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FGFR2 genomic aberrations: Achilles heel in the management of advanced cholangiocarcinoma

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ABSTRACT

Cholangiocarcinoma is the most common aggressive biliary tract malignancy with dismal prognosis. Though surgical resection of the primary tumors yields better prognosis, majority of patients present at advanced, inoperable stages rendering systemic therapy as the only option. A significant progress has been made in understanding the cholangiocarcinoma tumorigenesis and molecular markers over the last decade, which opens doors to precision medicine in this dismal cancer. Intrahepatic cholangiocarcinomas are most likely to harbor mutations in isocitrate dehydrogenase genes (*IDH1, IDH2*), fibroblast growth factor receptors (*FGFR1, FGFR2, FGFR3*), Eph receptor 2 (*EPHA2*), and *BAP1* (gene involved in chromatin remodeling) genes, whereas *ARID1B, ELF3, PBRM1,* cAMP dependent protein kinase (*PRKACA,* and *PRKACB*) genetic mutations were implicated more commonly in distal and perihilar subtypes. Genomic studies have shown that *FGFR2* aberrations are implicated in approximately 15% of intrahepatic cholangiocarcinomas, which make *FGFR2* aberrations (Achilles heel) as potential novel targets in the management of cholangiocarcinoma. The current review comprehensively focuses on the role of *FGFR2* inhibition either alone or in combination with other targeted therapy that act on downstream and alternate kinase pathways in cholangiocarcinoma.

Introduction

Cholangiocarcinomas are most common aggressive neoplasms of biliary tract having dismal prognosis with 5-year overall survival of 10% [1]. Etiological factors attributed to the tumorigenesis of cholangiocarcinoma include liver flukes (uncommon in Western world), inflammatory bowel disease-primary sclerosing cholangitis, choledochal cysts, viral hepatitis, hepatic cirrhosis, Lynch syndrome and biliary papillomatosis [2]. The tumors are broadly classified into intrahepatic, perihilar and distal cholangiocarcinomas based on their anatomical location [3]. Recent epidemiological studies have shown that there has been a significant rise in the incidence of intrahepatic cholangiocarcinoma [4]. In addition to the anatomical differentiation, these tumors are known to have notable differences in the molecular pathophysiology and tumorigenesis. Intrahepatic cholangiocarcinomas are most likely to harbor mutations or aberrations in isocitrate dehydrogenase genes (*IDH1, IDH2*), fibroblast growth factor receptors (*FGFR1, FGFR2, FGFR3*), Eph receptor 2 (*EPHA2*), and *BAP1* (gene involved in chromatin remodeling) genes, whereas *ARID1B, ELF3, PBRM1,* cAMP dependent protein kinase (*PRKACA,* and *PRKACB*) genetic mutations were implicated more commonly in distal and perihilar subtypes [2]. Whole exome sequencing studies have shown that liver fluke related cholangiocarcinoma harbored *TP53* mutations whereas *IDH1, IDH2,* and *BAP1* gene mutations were noticed in non-liver fluke related neoplasms [5].

Surgical resection of the primary tumor alone or in combination with liver transplantation, in intrahepatic and perihilar subtypes, remains the gold standard treatment in cholangiocarcinoma. However, surgery may not be feasible in majority of the cases as the disease is typically diagnosed at advanced stage. Systemic therapy with gemcitabine + cisplatin based on ABC-02 trial remains as the gold standard therapeutic option in patients with advanced disease [6].

Recently, integrated genomic and epigenomic analysis by the International Cancer Genome Consortium on 489 cholangiocarcinoma neoplasms have shown notable genetic heterogeneity of cholangiocarcinomas [7]. Authors identified 4 clusters (cluster 1 through 4) based on the genomic alterations and clinical features. Clusters 1 and 2 were identified in liver fluke positive tumors whereas clusters 3 and 4

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Table 1
Classification of cholangiocarcinoma tumors into 4 clusters based on the genomic and transcriptional analysis [8].

