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Targeting Fibroblast Growth Factor Receptor Pathway: Precision Medicine for Biliary Cancer and Beyond

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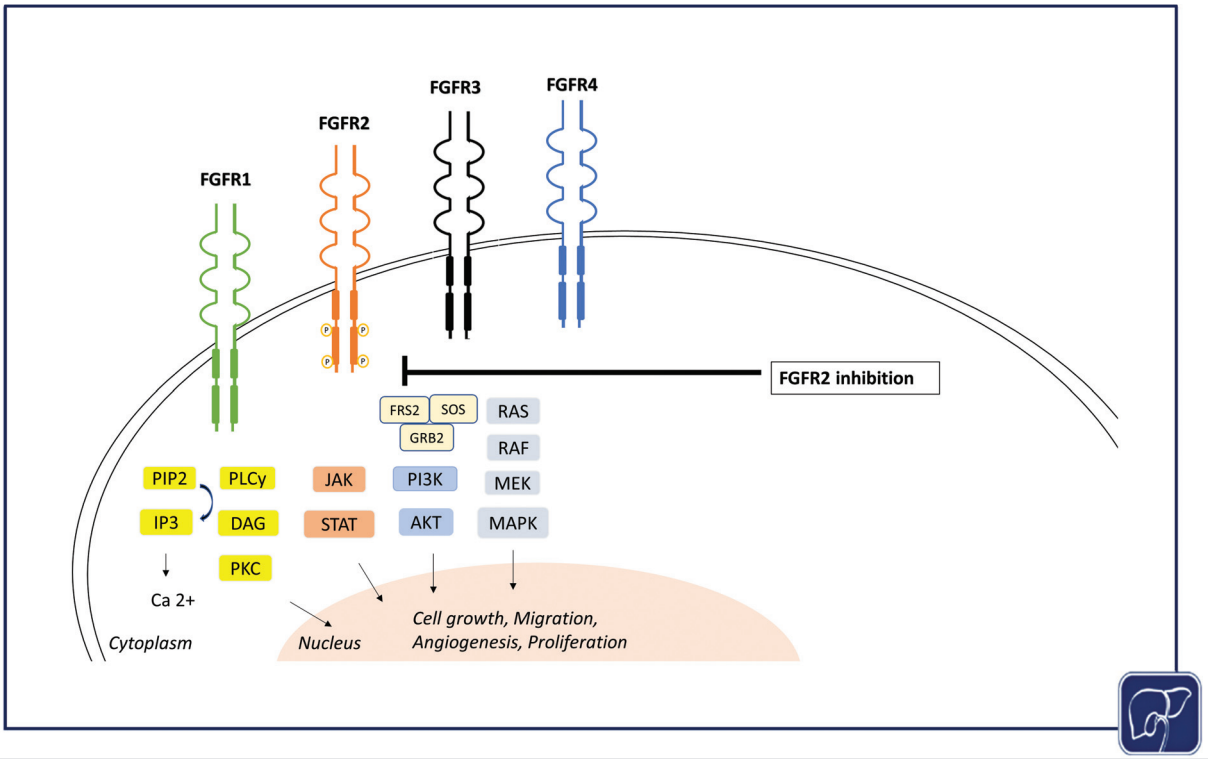
Graphical Abstract



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Abstract

Fibroblast growth factor receptor 2 (FGFR2) inhibitors are now being included in the treatment guidelines of multiple countries for patients with advanced cholangiocarcinoma (CCA). Activation of the FGF–FGFR pathway is related to proliferation and tumor progression. Targeting the FGF–FGFR pathway is effective and can yield durable responses in patients with CCA harboring FGFR2 fusions or rearrangements. In this review article, we address molecules and clinical trials evaluating FGFR inhibitors in advanced CCA. We will further discuss identified mechanisms of resistance and the strategies to overcome it. The incorporation of next-generation sequencing in advanced CCA and circulating tumor DNA on disease progression will unveil mechanisms of resistance and improve the development of future clinical trials and more selective drugs and combinations.

