time frame.[6,7] Thus, chemotherapy remains the cornerstone of first-line management, while the absolute clinical benefit of immunotherapy in unselected populations is incremental rather than transformative.[8] In parallel, broad molecular profiling efforts have shown that BTCs are enriched for potentially actionable genomic alterations—including FGFR2 fusions and rearrangements, IDH1/2 mutations, BRAF V600E, ERBB2 (HER2) amplification, NTRK and RET fusions, and MSI-H/dMMR—leading some to draw comparisons with lung cancer in terms of biological diversity within a single anatomical site.[9] National Comprehensive Cancer Network (NCCN) and the European Society for Medical Oncology (ESMO) guidelines now recommend universal molecular profiling for advanced BTC.[10,11] In practice, universal testing can be challenging: primary tumours often arise in anatomically difficult locations, biopsy samples may be sparse or unsafe to repeat, and access to high-quality sequencing remains uneven across regions. Liquid biopsy approaches, particularly plasma-based circulating tumour DNA (ctDNA) assays, are increasingly used as a minimally invasive complement when tissue is insufficient and to enable treatment-directed profiling, but broader implementation will require greater standardisation, reimbursement, and integration into routine care pathways.[12]

These advances have highlighted the molecular heterogeneity of BTCs and identified the FGFR pathway, particularly FGFR2 fusions, as a key oncogenic driver and an actionable therapeutic target. The FGFR family, comprising four transmembrane receptor tyrosine kinases (FGFR1–4), regulates essential physiological processes including embryonic development, tissue homeostasis, and metabolism.[13] Dysregulation of this pathway—particularly through gene fusions in FGFR2—has been identified as a primary oncogenic event in a significant subset of iCCA cases.[14,15] The validation of FGFR2 fusions as actionable targets has fundamentally shifted the treatment paradigm. Consequently, the regulatory approval of selective FGFR inhibitors—pemigatinib, infigratinib, and futibatinib—marks a new era of precision medicine for this disease.[16–18] This narrative review aims to synthesize the current state of knowledge regarding FGFR inhibition in cholangiocarcinoma, detailing the molecular biology of the FGFR pathway, the clinical efficacy of approved agents, and the emerging challenges of resistance mechanisms and management strategies.

Molecular Landscape & FGFR Biology

The FGFR Family and Signaling Architecture

The rationale for FGFR-directed therapy is best appreciated in the context of the structural biology and signalling architecture of the FGFR family. The FGFR family members (FGFR1–4) share 56–71% sequence identity and a highly conserved architecture.[13] Each receptor consists of an extracellular ligand-binding domain containing three immunoglobulin-like loops (D1–D3), a single transmembrane helix, and an intracellular split tyrosine kinase domain.[13,19] An "acid box" located in the D1–D2 linker region plays a regulatory role in receptor autoinhibition. Furthermore, alternative splicing of the D3 domain in FGFR1–3 generates "b" and "c" isoforms; "b" isoforms are expressed in epithelial tissues while "c" isoforms predominate in mesenchymal cells, establishing critical epithelial-mesenchymal signaling loops.[19]

Under physiological conditions, ligand binding induces receptor dimerization and trans-autophosphorylation. This recruits adaptor proteins, such as FGFR substrate 2 (FRS2) and PLCγ, to specific phosphotyrosine residues, triggering downstream signaling cascades.[13] Key pathways include the RAS-MAPK pathway (driving proliferation), the PI3K-AKT-mTOR axis (promoting survival and metabolism), and the JAK-STAT pathway.[13,19]

FGFR Alterations in Cholangiocarcinoma

While FGFR alterations are found in approximately 7% of all cancers, the landscape in CCA is dominated by FGFR2 gene fusions. These fusions are a unique molecular hallmark of intrahepatic disease, occurring in 10–20% of iCCA cases, while being virtually absent (<1%) in extrahepatic cholangiocarcinoma.[14,20] Mechanistically, these rearrangements

typically involve the fusion of the intact FGFR2 kinase domain (residues 1–768) to the sequence of a partner gene. Over 100 unique fusion partners have been identified, with BICC1 being the most prevalent, accounting for 24–43% of fusion-positive cases.[14,21] The FGFR2-BICC1 fusion arises from a chromosomal inversion that fuses the FGFR2 kinase domain to the coiled-coil domain of BICC1, promoting constitutive, ligand-independent dimerization and oncogenic signaling.[21] Other frequent partners include KIAA1217, WAC, CEP55, AHCYL1, and PPHLN1.[20,22] Importantly, clinical responses to FGFR inhibitors appear to be driven by the dependency on the kinase domain rather than the identity of the specific fusion partner.[16,22] Beyond fusions, other FGFR alterations exist but are less frequent. These include FGFR2 mutations (0.9%), amplifications (2.6%), and extracellular domain in-frame deletions (EIDs) (2.8% of iCCA).[20,23] Unlike fusions, which are highly predictive of response, the therapeutic relevance of these alternative mechanisms remains an area of active investigation, although EIDs have shown sensitivity to kinase inhibition in preclinical models.[23]

Diagnostic Considerations and Clinical Correlations

Accurate detection of these alterations is critical for patient selection. RNA-based Next-Generation Sequencing (NGS) is the preferred methodology, demonstrating a detection rate of over 80% for oncogenic fusions, significantly outperforming DNA-based NGS which may miss intronic breakpoints or large structural variants.[22,24] Clinically, FGFR2 fusion-positive iCCA represents a distinct molecular subgroup. These tumors are nearly exclusive to the small-duct type of iCCA and are associated with a more indolent disease course, younger age at diagnosis, and female predominance.[1,14] From a genomic perspective, FGFR2 fusions are generally mutually exclusive with KRAS and IDH1/2 mutations, though they frequently co-occur with BAP1 mutations (~40%) and alterations in CDKN2A/B.[20,25] Notably, patients with this molecular profile exhibit a better baseline prognosis compared to fusion-negative patients, even prior to the administration of targeted therapies.[22]

Clinical Efficacy & Safety

Notably, the current evidence base is largely built on single-arm Phase II trials and biomarker-selected cohorts with modest sample sizes, which restricts the precision of estimates and limits the generalisability of efficacy comparisons across studies. Currently, several small molecule FGFR inhibitors have been developed and are being clinically investigated for urothelial, gastric, lung, liver and uterine malignancies. Non-selective FGFR inhibitors include derazantinib, dovitinib, lucitanib, lenvatinib and nintedanib, with activity against other multiple receptor tyrosine kinases apart from FGFR.[26] These drugs also target the tumor microenvironment including angiogenesis and immunity leading to a complicated mechanism of action and adverse events compared to selective inhibitors. Classification of selective FGFR inhibitors is even more complex. They are divided into pan FGFR inhibitors (erdaftinib, futibatinib and rogaratinib), FGFR1/2/3 inhibitors (pemigatinib, infigratinib and zoligratinib), and selective FGFR2 inhibitors (eg, lirafugratinib). The latest entrants include LOXO-435 (selective FGFR3 inhibitor) and roblitinib (selective FGFR4 inhibitor).[27] Once an FGFR2 fusion or rearrangement is identified after progression on gemcitabine–cisplatin–based therapy, oral FGFR inhibitors are now a standard second-line option.[28] In this review, we will be discussing the various FGFR inhibitors that have shown clinical efficacy in advanced cholangiocarcinoma. To facilitate consistent comparison across studies, we summarised the pivotal trials of approved FGFR inhibitors in CCA using a common set of efficacy endpoints—objective response rate (ORR), disease control rate (DCR), median progression-free survival (mPFS), median overall survival (mOS), and median duration of response (DoR)—as well as line of therapy and trial design (Table 1). In the subsections below, we discuss individual agents with reference to this framework and to historical outcomes with cytotoxic chemotherapy, recognising that all cross-trial comparisons are exploratory and must be interpreted with caution.