Clusters	Genetic aberrations	Comments
Cluster 1	*ARID1A, BRCA1, BRCA2, and TP53* mutations. *ERBB2* amplifications	Fluke positive tumors with hypermethylation at promoter CpG islands. Predominantly seen in extrahepatic cholangiocarcinoma tumors
Cluster 2	*CTNNB1, AKT1*, and *WNT5B* upregulation; decreased expression of eukaryotic initiation factor (eIF) translation. *TP53* mutation, *ERBB2* amplifications	Fluke positive and fluke negative tumors. Predominantly seen in extrahepatic cholangiocarcinoma tumors
Cluster 3	Immune check point genes (PD-1, PD-L2) upregulation. Aberrations in T-cell transduction and CD-28 co-stimulation	Fluke negative tumors only. Intrahepatic cholangiocarcinoma tumors only
Cluster 4	Aberrations in *BAP1, IDH1 and 2* mutations, *FGFR* genes. Upregulation in FGFR and PI3K kinase pathways	Fluke negative tumors only. Hypermethylation in CpG promotor shores. Intrahepatic cholangiocarcinoma tumors only

Abbreviations: ARID1A: AT-rich interactive domain-containing protein 1A gene; *BRCA1:* Gene encoding Breast cancer type 1 susceptibility protein; *BRCA2:* Gene encoding Breast cancer type 2 susceptibility protein; *ERBB2:* Receptor tyrosine-protein kinase erbB-2 gene; *TP53:* Tumor protein 53 tumor suppressor gene; *CTNNB1:* Catenin beta 1 protein gene; *AKT1:* Protein Kinase B; *WNT5B:* Wnt family 5B gene; *PD-1*: Programmed cell death protein 1; *BAP1:* BRCA associated protein 1; *IDH:* Isocitrate dehydrogenase; FGFR: Fibroblast growth factor receptor.

were seen in fluke-negative tumors. Interestingly, after adjusting for fluke status, clusters 1/2 and clusters 3/4 were enriched in extrahepatic and intrahepatic tumors, respectively. Distinct prognosis was also noted among the clusters, cluster 4 having the better prognosis of all. Table 1 details the genomic alterations associated with each cluster. This better understanding of the molecular pathogenesis has revolutionized the targeted therapy approach in this abysmal cancer. *FGFR2* aberrations were exclusively seen in cluster 4, which had a better prognosis of all. Moreover, *FGFR2* aberrations were shown to be mutually exclusive of other mutations such as *KRAS*, *IDH1/2*, and *BRAF* [8]. Hence, targeting *FGFR2* aberrations has been a preferred target in managing cholangiocarcinoma.

In this review, we sought to discuss the role of *FGFR* aberrations in the molecular pathogenesis of cholangiocarcinoma and discuss the potential implications in targeting the FGFR pathway in the disease management. We also summarized the potential resistance mechanisms that could render FGFR inhibitors ineffective and discussed the future perspectives in targeting the FGFR pathway.

FGFR growth factor pathway and its role in tumorigenesis

FGF family comprises of 22 secreted signaling proteins (22 FGFs) in humans that function through 4 tyrosine kinase receptors, FGFR 1–4 (extracellular FGFs) or by serving as cofactors for voltage-gated sodium channels (intracellular FGFs) [9]. In humans, extracellular FGFs are ubiquitous and are involved in various cellular pathways such as organogenesis during embryonic development, carbohydrate-lipid metabolism, tissue repair, and regeneration [9]. Based on their function, FGFs are broadly classified into endocrine FGFs and paracrine/canonical FGFs. Endocrine FGFs play a key role in metabolism, and bile acid, and mineral-phosphate homeostasis, whereas paracrine FGFs regulate cell cycle differentiation, proliferation, and survival. FGFs are also known to play an essential role in the regulation of tissue fibrosis, cardioprotection following an ischemic injury, and epithelial/wound repair [10–12]. Given this pervasive role of FGFs in various metabolic and cell survival pathways, any aberrations in the FGF-FGFR signaling may potentially lead to tumorigenesis.