Keywords

- cholangiocarcinoma
- FGFR2
- biliary cancers
- pemigatinib
- infigratinib
- futibatinib

Biliary tract cancers (BTCs) are a set of malignances that arise from the bile ducts or the gallbladder.[1] In 2020, globally it was estimated that there were approximately 906,000 new cases and 830,000 deaths from primary liver cancers, estimating that about approximately 15% of these were cholangiocarcinoma (CCA).[2]

More than half of the patients diagnosed with CCA will have the diagnosis at advanced stages and the primary treatment of advanced CCA in these instances is systemic therapy.[3] Recently, the new standard of care for first-line treatment for these patients is chemotherapy associated with immunotherapy. The TOPAZ-1 trial is a randomized phase III trial with the primary objective to evaluate the incorporation of the anti-programmed death-ligand 1 (PD-L1) antibody durvalumab in the first-line chemotherapy regimen for advanced BTC.[4] A total of 685 patients were randomly assigned to durvalumab ($n = 341$) or placebo ($n = 344$) with chemotherapy. The trial met the endpoints, with improvement in objective response rate (ORR), progression-free survival (PFS), and overall survival (OS). The estimated 2-year OS was 24.9% for durvalumab and 10.4% for placebo; hazard ratio for OS was 0.80 (95% confidence interval [CI]; 0.66–0.97; $p = 0.021$).[4] However, median OS with chemotherapy plus durvalumab was still only 12.8 months.[4]

Another paradigm shift in the treatment of advanced BTC is the incorporation of precision medicine. Fibroblast growth factor receptor (FGFR) genomic alterations can be identified in roughly 10 to 15% of CCA, primarily of the intrahepatic type.[1] Aberrant FGFR stimulation activates intracellular pathways related to tumor progression, angiogenesis, and metastasis.[5] Lately multiple drugs have been evaluated in advanced CCA with FGFR2 genomic alterations. Three FGFR inhibitors are already Food and Drug Administration (FDA) approved for the treatment of patients with advanced CCA with FGFR2 fusions or rearrangements after standard first-line therapy (pemigatinib, infigratinib, and futibatinib). Treatment with FGFR inhibitors has also been incorporated in multiple society guidelines including American Society of Clinical Oncology (ASCO) and European Society of Medical Oncology (ESMO).[6] In this review article, we will address the most important molecules to date that target FGFR genomic alterations in biliary cancers; furthermore, we will address the perspectives in the field of FGFR inhibition in advanced CCA.

FGF/FGFR Signaling Pathway

The fibroblast growth factor (FGF) pathway consists of 22 functionally distinct FGF ligands and four FGF transmembrane receptors (FGFR1–4).[7] Although FGF receptors share general downstream signaling pathways, a structural diversity is observed across all isoforms of FGFRs attributed to the alternative splicing of endogenous mRNA.[7] The FGF glycoproteins bind to the FGFR leading to receptor dimerization and transphosphorylation of tyrosine kinase domains.[7] After activation, a downstream signal via intracellular receptor substrates, FGFR substrate 2 (FRS2) and phospholipase Cg (PLC-g), activates RAS/mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K)/AKT signaling pathways. It is also noted that other pathways can be activated, including STAT-dependent signaling pathways.[8] In normal cells, FGFR signaling pathway is an evolutionary-conserved signaling cascade that regulates several basic biologic processes, including tissue regeneration and development, as well angiogenesis.[7]

A constitutive activation of FGFR genes can occur due to multiple genomic alterations, including chromosomal translocations, gene fusions, activating mutations, and gene amplifications.[9] The aberrant activation of the FGFR pathway leads to proliferative effect and tumoral development. Initially, pan-TKI inhibitors with effect on FGFR were evaluated in patients with solid tumors harboring FGF alterations. As an example, in one of the first reports of FGFR fusions in CCA, pazopanib has shown antitumoral effect in a patient with a FGFR2–TACC3 fusion.[10] Lately, multiple specific FGFR inhibitors are being developed and evaluated in prospective cohorts of CCA, and randomized phase III trials against standard of care are also recruiting patients. Summarized data of FGFR inhibitors, efficacy, and safety will be addressed in this review.

Infigratinib

Infigratinib, formerly BJG398, is a pan-FGFR2 inhibitor with activity in FGFR-altered CCA. Data in 132 patients from the escalation and expansion arms from the phase I study were reported.[11] In the study, multiple tumors were treated with infigratinib in dose-escalation protocols. Antitumor activity was seen in patients with FGFR1-amplified lung cancer and