Lenvatinib

Lenvatinib, in view of its weak FGFR inhibitory potential has been tried as a second line therapy in advanced iCCA, but with modest returns. In a single arm open-label Phase 2 study involving 26 BTC patients (iCCA – n = 6), the ORR was 11.5% (90% CI: 3.2–27.2), and mPFS was 3.19 months (95% CI: 2.79–7.23). mOS was 7.35 months (95% CI: 4.5–11.27).[29] Lenvatinib, also being a VEGF (vascular endothelial growth factor inhibitor), has shown synergy with immune checkpoint inhibitors. A real world retrospective study showed similar mOS for the

Table 1 Approved FGFR Inhibitors for FGFR2-Altered Cholangiocarcinoma: Key Efficacy Outcomes

Drug	Target Selectivity/ Type	Pivotal Trial (Phase)	Line of Therapy/ Population	FGFR Alteration	ORR (%)	DCR (%)	Median PFS (Months)	Median OS (Months)	Median DoR (Months)	Notes
Pemigatinib	Reversible FGFR1–3 TKI	FIGHT-202 (phase II)	2L+ locally advanced/ metastatic CCA	FGFR2 fusions/ rearrangements	37	≈82	6.9	≈17–18	9.1	No confirmed responses in non-fusion cohort
Futibatinib	Irreversible FGFR1–4 TKI	FOENIX-CCA2 (phase II)	2L+ unresectable/ metastatic iCCA	FGFR2 fusions/ rearrangements	>40	82.5	≈9	21.7	9.7	Designed to retain activity against resistance mutations
Infigratinib	Reversible FGFR1–3 TKI	PROOF-301 (Phase III, early terminated)	1L FGFR2-rearranged CCA	FGFR2 fusions/ rearrangements	23.1	–	7.3	–	5	Trial closed early; feasibility issues in rare subset
Erdafitinib	Pan-FGFR TKI	RAGNAR (basket study)	2L+ FGFR2-altered BTC	FGFR2 fusions/ other alterations	≈55	–	≈8–9	≈18	Variable	Basket design; supports class activity in BTC

Abbreviations: FGFR, fibroblast growth factor receptor; TKI, tyrosine kinase inhibitor; CCA, cholangiocarcinoma; iCCA, intrahepatic cholangiocarcinoma; BTC, biliary tract cancer; ORR, objective response rate; DCR, disease control rate; PFS, progression-free survival; OS, overall survival; DoR, duration of response; 1L, first-line; 2L+, second-line or later.

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combination of pembrolizumab and lenvatinib versus systemic therapy as first line therapy for advanced iCCA.[30] Similarly, real world evidence has explored the feasibility of combination of pembrolizumab with lenvatinib and GEMOX, demonstrating an ORR of 38%, median PFS and OS of 7.1 and 17.3 months, respectively.[31] Nevertheless, randomized prospective trials are still needed to confirm benefit and optimal patient selection.

Pemigatinib

Within this framework, pemigatinib represents the most extensively studied reversible FGFR 1–3 inhibitor in FGFR2-rearranged cholangiocarcinoma, with FIGHT-202 providing the key efficacy and safety data that anchor much of the class comparison. Mechanistically, pemigatinib is a small-molecule, ATP-competitive tyrosine-kinase inhibitor with high selectivity for FGFR1, FGFR2 and FGFR3 and minimal activity against FGFR4 or other kinases (only weak inhibition of VEGFR and c-KIT has been described). By blocking receptor phosphorylation and downstream signalling, it induces cell death in tumours driven by FGFR fusions, rearrangements or activating mutations. FGFR1 is a key regulator of phosphate homeostasis; therefore, on-target disturbances of serum phosphate are an anticipated pharmacodynamic effect of pemigatinib and other FGFR inhibitors.[32] The recommended regimen is 13.5 mg once daily on a 2-weeks-on/1-week-off schedule in 21-day cycles. Steady-state exposure increases proportionally over the 1–20 mg dose range, and food has no relevant impact on absorption.[33] The drug is extensively metabolised via hepatic CYP3A4 with negligible renal clearance. Dose adjustment is generally unnecessary in mild–moderate hepatic or renal impairment, but a reduction to 9 mg daily is advised in severe impairment. Strong CYP3A4 inhibitors or inducers can alter pemigatinib exposure by approximately 50%, and concomitant medications should therefore be carefully reviewed.[34]

The initial dose finding study of pemigatinib was FIGHT 101, which explored doses ranging from 1–20 mg in various solid tumors. It was found that doses ≥4 mg were pharmacologically active. Hyperphosphatemia was the most common treatment-emergent adverse event (TEAE) (75%, grade ≥ 3, 2.3%). Five out of 12 partial responses were seen in cholangiocarcinoma. ORR was the highest for FGFR fusions and rearrangements, followed by a lower response rate in those with activating FGFR mutations.[35] These results paved way for the FIGHT-202 study which tested pemigatinib as monotherapy in previously treated advanced CCA with FGFR alterations. BICC1 was the most common fusion partner identified (29%). Cohort A included patients with FGFR2 fusions/rearrangements (n = 107), cohort B included other FGFR alterations (n = 20), and cohort C included no FGFR abnormalities (n = 18). All participants received pemigatinib 13.5 mg once daily (2 weeks on, 1 week off) until progression or unacceptable toxicity. The primary end-point was met with an ORR of 37% and a DCR of 82%. The median time to response was 2.7 months. In contrast, activity in the exploratory cohort with non-FGFR2 fusion alterations (cohort B and C – mainly amplifications or point mutations) was limited, with no confirmed responses and short PFS, reinforcing that FGFR2 fusions/rearrangements are the key predictive biomarker for benefit from FGFR TKIs in CCA.[16] An update of FIGHT-202 was published in 2024, which showed an encouraging PFS and OS of 7 and 17.5 months, respectively, with a DOR of 9.1 months.[36] Hyperphosphatemia was the most common TEAE (58%). Pemigatinib was discontinued in 15 (10.2%) patients due to TEAEs. A post hoc analysis showed numerically longer PFS in patients who had received only one prior line of therapy (7 vs 4.2 months).[37]

In real-world cohorts, pemigatinib has achieved ORRs approximately 60% and an mPFS of about 7.4 months, closely mirroring the efficacy observed in clinical trials and reinforcing that its antitumour activity translates into routine clinical practice.[38] Also, mPFS in responders was 30.1 months compared to 13.7 months in non-responders. Based on the results of FIGHT-202, pemigatinib became the first oral targeted therapy approved in recurrent unresectable advanced CCA with FGFR2 fusions or rearrangements. The ongoing Phase 3 FIGHT-302 study is testing the efficacy of pemigatinib versus cisplatin and gemcitabine as first line in advanced CCA with FGFR-2 fusions. The primary end-point is PFS with secondary end-points including ORR, DCR and OS. Given the risk of ocular adverse events associated with FGFR inhibition, comprehensive ophthalmological evaluations are planned at screening, and after every 3 cycles. The results of FIGHT 302 are expected around October 2027.[39]

Infigratinib

Infigratinib is an orally available, ATP-competitive small-molecule inhibitor that targets all four FGFR isoforms (FGFR1–4). Two major circulating metabolites (BHS697 and CQM15) retain similar binding affinity to the parent compound.[40] Early Phase I work defined a maximum tolerated dose of 125 mg once daily given continuously in 28-day cycles; dose-limiting toxicities were mainly hyperphosphataemia, elevations in liver enzymes and corneal changes.[41] Transitioning to an intermittent 3 weeks on/1 week off schedule reduced toxicity while maintaining pharmacodynamic activity. Infigratinib is rapidly absorbed, has a high oral bioavailability with ~99% plasma protein binding, and exhibits relatively low affinity for FGFR4, which may explain the comparatively modest rate of gastrointestinal adverse events with this agent. Hyperphosphataemia was reported in roughly three-quarters of treated patients (around 10% grade ≥ 3) and was generally controlled with dietary phosphate restriction and oral binders. Other characteristic toxicities included central serous retinopathy or retinal pigment epithelial detachment, as well as skin and nail changes.

The pivotal phase II trial evaluated infigratinib in patients with advanced CCA previously treated with gemcitabine-based chemotherapy. Of 122 enrolled patients, 108 received at least one dose of study drug. After a median follow-up of 10.6 months, the ORR was 23.1%, with an mPFS of 7.3 months and a mOS of 12.2 months.[42] Benefit appeared greatest when infigratinib was used in the second-line setting, where mOS reached 14.5 months, compared with 8.7–14.4 months in patients treated in later lines. These outcomes compared favourably with historical data from the ABC-06 trial, in which second-line modified FOLFOX6 chemotherapy achieved a mOS of 6.2 months versus 5.3 months with best supportive care alone.[43] Although cross-trial comparisons with FIGHT-202 suggest lower response rates than those seen with pemigatinib, differences in study design and baseline characteristics limit direct comparison. Importantly, infigratinib contributed one of the most substantial and long-term safety datasets among FGFR inhibitors in cholangiocarcinoma.

On the basis of the phase II results, the US FDA granted accelerated approval to infigratinib in May 2021 for previously treated, recurrent or unresectable CCA with FGFR2 fusions or rearrangements, contingent on confirmation of clinical benefit in a first-line Phase III study. That confirmatory trial, PROOF-301, compared infigratinib with cisplatin–gemcitabine in untreated FGFR2-rearranged disease. Despite screening close to 1100 patients with cholangiocarcinoma, only about 70 individuals with the requisite molecular subtype could be randomised, and the study was ultimately terminated due to slow accrual.[44] In 2024, the accelerated approval was withdrawn following the inability to complete the confirmatory study. This experience highlights both the antitumour potential of FGFR2 inhibition and the practical limitations of traditional, large phase III trials in rare, genomically defined subsets, underscoring the need for more flexible regulatory pathways and biomarker-driven confirmatory strategies.