Binding of FGF ligand to FGF receptors using heparin sulphate proteoglycan as a cofactor activates the FGF-FGFR axis [13]. Heparin co-factor is known to act as a bridge that binds two FGFs playing a crucial role in forming FGF-FGFR dimers. This FGF-FGFR dimer complex activates the downstream tyrosine kinase pathway leading in auto-phosphorylation of proteins at the C-terminus. This auto-phosphorylation of FGFR C-terminus proteins leads to activation of protein kinase C, phosphatidylinositol 3-kinase (PI3K)-protein kinase Akt/protein kinase B pathways, Janus Kinase (JAK)/ Signal Transducer and Activator of Transcription proteins (STAT) pathway, RAS-Mitogen activated protein kinase (MAPK)- Extracellular signal-regulated kinases (ERK) pathway, and other transcription activators [14]. The biological effects such as cellular proliferation, apoptosis, and migration depends on the interplay among the above FGF-FGFR related downstream pathways. Hence, aberrations in FGF-FGFR pathway lead to tumorigenesis by effecting cell survival/apoptosis, proliferation, migration, and angiogenesis. This oncogenic potential of FGF pathway aberrations can be attributed to chromosomal translocations leading to FGFR auto-dimerization and activation; interaction of FGFs with vascular endothelial growth factors (VEGFs) promoting angiogenesis; and lastly, chromosomal aberrations leading to ligand-dependent and independent tumor formation and proliferation [14,15]. In addition, *FGFR1* aberrations are known to promote tumorigenesis by recruitment of macrophages resulting in augmenting the production of proinflammatory chemokines, decreasing TGFβ expression, and activating C-X-C motif chemokine receptor 2 (CXCR2) [16]. The genomic aberrations in FGFR pathway vary among various tumor types. For instance, *FGFR1* amplifications are encountered in 9–25% of non-small cell lung cancer (associated with poor prognosis), 10% of hormone-receptor positive breast cancer (poor prognosis), gastric, colorectal, and ovarian cancers [17,18]. Activating mutations of *FGFR2* and *FGFR3* are implicated in 10% of muscle invasive bladder cancer and endometrial cancer, respectively. On the other hand, fusion aberrations are commonly encountered in intrahepatic cholangiocarcinoma (*FGFR2* fusions) and bladder cancer (*FGFR3* fusions) [19,20]. Fig. 1 summarizes some of the key signaling pathways in the molecular pathogenesis of intrahepatic cholangiocarcinoma.

FGFR aberrations in cholangiocarcinoma

Genomic studies have shown that *FGFR2* fusion aberrations are implicated in approximately 15% of intrahepatic cholangiocarcinomas, whereas *FGFR4* overexpression was noted in approximately 50% of all cholangiocarcinoma tumors (intrahepatic, perihilar, and distal) [7,19,21,22]. *FGFR4* overexpression predicted poor prognosis due to its stimulatory activity of cell cycle and invasion. An *in vitro* evaluation of cholangiocarcinoma cells revealed the feed forward pathway between yes-activated protein (YAP) and FGFR 1, 2, and 4. In addition, FGF5 mediated amplification of FGFR2 upregulated YAP, which was known to cause upregulation of matrix myeloid cell leukemia 1 (MCL-1) protein resulting in cell proliferation [23]. The same study in turn discovered that pan-FGFR inhibition resulted in cellular myeloid cell leukemia 1 (MCL-1) protein depletion leading to the death of tumor cells. Similar encouraging results of MCL-1 depletion were noticed with pan-FGFR inhibitor, LY2874455 on human cholangiocarcinoma cells [24].

Previous studies identified the presence of *FGFR2* gene fusions (*FGFR-BICCI, FGFR2-AHCYL1, FGFR2- TACC3, FGFR2-KIAA 1598*) in cholangiocarcinoma cell lines [19,21,25,26]. In addition, genomic analysis of approximately 500 cholangiocarcinoma cases across 10 countries have shown various *FGFR2* and *FGFR3* fusion