FGFR3-mutant urothelial cancer. The maximum tolerated dose (MTD) and recommended phase II dose (RP2D) was 125 mg daily, determined by dose-limiting toxicities (DLTs) in four patients. Common adverse events (AEs) included hyperphosphatemia (82.5%), constipation (50.9%), decreased appetite (45.6%), and stomatitis (45.6%). Later, in the phase II trial, the drug was evaluated in patients with CCA and FGFR genetic alterations.[12] In the first assessment of the phase II prospective cohort, a total of 61 patients received infigratinib 125 mg once daily for 21 days followed by 7 days off in 28-day cycles. All patients were previously treated with chemotherapy, with more than 65% treated with at least two regimens previously.[12] Most patients had FGFR2 genetic alterations, including 48 with fusions, 8 with mutations, and 3 with amplifications.[12] Also, one patient had a FGFR1 amplification and four FGFR3 amplifications.[12] More than half of the patients treated required a dose reduction, mostly because of AE. The overall response rate, the primary efficacy end point of the trial, was 14.8% (95% CI: 7.0–26.2%).[12] The overall disease control rate (DCR) was 75.4%, with a median PFS of 5.8 months (95% CI: 4.3–7.6 months). Treatment-emergent hyperphosphatemia was the AE most observed, in around 72% of the patients. Other all-grade frequent AEs included fatigue (36.1%), stomatitis (29.5%), alopecia (26.2%), dry eye (21.3%), blurred vision (14.8%), and onychomadesis (18%). Around 40% of the patients experienced a grade 3 or 4 AE suspected to be related to treatment (►**Table 1**).[12] Results of the phase II study were presented in a larger cohort of patients with FGFR2 fusions or rearrangements.[13] In the cohort of 108 patients, 81% had fusions and 19% had rearrangements.[13] Per blinded independent central review, the ORR was 23.1% (95% CI: 15.6–32.2%), the median PFS was 7.3 months (95% CI: 5.6–7.6 months), and the median OS was 12.2 months (95% CI: 10.7–14.9 months).[12,13] Comparing the results, we can clearly see that FGFR2 fusions or rearrangements are more actionable than mutations and amplifications. In patients with one or less previous treatment, the ORR was 34% (95% CI: 21.2–48.8%).[13]

Pemigatinib

Analysis from preclinical studies shows that pemigatinib, formerly INCB054828, is a potent tyrosine kinase FGFR1–3 inhibitor, with less effect on FGFR4.[14] The drug was evaluated initially in the pan-tumor trial FIGHT-101, in 128 patients with advanced malignances harboring FGFR/FGF alterations.[15] Patients were treated with pemigatinib monotherapy or in combination with other therapies, with a phase I study with a dose-escalation part. The RP2D identified was 13.5 mg once daily. Overall, the drug was well tolerated. No DLTs were identified.[15] The most common AE was hyperphosphatemia, observed in 73.4% of the patients treated. Hyperphosphatemia was successfully managed with diet, phosphate binders, and dose modifications.[15] Grade 3 or 4 toxicities included fatigue, hyperphosphatemia, hypophosphatemia, stomatitis, anemia, and nail toxicities. Of 12 patients with partial response, 5 were CCA.[15] Based on these results, the phase II study, FIGHT 202, evaluated the efficacy of pemigatinib 13.5 mg in a cohort of previously treated CCA patients with or without FGFR alterations.[16] All patients received a starting dose of 13.5 mg oral pemigatinib once daily (21-day cycle; 2 weeks on, 1 week off). Of 146 patients, 107 patients had a CCA with FGFR2 fusions or rearrangements, 20 with other FGF/FGFR alterations, 18 with no FGF/ FGFR alterations, and 1 with an undetermined FGF/FGFR alteration.[16] In the cohort of patients with fusions or rearrangements the ORR was 35.5% (95% CI: 26.5–45.4%). Eighty-eight (82% [95% CI: 74–89%]) of the 107 patients with fusions achieved disease control.[16] The median PFS was 6.9 months (95% CI: 6.2–9.6), and the median OS was 21.1 months (95% CI: 14.8 to not estimable). No patients with other FGF/FGFR alterations or no FGF/FGFR alterations achieved a response.[16] The median PFS was 2.1 months (95% CI: 1.2–4.9) in patients with other FGF/FGFR alterations and the median PFS was 1.7 months (95% CI: 1.3–1.8) in patients with no FGF/FGFR alterations.[16] The median OS was 6.7 months (95% CI: 2.1–10.6) in patients with other FGF/FGFR alterations and the median OS was 4 months (95% CI: 2.3–6.5) in patients with no FGF/FGFR alterations.[16] Like the findings of infigratinib, better responses and efficacy are primarily seen in CCA harboring fusions or rearrangements.[16] The grade 3 or 4 AE rates included hypophosphatemia (7%), stomatitis (5%), palmar–plantar erythrodysesthesia (4%), and arthralgia (4%)[16] (►**Table 1**).