Futibatinib

A major step forward in this field has been the development of irreversible FGFR blockade. Futibatinib is a structurally novel, covalent FGFR1–4 inhibitor that forms a stable bond with a conserved cysteine residue in the kinase domain, thereby locking the receptor in an inactive conformation.[45] This binding mode was intentionally engineered to maintain activity in the presence of resistance-associated FGFR2 mutations. Preclinical studies have shown potent inhibition not only of classical gatekeeper substitutions such as V565I/L, but also of "molecular brake" alterations that tend to blunt the efficacy of reversible ATP-competitive inhibitors.[46] Futibatinib is available as 4-mg tablets, with a recommended dose of 20 mg once daily. It is ~95% protein bound, has a mean terminal half-life of about 3 hours, and is predominantly metabolised via CYP3A4 in liver.[45,47]

Early phase I studies across solid tumours, including 83 patients with cholangiocarcinoma—many previously exposed to another FGFR inhibitor—demonstrated encouraging antitumour activity, with an ORR of roughly 17% in a heavily treated population. These data led to the single-arm, multicentre phase II FOENIX-CCA2 trial, which enrolled 103 patients with unresectable or metastatic FGFR2 fusion/rearranged iCCA who had progression on first-line gemcitabine–platinum chemotherapy. In this study, futibatinib achieved an ORR of 42%, a DCR of 82–83%, a median DoR of 9.7 months, and a mPFS of about 9 months; mOS reached 21.7 months (95% CI 14.5–not estimable), with sustained benefit on longer follow-up and maintenance of health-related quality of life.[13,18–21] Although FOENIX-CCA2 lacked

a randomised control arm, the depth and durability of responses in this refractory population supported regulatory approval by both the FDA and EMA, establishing futibatinib as a key irreversible FGFR inhibitor for FGFR2-altered iCCA.[18]

In the absence of direct comparative trials, the choice between pemigatinib and futibatinib is largely driven by availability, clinician experience and individual patient characteristics. Indirect simulated comparisons pooling published datasets suggest broadly similar progression-free and overall survival outcomes for futibatinib and pemigatinib, with both agents conferring a substantial reduction in the risk of death relative to conventional cytotoxic chemotherapy.[48] Exploratory analyses have suggested that co-occurring TP53 mutations may be associated with a lack of response to pemigatinib, whereas responses have been reported with futibatinib in this molecular context, although numbers are small and these findings remain hypothesis-generating. Whether sequential use of different FGFR TKIs meaningfully improves long-term outcomes compared with switching directly to a clinical trial of next-generation inhibitors is an open question and is a key focus of ongoing research.

More recently, the pan-FGFR inhibitor erdafitinib has shown promising activity in the RAGNAR basket study; in the cohort of patients with FGFR2-altered cholangiocarcinoma, ORR approached 55%, with a median DoR of ~7 months, PFS of ~8–9 months and OS around 18 months, further validating FGFR2 as a therapeutically relevant target[49] (Table-1).

Taken together, the available phase II and basket-trial data indicate a consistent level of activity for FGFR-directed therapy in FGFR2-altered cholangiocarcinoma. Across pemigatinib (FIGHT-202), futibatinib (FOENIX-CCA2), infigratinib and the CCA cohort of the RAGNAR erdafitinib study, ORR generally ranges from the low 20% to above 40% (reaching ~55% in selected basket cohorts), with mPFS clustering around 7–9 months and mOS often extending to 12–22 months in previously treated populations. By contrast, modified FOLFOX6 in the ABC-06 trial yielded an mOS of 6.2 months with modest response rates in the second-line setting. While differences in eligibility criteria, prior therapy and assessment schedules preclude definitive indirect comparisons, these patterns support a class-wide benefit of FGFR inhibition relative to historical chemotherapy in FGFR2-rearranged disease.

Accordingly, Table 1 collates the key efficacy outcomes and design features of approved FGFR inhibitors in FGFR2-altered cholangiocarcinoma, providing a side-by-side overview that complements the agent-specific narrative.

Other Novel Drugs

Several next-generation FGFR inhibitors are being developed specifically to overcome on-target resistance after first-generation FGFR2 TKIs. Lirafugratinib (RLY-4008) has been designed to sharpen the therapeutic index by minimising off-isoform FGFR1/3/4 blockade and its attendant toxicities, while retaining potent activity against a broad spectrum of oncogenic FGFR2 alterations, including gatekeeper and "molecular-brake" resistance mutations. In the REFOCUS programme, these agents produced objective responses in roughly half of FGFR-inhibitor–naïve patients with FGFR2 fusion–positive CCA and in about 10–15% of those previously exposed to an FGFR TKI, indicating that sequential FGFR2-targeted therapy may recapture disease control in a subset of patients and could eventually be tailored to the emerging resistance profile, analogous to EGFR-mutant NSCLC. A newer FGFR2-selective compound that engages a distinct binding site has also shown early antitumour activity not only in fusion-positive disease but also in tumours with FGFR2 amplification or non-fusion alterations, suggesting potential to extend the benefit of FGFR-directed therapy beyond the classical fusion-defined population.[50]

Derazantinib (ARQ 087) is one of the latest entrant in this class with a strong pan-FGFR inhibitory potential. The drug was well tolerated in its Phase 1 study exhibiting significant single agent activity with a manageable toxicity profile.[51] In the open label phase 2 study involving adult patients with unresectable iCCA, ORR was 20.7% and DCR was 82.8%. Estimated mPFS was 5.7 months.[52] mOS could not be estimated as very few events occurred during the short follow up. Although hyperphosphatemia was the predominant adverse event, none of the patients required chelation therapy and majority continued with full doses. Despite the promising response rates, the short DoR still remains an achilles heel. Little is known about the mechanisms of secondary resistance.

Zoligratinib (Debio 1347), with an exactly similar mechanism of action, was tested in the FUZE multicenter, multi-cohort study involving advanced solid tumors. Amongst cohort A patients (BTCs), the initial response rates did not meet the primary efficacy threshold. Hence the trial was terminated, and this molecule was not developed further.[53]

Tasurgratinib (E7090) is an orally administered, selective inhibitor of fibroblast growth factor receptors 1–3. In a phase II study conducted in Japan and China, including 63 patients with FGFR 2 fusion–positive CCA, the ORR was 30%. Overall, tasurgratinib demonstrated encouraging antitumour activity in patients with BTC harbouring FGFR-2 gene fusions who had previously received at least one line of chemotherapy.[54]

Tinengotinib (TT-00420) is a multikinase inhibitor (FGFR, VEGFR, CSF1R) that engages an FGFR2 binding site displaced from the inner ATP pocket and forms three hydrogen bonds with the active conformation of the receptor, a distinct mode of binding that preserves potency against a broad spectrum of kinase-domain mutations, including classic gatekeeper and molecular-brake substitutions. In a phase I cohort of 17 patients with CCA harbouring diverse FGFR2 alterations who had all received one or more prior FGFR inhibitors, tumour shrinkage of up to ~55% was observed,[55] with several partial responses despite the heavily pretreated setting. In a four-cohort phase II study of previously treated advanced cholangiocarcinoma, tinenogotinib demonstrated activity that varied by the biological context of FGFR alteration and prior FGFR inhibitor exposure. Among patients with FGFR2 fusion–positive disease and primary resistance to prior FGFR inhibition (Cohort A1), the ORR was 6.3%. In contrast, patients with FGFR2 fusions and acquired resistance after an initial FGFR inhibitor benefit (Cohort A2) achieved a higher ORR of 30.0%. Antitumour activity was also observed in individuals with non-fusion FGFR alterations (Cohort B), where the ORR was 23.1%. Collectively, these findings suggest that tinenogotinib may retain clinically meaningful activity after progression on earlier FGFR-targeted therapy—particularly in acquired-resistance settings—and can also show efficacy in selected patients with other FGFR alterations.[56] The phase I and II signal provided a strong rationale for the ongoing global phase III FIRST-308 trial, which will randomise approximately 150 patients with ≥3-line FGFR-altered CCA and prior exposure to an FDA-approved FGFR inhibitor to tinenogtinib versus physician's-choice chemotherapy (2:1).[57] A pooled cohort of 109 patients with cholangiocarcinoma, of whom 46% had previously received an FGFR inhibitor, tinenogtinib was evaluated for efficacy and safety. TRAEs were reported in 105 patients (96.3%), and 59 (54.1%) experienced grade ≥ 3 TRAEs. The most frequent grade 3–4 events occurring in ≥5% of patients were hypertension (24.8%), stomatitis (7.3%), palmar–plantar erythrodysaesthesia (7.3%) and diarrhoea (5.5%), a pattern that was broadly comparable to that seen in other advanced solid tumour settings. In the overall cohort, mPFS was 7.26 months (95% CI 5.55–9.20), and mOS was 15.93 months (95% CI 9.43–19.48). Among the 34 patients with FGFR2-altered CCA who had previously been treated with an FGFR inhibitor, once-daily tinenogtinib achieved an mPFS of 5.55 months (95% CI 4.90–9.10) and an mOS of 17.05 months (95% CI 8.05–19.48). Collectively, these data suggest that tinenogtinib offers clinically meaningful activity with an acceptable safety profile in FGFR2-altered CCA, including in patients who have progressed on prior FGFR-targeted therapy.[58] Parallel programmes are exploring highly selective, resistance-directed compounds.