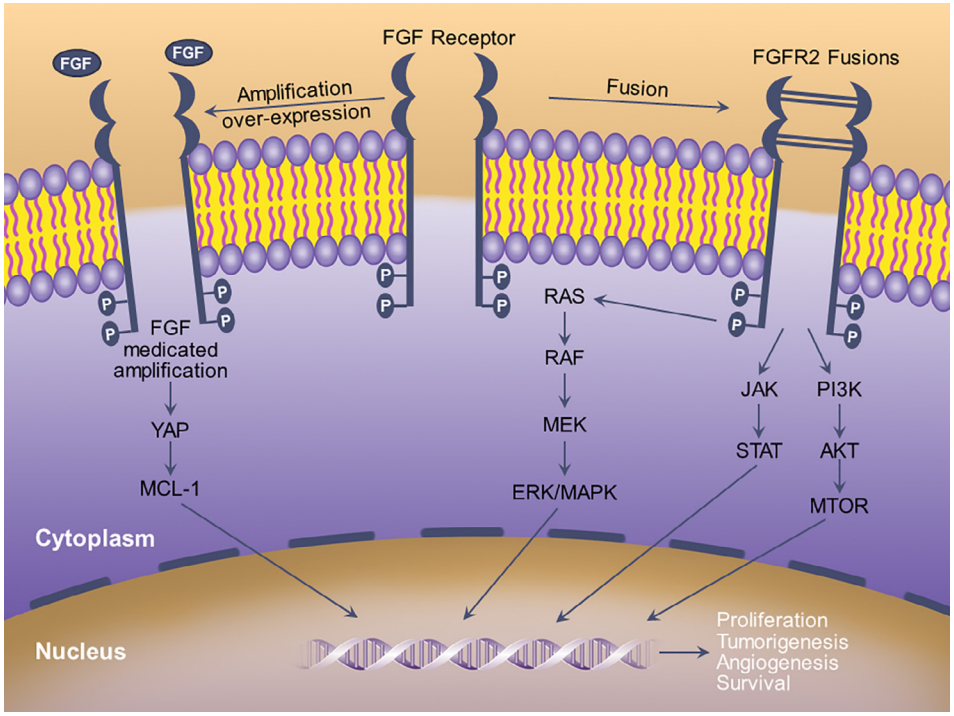

Fig. 1. Figure depicts some of the key signaling pathways in the intrahepatic cholangiocarcinoma tumorigenesis. FGF-mediated amplification and over-expression leads to activation of *YAP* and *MCL-1* promoting the tumorigenesis. *FGFR2* fusions upregulate the *RAS, JAK* and *PI3K/mTOR* pathways resulting in tumorigenesis, angiogenesis, and proliferation. FGF: Fibroblast Growth Factor; *FGFR2*: Fibroblast Growth Factor receptor 2; *YAP*: Yes-activated protein; *MCL-1*: Matric Myeloid Cell Leukemia-1; *RAF*: Raf proto-oncogene; *MAPK*: Mitogen Activated Protein Kinase pathway; *JAK/STAT*: Janus Kinases/Signal Transducer and Activator of Transcription proteins; *mTOR*: mechanistic target of rapamycin.

(*FGFR3–TACC3*) mutations [7]. Interestingly, presence of *FGFR2* gene fusions appeared to mutually exclusive of *KRAS* and *BRAF* mutations [19,25]. Graham et al., identified that the patients with tumors harboring *FGFR2* translocations had a better prognosis as compared to that of the patients without such translocations (123 vs. 37 months, $p = 0.03$) [26]. Cholangiocarcinoma tumors harboring *FGFR2* translocations were shown to have distinct histological features having intraductal growth, desmoplasia, weak expression of cytokeratin 19, and nonappearance of stem-like markers. In addition, recently, Jain et al., showed that *FGFR* genetic aberrations were more commonly seen in younger patients (age < 40 years) ($p = 0.001$), tumors presented at early stages ($p < 0.001$), and were associated with longer overall survival (37 vs 20 months, $p < 0.001$) [27]. The authors found no difference in OS between *FGFR2* fusion aberrations and other *FGFR2* genetic aberrations.

Targeting the FGFR pathway, the Achilles heel of cholangiocarcinoma

As detailed in Section 'FGFR aberrations in cholangiocarcinoma', *FGFR2* genetic aberrations, particularly *FGFR2* fusions have been identified as potential novel targets in the management of cholangiocarcinoma. As FGFs act through tyrosine kinase receptors (FGFRs), tyrosine kinase inhibitors (TKIs) have been extensively evaluated *in vitro* cholangiocarcinoma cell lines, phase I and phase II clinical trials. Depending upon the molecular structure and mechanisms of action, FGFR inhibitors are broadly classified into various classes such as- small molecule selective tyrosine kinase inhibitors (small molecule TKIs), non-selective small molecule TKIs, heat shock protein inhibitors, and FGFR monoclonal antibodies.