Futibatinib

Futibatinib, formerly TAS 120, is an irreversible FGFR 1–4 inhibitor.[17] In a phase I trial, futibatinib was evaluated in multiple tumors following a 3 + 3 dose-escalation study design. Of a total of 86 patients treated, 71 patients (83%) had tumors harboring FGF/FGFR aberrations.[17] In the 24-mg QD cohort, three of nine patients experienced DLTs, including an increase in alanine transaminase (ALT), aspartate transaminase (AST), and blood bilirubin. The RP2D was established at 20 mg QD. In this study, partial responses were observed in five patients (three with FGFR2-fused CCA).[17] The most common grade 3 or 4 AE were hyperphosphatemia, ALT increased, AST increased, nausea, vomiting, anemia, and hyponatremia.[17] In the phase II FOENIX-CCA2 trial, a total of 103 patients with CCA harboring FGFR2 fusion or rearrangements were treated with futibatinib 20 mg QD until disease progression or unacceptable toxicity.[18] From the total, 78% of patients had FGFR2 fusions, 22% had rearrangements, and 53% had two or more previous systemic treatments for advanced disease.[18] One patient exhibited a complete response; partial responses were observed in 40% (42) of the patients. The ORR was 41.7% (95% CI: 32.1–51.9%) and DCR was 82.5% (95% CI: 73.8–89.3%), with a median duration of response of 9.5 months (95% CI: 7.6–10.4).[18] The median PFS of the entire cohort was 8.9 months (95% CI: 6.7–11.0) and the median OS was 20 months (95% CI: 16.4–24.6). More than 70% of the patients were alive at 1 year.[17] Most common grade 3 or 4 AE included hyperphosphatemia (31%), increased ALT and AST (13%), palmar-plantar erythrodysesthesia (6%), and nail toxicities (2%).[18]

Table 1 FGFR inhibitors being evaluated in biliary cancer patients

FGFR inhibitor	Previous lines of treatment	No.	Dose	FGFR-GA	ORR% (95% CI)	DCR% (95% CI)	mPFS (95% CI)	mOS (95% CI)	G3–4% AE[a]
Infigratinib[6,7]	≤ 1	50	125 mg PO QD 21 d followed by 7 d off in 28-d cycles	FGFR2 fusions or rearrangements	34% (21.2–48.8)	88% (75.7–95.5)	7.3 (5.6–9.3)	12.2 (10.7–14.9)	↙ Hyperphosphatemia 16.4% ↙ Stomatitis 6.6% ↙ Palmar-plantar erythrodysesthesia 4.9% ↙ Hypophosphatemia 4.9%
	≥ 2	58			13.8% (6.1–25.4)	81% (68.6–90.1)	7.4 (5.6–7.7)		
Pemigatinib[11]	≥ 1	107	13.5 mg PO QD 14 d followed by 7 d off therapy in 21-d cycles	FGFR2 fusions or rearrangements	35.5% (26.5–45.4)	82% (74–89)	6.9 (6.2–9.6)	21.1 (14.8 to not estimable)	↙ Hypophosphatemia 7% ↙ Stomatitis 5% ↙ Palmar-plantar erythrodysesthesia 4% ↙ Arthralgia 4%
Futibatinib[17]	≥ 1	103	20 mg PO QD	FGFR2 fusions or rearrangements	41.7% (32.1–51.9)	82.5% (73.8–89.3)	8.9 (6.7–11.0)	20.0 (16.4–24.6)	↙ Hyperphosphatemia 16.4% ↙ Stomatitis 6.6% ↙ Palmar-plantar erythrodysesthesia 4.9% ↙ Hypophosphatemia 4.9%
Derazantinib[23]	≥ 1	103	300 mg PO QD	FGFR2 fusions or rearrangements	21.4% (13.9–30.5)	75.7% (66.3–83.6)	8.0 (5.5–8.3)	17.2 (12.5–22.4)	↙ Transaminase elevations 12% ↙ Asthenia/fatigue 5% ↙ Hyperphosphatemia 3% ↙ Nausea 1%
		40		FGFR2 mutations or amplifications	6.5% (0.8–21.4)	58.1% (39.1–75.5)	8.3 (1.9–16.7)	15.9 (8.4-NR)	
Erdafitinib[26]	≥ 1	31	9 mg PO QD	FGFR alterations	41.9% (NR)	90.3% (NR)	NR	NR	↙ Stomatitis 9% ↙ Palmar-plantar erythrodysesthesia 6.2% ↙ Hyperphosphatemia 5.6% ↙ Diarrhea 4.5%
RLY-4008[29]	≥ 1	38	20–100 mg different schedules	FGFR2 fusions or rearrangements	63.2% (46–78.2)	94.7% (82.3–99.4)	NR	NR	↙ Stomatitis 8% ↙ Palmar-plantar erythrodysesthesia 15% ↙ Nail toxicities 2%
		17	70 mg PO QD		88.2% (63.6–98.5)	100% (80.5–100)			