TYRA-200 is a reversible FGFR1–3 inhibitor whose in-vitro enzymatic IC_{50} values remain in the low-nanomolar range across multiple FGFR2 gatekeeper and N550 "molecular-brake" variants; its phase I study incorporates a dedicated expansion for FGFR2-positive iCCA with prior FGFRi exposure.[59] CGT4859, another reversible FGFR2-focused agent, demonstrates roughly 140-fold selectivity for FGFR2/3 over FGFR1 and retains activity against a wide panel of FGFR2 resistance mutations while sparing most of the kinome (only FGFR2, FGFR3 and ROS showing ≥50% inhibition in a 371-kinase screen), a profile designed to reduce hyperphosphataemia and off-target toxicities[60] (Table-2).

Common Side Effects and Management

FGFR inhibitors share a broadly similar, mechanism-driven toxicity profile. Across pivotal trials, any-grade hyperphosphataemia is reported in roughly 60–80% of patients (grade ≥ 3 in about 15–20%), while alopecia, diarrhoea, dry mouth and fatigue each occur in ~40–70% of cases, and nail changes or other dermatologic events in about one-third.[61] Stomatitis/oral mucositis and palmar–plantar erythrodysaesthesia are also common (≈20–35%), often becoming the dose-limiting chronic toxicities that most affect daily functioning.[62]

FGFR1 and its ligand FGFR23 are involved in the tight regulation of phosphate balance along with parathyroid hormone. The binding of FGF23 in the presence of klotho activates the downstream FGFR1 signaling pathway. This in-turn inhibits the sodium phosphate co-transporters (SLC34A1, SLC34A3), limiting renal phosphate reabsorption. Also, FGF23 notoriously blocks the conversion of 25-hydroxy vitamin D3 to its activated form, which limits the phosphate

Table 2 Next-Generation FGFR Inhibitors Under Development for FGFR2-Altered Cholangiocarcinoma

Agent	Type/Selectivity	Key Design Features	Population of Interest	Early Efficacy Signals	Ongoing Trials/ Development Stage
Lirafugratinib (RLY-4008)	Highly selective, irreversible FGFR2 inhibitor	Minimal FGFR1/3/4 inhibition, retains potency against gatekeeper and molecular-brake FGFR2 mutations	FGFR2 fusion–positive iCCA, FGFRi-naïve and FGFRi-pretreated	ORR ≈50% in FGFRi-naïve; ≈10–15% in patients previously treated with an FGFR TKI	REFOCUS programme (phase I/II dose-expansion)
Tinenogtinib (TT-00420)	Multi-kinase inhibitor with FGFR1–3 activity plus additional targets (eg, JAK1/2, VEGFRs, Aurora A/B, CSF1R)	Binds FGFR2 at a site displaced from the inner ATP pocket, forms three H-bonds; maintains activity against multiple kinase-domain resistance mutations	FGFR2-altered CCA after prior FGFR inhibitor phase II; four cohorts stratified by FGFR status and prior FGFR inhibitor resistance (A1: FGFR2 fusion + primary FGFRi resistance; A2: FGFR2 fusion + acquired FGFRi resistance; B: other FGFR alterations; C: FGFR wild-type)	Tumour shrinkage up to ~55% and several partial responses in a 17-patient phase I cohort ORR A1 6.3%, A2 30.0%, B 23.1%, C 0% (evaluable n = 51); DCR A1 100%, A2 90.0%, B 84.6%, C 66.7%—suggesting activity particularly in FGFR2 fusion disease progressing after prior FGFR inhibition	FIRST-308 phase III trial vs physician's-choice chemotherapy (≥3L setting)
TYRA-200	Reversible FGFR1–3 inhibitor	Low-nanomolar IC50 across multiple FGFR2 gatekeeper and N550 "molecular-brake" variants	FGFR2-positive iCCA with prior FGFRi exposure	Early radiologic responses anticipated; full ORR data pending	Ongoing phase I dose-escalation and expansion including a dedicated FGFR2+ iCCA cohort
Tasurgratinib (E7090)	Reversible FGFR1–3 TKI (selective)	Pivotal single-arm phase II	Previously treated, unresectable/metastatic CCA; FGFR2 gene fusion+; prior ≥ 1 gemcitabine-based regimen; prior FGFRi excluded (Japanese + Chinese cohort)	In 63 treated patients, objective response rate 30% (all partial responses); DCR 79%; median PFS 5.4 months and median OS 13.1 months	Registered trial: NCT04238715
CGT4859	Reversible FGFR2/3-focused inhibitor	≈140-fold selectivity for FGFR2/3 over FGFR1; active against a wide panel of FGFR2 resistance mutations; minimal off-kinome activity	FGFR2-altered solid tumours, especially CCA progressing on earlier-generation FGFR TKIs	Preclinical models show sustained tumour regression with reduced hyperphosphataemia risk	First-in-human phase I study in dose-escalation (clinical development ongoing)

(*Continued*)

Table 2 (Continued).

Agent	Type/Selectivity	Key Design Features	Population of Interest	Early Efficacy Signals	Ongoing Trials/ Development Stage
Derazantinib (ARQ-087)	Oral, reversible, spectrum-selective FGFR1–3 inhibitor with additional CSF1R and VEGFR2 inhibition (multi-kinase)	ATP-competitive pan-FGFR1–3 blockade; concurrent CSF1R and VEGFR2 inhibition may modulate the tumour micro-environment and angiogenesis; active against a range of FGFR2 alterations (fusions, mutations, amplifications).	FGFR2 fusion- or rearrangement-positive iCCA (post-platinum chemotherapy); additional cohorts with FGFR2 mutations/ amplifications.	FIDES-01 phase II (FGFR2 fusion-positive CCA): ORR ≈22%, DCR ≈76%, median PFS ≈7.8–8.0 months.	FIDES-01 phase II in FGFR2-altered CCA (monotherapy); additional FIDES-02/ FIDES-03 studies in other FGFR-altered tumours and combinations (eg, with atezolizumab, ramucirumab + paclitaxel).
Debio-1347 (CH5183284, zoligratinib)	Oral, highly selective, ATP-competitive FGFR1–3 inhibitor; minimal activity on KDR/VEGFR2 and most other kinases.	Non-covalent reversible TKI with a unique binding mode that can inhibit certain FGFR2 gatekeeper mutations (eg, V564F) associated with resistance to other FGFR inhibitors; designed for high selectivity to limit off-target toxicity.	Advanced/metastatic CCA and other GI cancers harbouring FGFR1–3 gene fusions or rearrangements (predominantly FGFR2 fusions), usually after ≥1 prior systemic therapy, FGFR-TKI–naïve.	FUZE phase II basket trial in FGFR1–3 fusion-positive solid tumours showed lower than anticipated ORR overall, and the study was stopped early for limited activity.	Completed phase I trials and the FUZE phase II basket trial (NCT03834220) in FGFR1–3 fusion-positive solid tumours, including BTCs; current development status uncertain after early termination of FUZE for insufficient efficacy.