Selective small molecule TKIs

Wu et al., and Arai et al., have demonstrated that FGFR inhibitors showed promising results in targeting the cholangiocarcinoma cell lines harboring *FGFR* genetic aberrations, opening the doors for precision medicine in the management of cholangiocarcinoma [19,25]. These studies have shown that small molecule TKI suppressed the *FGFR* fusion oncogenic activity and inhibited the downstream MAPK signaling pathway. Since then, small molecule TKIs- Infigratinib (BGJ398) and Derazantinib (ARQ 087) have been well-explored with specificity against FGFRs.

Infigratinib (BGJ398) is a pan-FGFR TKI that was initially evaluated in a phase I basket trial involving patients with solid malignancies harboring *FGFR2* aberrations. A total of 3 cholangiocarcinoma patients (two patients had *FGFR2* fusions while the other had *FGFR2* genetic mutation) were included in the basket trial [28]. All the three patients who received BGJ398 had a notable reduction in the tumor size (5–20%). Later, BGJ398 (125 mg, 21 days on and 1 week off cycle) was evaluated in a phase II trial that included 61 patients with gemcitabine refractory cholangiocarcinoma harboring FGFR gene aberrations (FGFR fusions, mutations, and amplifications in 48, 8, and 3 patients, respectively) [29]. In the patients that harbored *FGFR2* fusion aberrations, BGJ398 resulted in overall response and disease control rate of ~19% and ~83%, respectively. Along with the encouraging results seen in patients with *FGFR2* fusion, a couple of patients with *FGFR2* mutation ($n = 1$) and *FGFR2* amplification ($n = 1$) had a tumor size reduction of 23% and 27%, respectively. On the contrary, patients harboring *FGFR3* amplifications ($n = 4$) showed no response to infigratinib. A total of 50 patients discontinued the therapy and most common adverse events noted were hyperphosphatemia, fatigue, stomatitis, alopecia, and palmar-plantar syndrome [29]. A recent update on the trial involving 71 patients with *FGFR2* fusions was presented at European Society of Medical Oncology (ESMO) 2018 annual meeting [30]. Among the 71 patients who received infigratinib, 25% and 58% of patients had partial response and stable disease, respectively, whereas progressive disease was seen in 11%. In patients who were able to be on infigratinib for at least 6 cycles, median progression free survival and overall survival were 7 and 12 months, respectively.

Derazantinib (ARQ087) is an orally administered pan-FGFR inhibitor with strong activity on FGFR (1–3) kinases. The drug showed encouraging results in pre-clinical studies that involved FGFR2-driven (amplifications and fusions) tumor models- NCI-H716 and SNU-16 [31]. ARQ087 had more potent activity against FGFR2 with half-maximal inhibitory concentration (IC50) of 1.8 nM as compared to that of FGFR1 and 3 (IC50 = 4.5 nM) [31]. Table 2 summarizes the IC50 of

Table 2
Half- maximal Inhibitory Concentration (IC50) of selective tyrosine kinase inhibitors on various FGF receptors (FGFR1, 2, 3, and 4).

Drug	FGFR1	FGFR2	FGFR3	FGFR4
Infigratinib	0.9 nM	1.4 nM	1.0 nM	60 nM
Derazantinib	4.5 nM	1.8 nM	4.5 nM	34 Nm
TAS 120	3.9 nM	1.3 nM	1.6 nM	8.3 nM
AZD 4547	0.2 nM	2.5 nM	1.8 nM	
CH5183284	9.3 nM	7.6 nM	22 nM	290 nM
Ponatinib	2.2 nM	8.0 nM		
LY2874455	2.8 nM	2.6 nM	6.4 nM	6 nM

nM = nanomole.