Abbreviations: DCR, disease control rate; FDA, Food and Drug administration; FGFR, fibroblast growth factor receptor; G3–4 AE, grades 3 or 4 adverse events rate; GA, genomic alteration; mOS, median overall survival in months; mPFS, median progression-free survival in months; No., number of patients; NR, not reported; ORR, objective response rate.
[a]Most common grade 3 or 4 adverse events.

Derazantinib

Derazantinib, formerly ARQ 087, is potent FGFR inhibitor with multikinase activity.[19] In the phase I study, 80 patients with multiple tumors were treated in a dose-escalation and expansion cohorts. The most common AE were fatigue (49%), nausea (46%), AST increase (30%), and diarrhea (23%). The RP2D was 300 mg QD There were three confirmed partial responses (two CCA with FGFR2 fusions and one urothelial cancer with FGFR2 and FGF19 amplification).[20] The multicenter phase I/II trial presented data from patients with advanced CCA and FGFR2 fusions.[21] A total of 29 patients were treated with derazantinib 300 mg QD. Twenty-seven had progressed on at least one systemic treatment, two were treatment naive.[21] The ORR was 20.7%, with six partial responses with a median duration of response of 4.6 months (95% CI: 2.3–8.9). The DCR was 82.8%. At the data cutoff, the median PFS was 5.7 months (95% CI: 4.04–9.2).[21] Interestingly, a pooled analysis of patients treated in early clinical trials and access programs suggested some activity of derazantinib in patients with CCA harboring FGFR2 mutations or amplifications.[22] Although it is a small sample size of 20 patients with FGFR2 short variants, truncations, deletions, and amplifications, a median PFS of 8.1 months (95% CI: 4.6–14.8) and a duration of treatment of 8.2 months (95% CI: 5.4–11.1) was reached.[22] Finally, the phase II FIDES-01 study evaluated derazantinib in 147 patients with previously treated CCA harboring FGFR fusions, mutations, or amplifications.[23] In the 103 patients with FGFR2 fusions, the ORR was 21.4% (95% CI: 13.9–30.5%).[23] The DCR in this group of patients was 75.7% (95% CI: 66.3–83.6%). Median PFS and OS were 8.0 months (95% CI: 5.5–8.3) and 17.2 months (95% CI: 12.5–22.4) in patients with FGFR2 fusions.[23] In the 44 patients with FGFR2 mutations or amplifications, the ORR was 6.5% (95% CI: 0.8–21.4%). The DCR in this group of patients was 58.1% (95% CI: 39.1–75.5%).[23] Median PFS and OS were 8.3 months (95% CI: 1.9–16.7) and 15.9 months (95% CI: 8.4 to not reached) in patients with FGFR2 mutations or amplifications.[23] Most common grade 3 or 4 AE included hyperphosphatemia (3%), asthenia/fatigue (5%), and transaminase elevations (12%).[23]