Abbreviations: FGFR, fibroblast growth factor receptor; FGFRi, FGFR inhibitor; iCCA, intrahepatic cholangiocarcinoma; CCA, cholangiocarcinoma; ORR, objective response rate; DCR, disease control rate; PFS, progression-free survival; VEGFR, vascular endothelial growth factor receptor; CSF1R, colony-stimulating factor 1 receptor; TKI, tyrosine kinase inhibitor; GI, gastrointestinal; ATP, adenosine triphosphate; IC50, half-maximal inhibitory concentration; 3L, third-line treatment setting.

absorption from intestines. Hence, hyperphosphatemia is seen as an on-target effect, while hypophosphatemia which is also reported with FGFR inhibitors arises as a result of overcorrection with phosphate binders or due to decreased oral intake because of stomatitis. Management of hyperphosphatemia includes measures like dietary modification which involves avoiding items like processed, diary and animal foods. Also, it has been seen that shifting to a plant-based diet is known to reduce phosphate levels. Along with these measures, phosphate lowering agents should be administered when serum levels exceed ≥7 mg/dl. In trials involving pemigatinib, hardly 30% of patients received any form of phosphate-lowering therapy.[63] Available drugs in the market include sevelamer, magnesium hydroxide, calcium carbonate/acetate and lanthanum carbonate. Adherence is key as it has been reported from trials involving chronic kidney patients that only 50% of patients are compliant to phosphate binders.[64] Hence starting off at a lower dose and gradual escalation is the key. As FGFR inhibitors are also known to cause diarrhea, lanthanum and calcium-based therapies should be given preference over sevelamer and magnesium-based therapies in these instances. Any serum phosphate ≥7 mg/dl is grade 3 hyperphosphatemia and warrants dose reduction. Serum phosphate levels are to be monitored weekly. If levels decrease to <5.5mg/dl, rechallenge can be tried. Repeat elevation above 7mg/dl should prompt a switch to an alternate FGFR inhibitor. Repeat values above 10mg/dl are an indication for permanent discontinuation.[65]

Fatigue is another commonly reported adverse event seen with FGFR inhibitors (30–70%).[66] Exact pathogenesis is yet to be well elucidated. Purported mechanisms include drug related mineral and electrolyte imbalance, presence of disease perse or patient-related factors including psychosocial stressors. Every patient experiencing fatigue should undergo a detailed work up including complete blood count, mineral and metabolic panel, reticulocyte count, thyroid functions and iron studies. Patients should be counselled to engage in moderate physical activity, yoga and mental

relaxation programs. Pharmacological interventions like methylphenidate are investigational. Grade 3 fatigue may be an indication for dose reduction.[62]

Incidence of diarrhea is reported anywhere ranging from 15% to 60% as per the major trials involving FGFR inhibitors.[66] The major receptor concerned with diarrhea is FGFR4. Due to its weak FGFR4 inhibitory potential, infigratinib has the least incidence of diarrhea. It is postulated that bile acids stimulate FGF19/FGFR4/ERK1/2 signaling pathway, causing feedback inhibition of bile acid synthesis. Altered bile acid metabolism leads to increase mucosal permeability, peristalsis and water secretion resulting in diarrhea. Management includes optimization of fluid intake, probiotics and liberalizing sugar and salt intake. Other causes of diarrhea including infectious etiologies should be ruled out. In grade 1 diarrhea, supportive medications include loperamide and racecadotril, along with oral rehydration. Maximum dose of loperamide should not exceed 20mg/day. In cases of grade 2 and above, FGFR inhibitor should be withheld, alongside detailed evaluation for electrolyte imbalance. For grade 3 cases, admission to a medical facility with aggressive fluid and electrolyte correction should be carried out. The drug may be restarted when diarrhea settles to grade 1. Permanent discontinuation is warranted for grade 4 events.[66]

Centra serous retinopathy (CSR) and retinal detachment are the 2 unique side ocular adverse events associated with FGFR inhibitors. In trials of urothelial carcinoma treated with erdafitinib, CSR was seen in 21% of patients (3% grade 3).[67] Dry eyes, cataract and corneal epithelial dysmaturation are other rarely reported events. Baseline ophthalmological evaluation is mandatory before initiating FGFR inhibitors. A characteristic feature of CSR is its reversibility upon drug discontinuation. Early identification and timely ophthalmology consultation is the key. In cases with grade ≤ 3 that resolves after 4 weeks, drug may be restarted at a lower dose under close supervision. Recurrent grade ≥ 2 and any grade 4 event calls for permanent discontinuation.

Alopecia is a common TEAE seen in 49% and 34% of patients on pemigatinib or futibatinib respectively. It should be noted that traditional methods like scalp cooling and compression are not recommended for patients on FGFR inhibitors. Prophylactic use of minoxidil may work in some cases. Alopecia is completely reversible upon drug discontinuation. Nail toxicities like paronychia and onycholysis are predominantly grade 1. Hardly 2–3% of patients require dose reduction or interruption because of nail toxicities. For early grade events, general education measures include keeping hands and feet clean, avoiding trauma, irritants and restrictive shoes and use of protective gloves and emollients. For grade 1 events, use of topical povidone iodine or soaking hands/feet in water mixed with vinegar is encouraged. For grade 2/3 events, oral antibiotics and referral to a dermatologist are recommended. Other dermatological adverse events include xerosis and xerostomia, which are usually managed with supportive care alone and do not require drug discontinuation[67] (Table 3).

Table 3 Common Adverse Events of FGFR Inhibitors and Practical Management Considerations

Adverse Event	Incidence (All-Grade/Grade ≥ 3, %)	Mechanism	Typical Onset/ Pattern	Key Management Measures
Hyperphosphataemia	≈60–80/15–20	On-target (renal FGFR inhibition)	Early, often within first 1–2 cycles	Dietary restriction, start phosphate binders around 5–6 mg/dL in asymptomatic patients; dose hold/reduction for higher or symptomatic levels; avoid over-correction to hypophosphataemia
Stomatitis/oral mucositis	≈20–35/<10	Class-related mucosal toxicity	Weeks 1–2	Alcohol-free mouthwashes, topical steroid rinses, meticulous oral hygiene; dose modification if persistent ≥grade 2
Palmar–plantar erythrodysaesthesia	≈20–30/<10	Class-related dermatologic toxicity	Weeks 2–6	Urea-based emollients, high-potency topical steroids, footwear modification; dose reductions or interruptions for ≥grade 2

(*Continued*)

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Table 3 (Continued).

Adverse Event	Incidence (All-Grade/Grade ≥ 3, %)	Mechanism	Typical Onset/ Pattern	Key Management Measures
Nail changes (paronychia, onycholysis)	≈30/rare ≥grade 3	Class-related dermatologic toxicity	Weeks 4–8	Nail care, avoidance of trauma, antiseptic soaks, topical antibiotics ± steroids; dermatology referral for refractory cases
Diarrhoea	≈40–60/<10	Mixed, partly off-target	Any time during treatment	Early use of loperamide, hydration and electrolyte replacement; rule out infection; dose modification if persistent
Ocular AEs (dry eye, CSR, retinal detachment, cataract)	Dry eye ≈20; CSR ≈9; retinal detachment ≈4; cataract ≈6	On-target retinal/ocular effects	Variable; may be insidious	Baseline eye examination for all patients; prompt ophthalmology review for visual symptoms; treatment interruption for ≥grade 3; restart at reduced dose only under specialist supervision

Abbreviations: AE, adverse event; CSR, central serous retinopathy; FGFR, fibroblast growth factor receptor; mg/dL, milligrams per decilitre.

Resistance Mechanisms

Despite recent advances in precision oncology and the successful development of FGFR inhibitors, objective response rates in clinical trials remain in the range of approximately 20–40%, and among responders, the DoR is typically limited to about 6–10 months. These modest and often short-lived responses highlight the critical need to elucidate the mechanisms underlying primary and acquired resistance to FGFR inhibition.[68]

Resistance to targeted therapies is often conceptually divided into two categories. Intrinsic (primary) resistance refers to patients who fail to derive meaningful benefit from treatment; their tumors harbor a substantial proportion of resistant cells at baseline. In contrast, acquired resistance describes patients who initially respond but subsequently experience disease progression. In these cases, tumor cells are thought to be largely sensitive at treatment initiation, with a subset of cells later acquiring—or manifesting—properties that confer resistance. In practice, this distinction is not absolute.[68] Resistant subclones responsible for so-called acquired resistance may already be present at very low frequencies before therapy and only become detectable after prolonged selective pressure. Nevertheless, the classification remains clinically useful. For example, patients with intrinsic resistance typically lack secondary kinase-domain mutations in the therapeutic target, whereas such mutations are frequently observed in patients with acquired resistance, underscoring a categorical biological difference between these two patterns of failure.[69]

All protein kinases share a conserved bilobal architecture, comprising an N-terminal lobe and a C-terminal lobe connected by a hinge region. Activation involves a coordinated conformational change in which the N-lobe pivots toward the C-lobe, the αC-helix moves into an "in" position, and the activation loop adopts an open configuration. These movements generate an ATP- and substrate-binding pocket that supports efficient phosphoryl transfer and downstream signal propagation. Kinase activity is tightly constrained by intramolecular regulatory elements that function as a "molecular brake". In FGFR2, a triad of residues (classically mapped to N550, E566 and K642) forms a hydrogen-bond network that stabilizes the inactive conformation and restrains activation.[70] In parallel, a highly conserved "gatekeeper" residue at the entrance to the hydrophobic back pocket—V565 in FGFR2—controls access of ATP and inhibitors, thereby contributing to both substrate specificity and drug sensitivity. Mutations affecting the molecular brake, gatekeeper, activation loop (eg, K660), or other structural elements can shift the equilibrium toward the active state, alter inhibitor binding, or both. Composite datasets of patients with FGFR2-rearranged CCA who relapse on FGFR tyrosine kinase inhibitors show a striking enrichment of secondary on-target mutations at these key residues within the kinase domain.[70] Although at first glance these alterations appear scattered throughout the domain, many cluster within structural motifs that regulate either conformational dynamics (molecular brake and activation loop) or steric access to the ATP pocket (gatekeeper and surrounding residues).[71] Conceptually, each mutation can be viewed along two

functional axes: (i) its steric effect on inhibitor binding and (ii) its impact on basal kinase activity and signaling output. The clinical prevalence of a given variant likely reflects the net balance of these properties under the selective pressure imposed by a particular drug.