Erdafitinib

Erdafitinib is a potent FGFR1–4 tyrosine kinase competitive inhibitor.[24] In the dose-finding phase I study, a total of 187 patients with multiple types of solid tumors were treated with erdafitinib, and two dosing schedules of RP2D were evaluated: 9 mg daily and 10 mg intermittent dosing. In this study, 11 patients with CCA were treated, 8 of them with fusions and the rest with mutations and amplifications.[24] Three CCA patients had a partial response. The drug was tolerable, anemia was the most frequently reported grade 3 AE (17.9%), followed by stomatitis (6%), general physical health deterioration (6%), asthenia (5%), AST increased (5%), and hyponatremia (6%).[24] Recently, results from the phase II multicenter study LUC2001 evaluating erdafitinib in Asian patients with CCA and FGFR alterations were presented.[25] Of 34 patients, 8 had FGFR2 fusions. In the 10 patients with FGFR2 alterations (including mutations), there were 6 cases with confirmed PR (ORR: 60%) with a DCR of 100%.[25] The median PFS of this group was 12.3 months (95% CI: 3.15–19.3). Common AEs were hyperphosphatemia, dry mouth, stomatitis, and dry skin.[25] An agnostic trial, RAGNAR, is a phase II study evaluating erdafitinib in multiple tumors with FGFR alterations.[26] In this trial, around half have FGFR2 alterations, mostly fusions. The ORR between patients with FGFR mutations or fusions was similar, 26.8 versus 27%, respectively. In the CCA cohort, 31 patients in total, the ORR was 41.9% with a DCR of 90.3%.[26] Grade 3 and 4 AE included stomatitis (9%), palmar-plantar erythrodysesthesia (6.2%), hyperphosphatemia (5.6%), and diarrhea (4.5%).[26]

Debio-1347

Debio-1347 is a highly selective FGFR1–3 inhibitor.[27] A pan-tumor phase I study evaluated debio-1347 at 80 mg PO QD in patients with advanced solid tumors with FGFR 1–3 fusions. Among 18 patients included in the trial, 5 had CCA and 2 had partial responses, both with FGFR2 fusions.[27] The planned FUZE Phase II Basket trial was terminated due to low antitumor activity (NCT03834220).

Ponatinib

Ponatinib is a pan tyrosine kinase inhibitor (TKI); along with FGFR inhibition, activity is seen in other receptors including RET, SRC, KIT, PDGFR, and VEGFR.[28] The phase I trial in BTC was terminated early due to low activity.[28] From 11 patients treated with advanced BTC and FGFR alterations, objective response was seen in 1 patient. The overall DCR was 45.5%.[28]

RLY-4008

RLY-4008 is a potent selective FGFR2 inhibitor, initially evaluated in the ReFocus trial.[29] In this phase I dose escalating trial, patients with CCA and FGFR alterations who were previously exposed to at least one systemic regimen were treated with RLY-4008 at different doses levels.[29] The RP2D achieved was 70 mg daily. In 38 patients with CCA and FGFR2 fusions or rearrangements treated with doses ranging between 20 and 100 mg with different schedules, the ORR was 63.2% (95% CI: 46–78.2), and 92% of the patients had tumor reduction.[29] Evaluating just the patients treated with the RP2D 70 mg daily, from 17 patients, the ORR was 88.2% (63.6–98.5), with all patients reaching some tumor reduction in scans.[29] Overall, the AEs were of low grade; grade 3 AE included stomatitis and palmar-plantar erythrodysesthesia.[29]

Tinengotinib

Tinengotinib is a reversible FGFR1–3 inhibitor.[30] Interim analysis from the phase II study was presented in the 2023 ASCO Gastrointestinal Symposium.[30] A total of 25 patients, including patients with FGFR genomic alterations and FGFR wild type, were treated with tinengotinib 10 mg once daily in

a 28-day cycle.[30] The overall DCR in patients with FGFR2 fusions ($n = 13$) was 92.3%, with a median PFS of 5.26 months (95% CI: 2.86 to not reached). However, not all data were mature for final analysis.[30]

Challenges and Perspectives

Treatment with FGFR inhibitors is tolerable, most patients will develop hyperphosphatemia, and in most cases this alteration was successfully managed with phosphate binders, dietary modifications, and/or dose modifications.[16] Furthermore, similar to other TKIs, stomatitis and palmar-plantar erythrodysesthesia are managed with corticosteroids and other topical treatments.[16] The majority of patients will stop FGFR inhibitors due to disease progression.

Although high responses and tumor control are obtainable with FGFR inhibitors, the development of resistant clones to these drugs is inevitable. Evolutionary studies combining post disease progression biopsy and evaluation of circulating tumor DNA have shown that mechanisms of resistance occur in multiple ways. As an example, studies evaluating disease progression on FGFR inhibitors have shown that alternative pathways are activated and contribute to tumor resistance.