Larger sequencing series of BTCs, including several thousand tumor samples, reinforce this pattern: secondary FGFR2 kinase-domain (KD) mutations are rarely detected before therapy but recur at similar hotspots after exposure to FGFR inhibitors, strongly implicating them as acquired resistance events.[72] However, different FGFR TKIs display distinct in vitro activity profiles against individual mutants, suggesting that each agent may drive a characteristic resistance "fingerprint". Across post-progression tissue/ctDNA analyses in FGFR2-rearranged iCCA, secondary FGFR2 KD mutations—especially at the molecular brake (portion of the domain with a role to turn-down the activation-N550) and gatekeeper (mutations at the entry of the kinase pocket-V565)—are the most frequent mechanism after reversible pan-FGFR TKIs (pemigatinib/infigratinib).[70] Irreversible FGFR1–3 inhibitor futibatinib suppresses many (not all) such KD variants; the spectrum of emergent mutations after futibatinib appears narrower than after reversible TKIs. In the exploratory analysis of co-occurring genomic events, no specific alteration was clearly linked to primary resistance to futibatinib, as response rates remained similar across subgroups. The only exception was CDKN2B alteration, which was associated with a shorter PFS but did not affect objective response, suggesting a predominantly prognostic rather than predictive impact on outcome.[71]

The isoform-selective FGFR2 inhibitor lirafugratinib/RLY-4008 was rationally engineered to retain potency across common on-target resistance variants and shows encouraging clinical activity in FGFRi-naïve and pre-treated patients. Because many published cohorts lack detailed information on prior drug(s), dose intensity and pharmacokinetics, current maps of drug-specific resistance remain incomplete.

An additional layer of complexity is the frequent emergence of polyclonal resistance.[18] In multiple reports, individual patients develop several distinct FGFR2 kinase-domain mutations simultaneously, sometimes including multiple substitutions at the same residue (eg, different N550 variants).[73] Liquid-biopsy with ctDNA serial profiling indicates substantial spatial heterogeneity: multiple concurrent FGFR2 KD mutations (polyclonality) at progression, often missed by single-site biopsies; this supports liquid biopsy for real-time resistance tracking and for sequencing next-line FGFR strategies.[74,75] These observations are most consistent with the parallel evolution of multiple independent resistant clones within the same patient, while a proportion of lesions may escape through non–KD mechanisms such as bypass/parallel-pathway activation. Preclinical/clinical correlative work shows adaptive signaling through EGFR, RAS–MAPK/ERK, PI3K–AKT–mTOR, and SHP2 nodes, enabling escape even without new FGFR2 alterations.[76] Co-inhibition (eg, EGFR + FGFR) restores sensitivity in FGFR2-fusion models and early translational settings. Pharmacokinetic constraints probably contribute to this unusually broad spectrum of resistance variants.[76] Compared with other oncogenic kinase settings (for example EGFR-mutant non–small cell lung cancer), currently approved FGFR inhibitors achieve relatively low free (unbound) plasma concentrations at tolerated doses. In vitro, many resistance mutations confer only modest increases in inhibitory concentration (IC_{50}). Under conditions of limited systemic exposure, even small rightward shifts in IC_{50} may suffice to confer clinically meaningful resistance, thereby permitting the outgrowth of a wide variety of mutants rather than a single dominant alteration. Additionally, EMT/YAP-TAZ programs, ligand rewiring, and FGFR2 fusion heterogeneity may contribute; evidence remains more preclinical[77] (Figure 1).

These considerations highlight several priorities for the field. First, intrinsic (primary) resistance to FGFR inhibition —where no meaningful clinical benefit is achieved despite the presence of an apparently druggable alteration—requires systematic study, as it directly limits response rates. Second, the landscape of acquired resistance must be defined more rigorously through integrated analyses of serial tissue biopsies, ctDNA and, where feasible, rapid autopsy sampling to resolve clonal architecture and evolutionary trajectories. Third, comprehensive functional characterization of recurrent mutations, combined with accurate pharmacokinetic and pharmacodynamic data, is needed to guide the rational design of next-generation FGFR inhibitors capable of suppressing the most clinically relevant resistance variants. Because FGFR-rearranged CCA is a rare disease, no single center can accrue sufficient cases to answer these questions alone. Progress will depend on collaborative efforts, shared datasets and harmonized analytical frameworks. Such an approach will be essential to anticipate resistance pathways prospectively and to design FGFR-targeted therapies that deliver deeper and more durable benefit for patients.

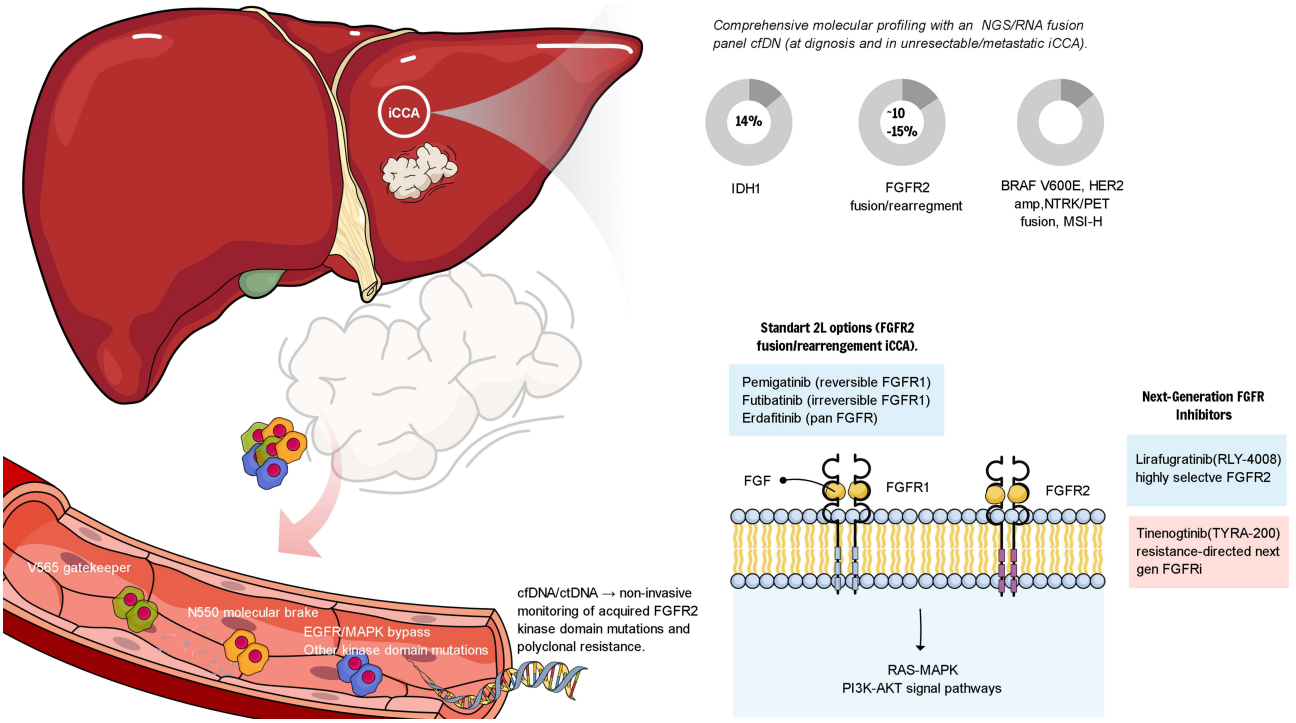

Figure 1 Schematic overview of FGFR2-driven oncogenic signalling in intrahepatic cholangiocarcinoma and the evolving therapeutic landscape of FGFR inhibition, illustrating the FGFR receptor architecture, key downstream pathways (RAS–MAPK, PI3K–AKT–mTOR) and the positioning of approved (pemigatinib, futibatinib, infigratinib, erdafitinib) and next-generation FGFR-targeted agents in relation to typical sites of on-target resistance within the kinase domain.

Combination Strategies & Ongoing Trials

Once results from the current first-line and later-line monotherapy trials of FGFR inhibitors are fully available, a natural next step will be the systematic evaluation of biologically grounded combination strategies.[8,78] Multiple preclinical studies in genetically engineered mouse models and patient-derived FGFR2 fusion–positive iCCA systems have demonstrated that signalling through the *RAS–MEK–ERK* cascade is a critical downstream effector of FGFR2 fusions.[78,79] Tumour organoids and 2D cell lines derived from FGFR2 fusion–driven lesions show sustained dependence on this axis, regardless of the specific fusion partner or the presence of gatekeeper mutations such as V565F.[80] In these models, concurrent inhibition of FGFR2 and MEK1/2 consistently achieves deeper and more durable anti-tumour effects than FGFR blockade alone, in both in vitro and in vivo settings, supporting the clinical investigation of dual FGFR–MEK targeting in FGFR2 fusion–positive iCCA.[79,80]

Complementary murine work in TP53-deficient backgrounds has further recapitulated FGFR2 fusion–driven cholangiocarcinogenesis and highlighted biological heterogeneity among different fusion constructs, while converging on FF–ERK signalling as a shared pathogenic axis.[79] Parallel translational studies using pharmacologic inhibitors and RNA interference have shown that KRAS-mediated MAPK activation can drive primary resistance to FGFR inhibition in FGFR2 fusion–positive models. Transcriptomic analyses suggest that a subset of human FGFR2 fusion–positive tumours exhibits expression patterns akin to KRAS-mutant iCCA, and in such contexts, combined targeting of FGFR and the MAPK pathway can overcome intrinsic resistance and restore sensitivity to FGFR blockade. More broadly, FGFR2-driven iCCA models indicate that rebound activation of MEK/ERK signalling can maintain proliferation and limit apoptosis after FGFR inhibition, while compensatory upregulation of EGFR signalling contributes to both de novo and acquired resistance; in experimental systems, dual FGFR–EGFR inhibition can re-establish tumour control.[76] Although these approaches have not yet been rigorously evaluated in clinical trials, the converging preclinical data provide a strong mechanistic rationale and define a clear priority for future translational and early-phase clinical research.[76]

Several phase III trials are now exploring whether FGFR inhibition can be moved into the first-line setting for FGFR2-rearranged CCA. FIGHT-302 (NCT03656536) is an open-label, randomized, active-controlled, multicenter,

global phase III study designed to compare the efficacy and safety of pemigatinib versus standard gemcitabine–cisplatin as initial systemic therapy in patients with advanced CCA harbouring FGFR2 rearrangements.[39] In parallel, the FOENIX-CCA3 trial (NCT04093362) is evaluating futibatinib against gemcitabine–cisplatin in a similar first-line population, reflecting the growing interest in directly challenging chemotherapy backbones with FGFR-targeted approaches in biomarker-selected disease. This trial is also randomising patients with previously treated, FGFR2-rearranged BTC to futibatinib 16 mg or 20 mg once daily to determine whether a reduced dose can preserve antitumour activity while improving the toxicity profile.[81] Beyond phase III trials that directly compare FGFR TKIs with chemotherapy, several early-phase studies are testing combination strategies. One example is an ongoing phase I trial (NCT04088188) evaluating gemcitabine–cisplatin together with pemigatinib in patients with unresectable or metastatic FGFR2-altered CCA, or with ivosidenib in those with IDH1-mutated disease. In this study, the primary objectives are to define the safety profile and recommended phase II doses of the combinations, based on the rationale that pairing standard cytotoxic doublet chemotherapy—which induces tumour cell death through DNA damage and inhibition of cell division—with targeted inhibition of oncogenic signalling (via FGFR2 or mutant IDH1 blockade) may enhance antitumour activity compared with gemcitabine–cisplatin alone.[82]

Building on experience from other tumour types, there is growing preclinical evidence that FGFR inhibition may favourably remodel the tumour immune microenvironment and thereby synergise with immune checkpoint blockade. iCCA with FGFR2 fusions tends to be "cold"; nonetheless, early-phase efforts are ongoing to test combination strategies with immunotherapy. In FGFR1-expressing head and neck squamous cell carcinoma models, FGFR TKIs enhanced the activity of PD-1/PD-L1–directed immunotherapy, upregulated MHC class I/II expression, and enabled FGFR1-specific $CD4^+$ T cells to exert more potent cytotoxic effects.[83] Similarly, in FGFR2-driven lung cancer and renal cell carcinoma models, combining FGFR-targeted agents (erdafitinib or lenvatinib) with anti-PD-1 antibodies led to deeper tumour regressions and improved survival, accompanied by increased effector T-cell infiltration, reductions in regulatory T cells and tumour-associated macrophages, and restoration of IFN-γ signalling (Table 4).[84,85] Although these data derive from non-biliary settings, they suggest that FGFR blockade can both kill tumour cells and alleviate FGFR-mediated immune suppression, providing a strong mechanistic rationale to test FGFR–IO combinations in FGFR2-altered CCA within carefully designed early-phase trials. A prospective, multicentre, single-arm phase II trial (NCT05913661) is currently assessing pemigatinib in combination with the anti–PD-1 immune checkpoint inhibitor sintilimab as first-line therapy for patients with advanced, unresectable or metastatic iCCA harbouring FGFR fusions. The primary aim of this study is to characterise the efficacy and safety of this chemo-free targeted–immunotherapy regimen in a biomarker-selected population.[86] A conceptually similar approach is being evaluated in a multicentre, open-label, single-arm phase II study (NCT05174650), which is testing the combination of the FGFR inhibitor derazantinib with the anti–PD-L1 antibody atezolizumab in patients with advanced iCCA harbouring FGFR2 fusions or rearrangements who have received prior therapy.[87]

Knowledge Gaps & Future Perspectives

In the era of precision oncology, it is increasingly clear that patients with the same nominal diagnosis may differ substantially at the molecular and clinical levels. In response to the limitations of traditional "one-size-fits-all" trials, a range of biomarker-driven master protocol designs—basket, umbrella and platform trials—has emerged to enable more tailored therapy allocation.[71] These designs have already supported several regulatory approvals and illustrate the potential of patient-centred trial frameworks; however, most work to date has focused on statistical and operational methodology, with relatively less emphasis on the underlying biological assumptions that should guide their use in specific tumour types.[88] Beyond FGFR2, BTC as a whole is a rare and molecularly heterogeneous disease in which many potentially actionable alterations occur at very low frequencies. This biology poses major challenges for conventional phase III trials and has prompted interest in agnostic basket designs similar to those that led to the approval of NTRK inhibitors. However, when rare BTC subsets are pooled with more common and biologically homogeneous malignancies, there is a risk that pan-tumour approvals will be driven by strong efficacy signals in other cancers, while the benefit in BTC remains modest or poorly characterised. Indeed, existing data on BTC within tissue-agnostic programmes are sparse, and it is not yet clear whether subsequent evidence will confirm meaningful benefit in this setting. An alternative

Table 4 Key FGFR-Based Combination Strategies in Intrahepatic Cholangiocarcinoma (iCCA)

Agent(s)	Mechanistic Rationale	Phase/ Design	Population	Primary Endpoint	Status/Early Readouts	NCT ID
Gemcitabine + cisplatin + pemigatinib (± ivosidenib)[82]	Standard cisplatin–gemcitabine backbone combined with targeted inhibition of FGFR2 signalling (pemigatinib) or mutant IDH1 (ivosidenib) to enhance tumour cell kill and delay resistance compared with chemotherapy alone.	Phase I, open-label, multi-arm, dose-finding study	Unresectable or metastatic CCA carcinoma with FGFR2 alterations (pemigatinib arm) or IDH1 mutation (ivosidenib arm)	Safety, dose-limiting toxicities (DLTs), recommended phase II dose (RP2D); exploratory ORR, PFS, OS	Early-phase feasibility study designed to establish safety and dosing of the doublet combinations; mature efficacy data are limited or pending.	NCT04088188
Pemigatinib + sintilimab (PD-1 inhibitor)[86]	FGFR1–3 blockade in FGFR2-rearranged iCCA combined with PD-1 inhibition to augment antitumour T-cell responses and potentially convert an "immune-cold" phenotype into a more inflamed microenvironment.	Phase II, prospective, single-arm, multicentre study	Advanced, unresectable or metastatic iCCA with FGFR fusions/ rearrangements	ORR by RECIST v1.1	Ongoing; chemo-free targeted–immunotherapy regimen under evaluation as first-line treatment in a biomarker-selected population.	NCT05913661
Derazantinib + atezolizumab (anti–PD-L1 antibody)[87]	Multi-target FGFR1/2/3 inhibition (with additional CSF1R/ VEGFR activity) combined with PD-L1 blockade to couple direct FGFR-addicted tumour killing with relief of FGFR-driven immune suppression.	Phase II, open-label, single-arm, multicentre study	Advanced, non-resectable iCCA with FGFR2 fusions/ rearrangements, previously treated	ORR by RECIST v1.1	Active trial designed to assess efficacy and safety of FGFR–IO combination in pretreated FGFR2-positive iCCA; formal results are awaited.	NCT05174650