Tyrosine kinases such as EGFR, HER-2, MET, and Eph3B are abnormal signaling pathways identified as mechanisms of resistance to FGFR inhibition in multiple tumors including CCA, gastric, urothelial, and lung cancer (►**Fig. 1**).[31] Other cell processes associated with disease progression during treatment to TKIs include epithelial-mesenchymal transition (EMT).[32] Resistant cells exposed to FGFR inhibitor displayed downregulation of the epithelial marker E-cadherin and upregulation of vimentin, and enhanced potential to migration and invasion, consistent with EMT (►**Fig. 1**).[33–35]

One of the mechanisms that is related to resistance of FGFR inhibitors is development of mutations that modify the binding site of the drugs (►**Fig. 1**).[33] As an example, samples obtained from an autopsy of a patient with a CCA and a FGFR fusion were analyzed.[36] The patient with a FGFR2-CLIP1 fused CCA was treated with pemigatinib after disease progression to chemotherapy. Samples sequencing revealed 242 unique mutations to post progression and a FGFR2 mutation, $FGFR2^{N549H}$, that results in a ligand-independent constitutive activation.[36] In another report,[37] sequencing from circulating tumor DNA (ctDNA) and tissue for three patients with CCA treated with infigratinib detected multiple acquired mutations related to resistance of the drug, including the $FGFR2^{N549H}$ previously reported.[37] Other mutations identified included $FGFR2^{N549K}$, $FGFR2^{V564F}$, $FGFR2^{E565A}$, $FGFR2^{K659M}$, $FGFR2^{L617V}$, and $FGFR2^{K641R}$. The tissue analysis detected PI3K/PTEN pathway mutations.[37]

Reports suggest that irreversible inhibitors, like futibatinib, could overcome some mutations related to resistance to debio-1347 or infigratinib.[38] In the study, efficacy of futibatinib against CCA with acquired mutations after treatment with infigratinib including $FGFR2^{K660M}$ and $FGFR2^{N550H}$ was reported.[38] Data from RLY-4008 indicated that the drug presents activity against primary and acquired FGFR2 resistance mutations in cellular assays.[39] In a pan tumor model, RLY-4008 induced regression in an FGFR2 fusion positive CCA

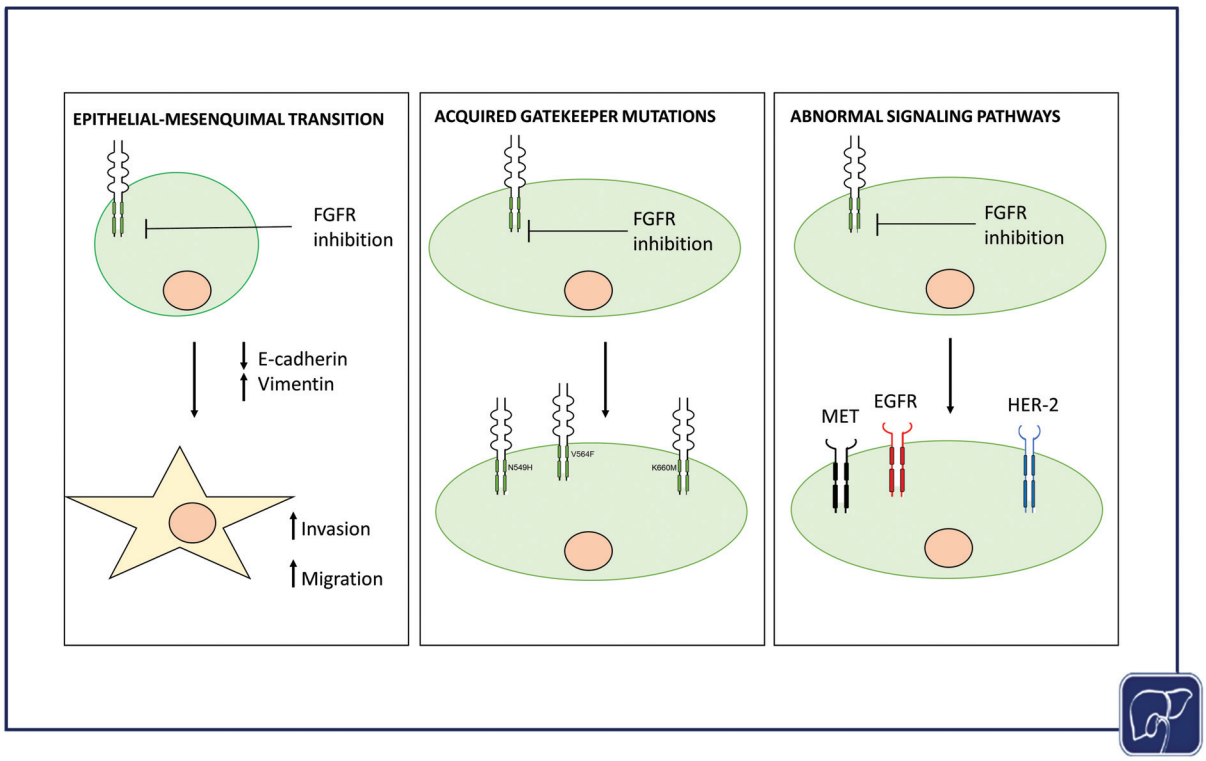

Fig. 1 Mechanisms of resistance to FGFR inhibition: epithelial to mesenchymal transition, acquisition of FGFR gatekeeper mutations, and activation of abnormal signaling pathways.

model harboring the FGFR2^{V564F} mutation and in an endometrial cancer model harboring the FGFR2^{N549K} mutation.[39] In the FGFR2^{V564F} model, where pan-FGFR inhibitors were ineffective, RLY-4008 induced tumor regression.[39] Taken together, these results suggest that potential sequencing of FGFR inhibitors would be possible and that development of highly selective FGFR2 inhibitors based on understanding of clonal evolution will enable better efficacy of FGFR targeting.

A comprehensive analysis of genomic sequencing in CCA harboring FGFR2 fusions from the pemigatinib FIGHT 202 trial brought insights about the importance of co-mutations.[40] No differences of pemigatinib efficacy related to fusions or rearrangements were observed. Moreover, the fusion partner also did not have impact on outcomes.[40] Interestingly, the presence of cooccurring mutations in CDKN2A/B was associated with shorter PFS (6.4 vs. 9.0 months, $p = 0.03$).[40] Also, patients with TP53 mutations had shorter median PFS (2.8 vs. 9.0 months, $p = 0.0003$) and patients with any tumor suppression gene loss (e.g., BAP1, CDKN2A/B, TP53, PBRM1, ARID1A, or PTEN) had shorter median PFS (6.8 vs. 11.7 months, $p = 0.0003$).[40]

Due to the impressive results in early trials, three randomized trials were developed. The distinct trials would compare FGFR inhibitors: pemigatinib (FIGHT-302 trial), infigratinib (PROOF trial), and futibatinib (FOENIX-CCA3 trial) against chemotherapy.[41–43] However, several problems could be related to the failure of this trials. First, problems with recruitment may occur, considering that the prevalence of FGFR2 fusions or rearrangement could be less than 10%.[1] Second, first-line chemotherapy should be updated with Durvalumab in those trials.[4] Third, multiple limitations in detecting FGFR2 fusions, due to poor logistics in some centers, different methods of diagnosis, and turnaround time, can hinder recruitment in cancer centers located in low- and middle-income countries.[44] Finally, for future trials evaluating FGFR inhibitors, data from cooccurring mutations would be necessary to be informed and included in the report of outcomes. Furthermore, ctDNA would need to be incorporated as the choice for detecting acquired mutations and cooccurring mutations related to primary and secondary resistance to FGFR inhibitors.[45,46]

Conclusion

Based on the findings and development of drugs, FGFR2 inhibition could be a desirable treatment choice for CCA harboring fusions or rearrangements. Trials evaluating FGFR inhibitors as first-line treatment are underway. Molecular understanding and incorporation of ctDNA would improve efficacy and screening in future trials.

Conflicts of Interest

P.L.S.U.J. has no disclosures to report. M.J.B. has received a grant to the institution from Senhwa Pharmaceuticals, Adaptimmune, Agios Pharmaceuticals, Halozyme Pharmaceuticals, Celgene Pharmaceuticals, EMD Merck Serono, Toray, Dicerna, Taiho Pharmaceuticals, Sun Biopharma, Isis Pharmaceuticals, Redhill Pharmaceuticals, Boston Biomed, Basilea, Incyte Pharmaceuticals, Mirna Pharmaceuticals, Medimmune, Bioline, Sillajen, ARIAD Pharmaceuticals, PUMA Pharmaceuticals, Novartis Pharmaceuticals, QED Pharmaceuticals, Pieris Pharmaceuticals, consultancy from ADC Therapeutics, Exelixis Pharmaceuticals, Inspyr Therapeutics, G1 Therapeutics, Immunovative Therapies, OncBioMune Pharmaceuticals, Western Oncolytics, Lynx Group, and travel support from Astra Zeneca.

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