Abbreviations: iCCA, intrahepatic cholangiocarcinoma; FGFR, fibroblast growth factor receptor; IDH1, isocitrate dehydrogenase 1; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; CSF1R, colony-stimulating factor 1 receptor; VEGFR, vascular endothelial growth factor receptor; DLT, dose-limiting toxicity; RP2D, recommended phase II dose; ORR, objective response rate; PFS, progression-free survival; OS, overall survival; RECIST, Response Evaluation Criteria in Solid Tumours.

strategy is to develop trials explicitly designed around personalised, mutation-matched approaches for BTC, in which each patient undergoes comprehensive genomic profiling and is assigned to a rationally selected targeted agent or combination. Such adaptive or platform-style precision trials may offer a more biologically coherent framework to evaluate targeted therapies in this rare, genomically diverse disease. Therefore, there is a need adaptive designs incorporating molecular response in ctDNA, mutation-level resistance endotypes, and basket/platform structures to accelerate learning across FGFR agents.[71,88]

Current selection of patients with iCCA for FGFR inhibitors is largely based on the presence of FGFR2 genomic alterations in tissue or ctDNA, without parallel assessment of pathway activation at the protein or signalling level. A recent multi-omic analysis of treatment-naïve iCCA demonstrated gain-of-function FGFR2 alterations in a subset of tumours, but also identified a small group of patients with wild-type FGFR2 who nonetheless exhibited clear evidence of FGFR2 pathway activation (FGF10 expression and phosphorylated FGFR2/FRS2α). Conversely, many apparently

FGFR2–wild-type cases showed no activation of the pathway. These findings suggest that a purely genotype-based approach may miss a biologically relevant fraction of patients with functional FGFR2 signalling, raising the hypothesis that pathway activity, rather than genotype alone, could be used to broaden eligibility for FGFR-targeted therapies—an idea that warrants prospective clinical validation.[89]

These advances have important practical implications. Comprehensive molecular profiling of CCA is now considered essential, ideally using assays capable of detecting FGFR2 fusions and rearrangements—preferably RNA-based platforms, given the extensive diversity of potential fusion partners, which smaller DNA-only panels may fail to capture.[90] Liquid biopsy approaches are also gaining prominence: in one study, FGFR fusions were detected in 87% of patients using ctDNA, highlighting the potential of plasma-based testing to complement or, in some settings, substitute for tissue analysis. At the same time, the rapid expansion of FGFR-directed options has exposed substantial inequities in access to both molecular diagnostics and drugs. Although multiple agents have received regulatory approval over the past few years, many centres—particularly outside large academic hubs—struggle to deliver timely profiling and to secure reimbursement for these high-cost therapies.[12,91,92]

Therapeutic innovation in FGFR2-altered iCCA is likely to extend beyond first-generation oral TKIs. Next-generation, FGFR2-isoform–selective and covalent inhibitors with distinct resistance spectra are entering clinical development, and their optimal place in post-TKI sequencing—either as salvage for specific kinase-domain mutations or as earlier-line options—remains an open but highly relevant question.[77] In parallel, non-TKI modalities targeting FGFR are being explored: bemarituzumab, a first-in-class monoclonal antibody directed against FGFR2b, has shown clinically meaningful benefit in FGFR2b-overexpressing gastric and gastro-oesophageal cancers[93] and is now being evaluated in phase III trials, raising the possibility that similar antibody-based strategies could eventually be adapted to FGFR2-driven BTCs.[94] By contrast, the FGFR2-targeted antibody–drug conjugate (ADC) aprutumab ixadotin proved poorly tolerated in a first-in-human study, with an MTD below the predicted therapeutic range and no objective responses, underscoring the need for careful payload, linker and schedule optimisation if ADC approaches are to succeed in this space.[95] Collectively, these developments suggest that future FGFR-directed therapy in iCCA may evolve into a multimodal landscape—spanning highly selective TKIs, antibodies and potentially refined ADCs—provided that subsequent trials can demonstrate acceptable safety and clear incremental benefit over existing small-molecule inhibitors.

Looking ahead, several questions remain. Randomised data comparing FGFR inhibitors with standard chemotherapy in the first-line setting are scarce, and front-line FGFR-targeted strategies have proved difficult to study because of the rarity of the eligible population and competition among trials. Rational combination approaches—for example, pairing FGFR inhibitors with immune checkpoint blockade or cytotoxic chemotherapy—are conceptually appealing but often lack robust translational evidence to justify specific regimens or sequences.[96] A better understanding of the molecular basis of primary and acquired resistance, including the spectrum of FGFR2 KD mutations and co-occurring genomic events, will be crucial to designing logical sequencing strategies and biomarker-driven combinations. Ultimately, close integration of laboratory work with clinical trial design, and stronger international collaboration, will be needed to optimise the use of FGFR-directed therapies across the disease course.

Conclusion

Overall, the development of FGFR inhibitors has marked a major advance in the management of cholangiocarcinoma, but substantial challenges remain. Most pivotal datasets in FGFR2-rearranged CCA come from non-randomised studies with limited sample sizes, constraining definitive cross-study comparisons and robust subgroup conclusions. Larger prospective registries and fit-for-purpose confirmatory strategies will be essential to refine patient selection and clarify real-world effectiveness. A deeper understanding of acquired resistance—particularly the emergence of polyclonal secondary mutations within the FGFR2 kinase domain—is urgently needed to inform rational combination strategies and the optimal use of next-generation, FGFR2-selective agents such as lirafugratinib. In parallel, improved approaches to chronic toxicity management (notably hyperphosphataemia) and dedicated studies in patients with non-fusion FGFR alterations will be essential to close current knowledge gaps and to fully realise the potential of FGFR-directed precision therapy in this rare, molecularly defined disease.

Abbreviations

BTC, Biliary tract cancer; CCA, Cholangiocarcinoma; iCCA, Intrahepatic cholangiocarcinoma; eCCA, Extrahepatic cholangiocarcinoma; HCC, Hepatocellular carcinoma; CUP, Cancer of unknown primary; FGFR, Fibroblast growth factor receptor; FGFR1–4, Fibroblast growth factor receptor 1–4; FGFR2, Fibroblast growth factor receptor 2; FGFRi, Fibroblast growth factor receptor inhibitor; EGFR, Epidermal growth factor receptor; IDH, Isocitrate dehydrogenase; IDH1/IDH2, Isocitrate dehydrogenase 1/2; BRAF, B-Raf proto-oncogene, serine/threonine kinase; NTRK, Neurotrophic tyrosine receptor kinase; RET, Rearranged during transfection; VEGFR, Vascular endothelial growth factor receptor; CSF1R, Colony-stimulating factor 1 receptor; PD-1, Programmed cell death protein 1; PD-L1, Programmed death-ligand 1; KD, kinase-domain; MAPK, Mitogen-activated protein kinase; ERK, Extracellular signal-regulated kinase; PI3K, Phosphatidylinositol 3-kinase; AKT, Protein kinase B; mTOR, Mechanistic target of rapamycin; EMT, Epithelial–mesenchymal transition; YAP, Yes-associated protein; TAZ, Transcriptional co-activator with PDZ-binding motif; NGS, Next-generation sequencing; cfDNA, Cell-free DNA; ctDNA, Circulating tumour DNA; MSI, Microsatellite instability; MSI-H, Microsatellite instability-high; IHC, Immunohistochemistry; MMR, Mismatch repair; CSR, Central serous retinopathy; TKI, Tyrosine kinase inhibitor; ADC, Antibody–drug conjugate; IO, Immuno-oncology/immunotherapy; ORR, Objective response rate; DCR, Disease control rate; PFS, Progression-free survival; OS, Overall survival; DLT, Dose-limiting toxicity; RP2D, Recommended phase II dose; AE, Adverse event; MTD, Maximum tolerated dose; PD, Progressive disease; 1L/2L/3L/2L+, First-line/second-line/third-line/second line or later.

Disclosure

The authors declare that they have no competing interests related to this work.

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