selected tyrosine kinase inhibitors of various FGFRs. In a phase I trial, at 16 weeks follow up, ARQ 087 resulted in a partial response in a couple of patients and stable disease in 1 patient with cholangiocarcinoma harboring FGFR2 fusions [32]. A phase I/II open label trial evaluated the role of ARQ 087 at a dose of 300 mg once daily in 29 advanced, unresectable intrahepatic cholangiocarcinoma patients harboring *FGFR2* fusions [8]. After a median exposure to ARQ 087 for 5.6 (range, 1.5–18.2) months, approximately 21% and 62% had partial response and stable disease, respectively. Though none of the patients had complete remission, ARQ 087 was shown to have superior efficacy as compared to that of "other" second line therapies used in the patients who progressed on first-line therapy ($p < 0.01$). The fact that 17% of the patients had progressive disease while on ARQ 087 indicates that FGFR inhibition resistant mutations exist. Most common side effects noted were nausea, vomiting, fatigue, liver enzyme elevation, and hyperphosphatemia. This phase I/II clinical trial is still enrolling advanced cholangiocarcinoma patients harboring *FGFR2* fusion aberrations to evaluate the objective response rate and overall safety of ARQ 087 (NCT03230318) (Table 3).

Erdafitinib (JNJ-42756493), an orally administered pan-FGFR TKI showed promising results in a phase I trial (NCT01703481) that enrolled 11 cholangiocarcinoma patients with FGFR aberrations [33]. After receiving erdafitinib (10 mg dose intermittent dose) for a median duration of 5.3 months, 3 out of 11 patients (27%) had partial response, which was maintained for a median duration of 12.9 months. Three more enrollees had stable disease. The drug is currently being evaluated in a phase IIa trial in Asian cholangiocarcinoma patients (NCT02699606).

TAS-120, an irreversible and covalent FGFR 1–4 inhibitor was evaluated in 45 cholangiocarcinoma patients harboring *FGFR* aberrations [34]. Among these, 28 patients had *FGFR2* fusion aberrations. *FGFR* aberrations in other enrollees are described in detail in Table 3. It is important to note that along with the FGFR inhibitor naïve patients, the study also included the cholangiocarcinoma patients who progressed on other FGFR inhibitors. Out of the 28 patients with *FGFR2* fusions, 71% (n = 20) had tumor shrinkage while 25% (n = 7) patients had partial response. Hyperphosphatemia (78%), elevated liver enzymes (29%), diarrhea (29%), and dry mouth (27%) were among the most common side effects. The drug is currently being evaluated in a phase I/II study to determine the pharmacokinetic, pharmacodynamic, safety, and objective response rate in cholangiocarcinoma patients harboring *FGFR2* gene fusions (NCT02052778).

Pemigatinib (INCB054828), another highly selective FGFR-1, 2, and 3 TKI that was evaluated in solid malignancies (cholangiocarcinoma, breast, and esophagus) that harbor *FGFR* genetic aberrations [35]. A total of 4 cholangiocarcinoma patients received the drug and partial response was seen in one patient with *FGFR2-CCDC6* fusion. A phase II trial is currently enrolling inoperable, advanced cholangiocarcinoma patients that harbor *FGFR2* fusions (cohort A), other FGF/FGFR genetic alterations, and no *FGFR* genetic aberrations (cohort C) [36]. The interim results of the trial were presented at ESMO 2018 annual meeting [37]. Out of the 45 evaluable patients in cohort A, 58% (n = 26) had stable disease while partial response was seen in 18% (n = 8). The overall response rate in patients with FGFR fusion was 24% with a progression free survival of 6.8 months [95%CI: 3.6–9.2]. On the contrary, no objective response was seen in patients in cohorts B and C. The most common adverse event noted was hyperphosphatemia (56%), which was managed with diet and phosphate binders. This study again signifies the fact that FGFR inhibitors have little effect on on-fusion FGFR genetic aberrations. A phase III trial is planned to compare the efficacy of pemigatinib to that of gemcitabine + cisplatin in cholangiocarcinoma patients with *FGFR2* fusion [38]. The trial is designed to evaluate the progression free survival (primary end point), and other survival end points along with the quality of life (secondary end points) [38].

Two other small molecule TKIs, CH5183284/Debio 1347 and AZD4547 demonstrated promising results in solid malignancies that harbored FGFR aberrations [39,40]. Table 3 summarizes the selected key clinical trials of small molecule TKIs targeting *FGFR* pathway in the management of advanced cholangiocarcinoma.

Table 4 summarizes the common side effects noted in the key clinical trials that evaluated the inhibition of FGFR pathway in cholangiocarcinoma. It would be interesting if the future studies focus on the side effect profile of the FGFR inhibitors based on their efficacy in blocking specific type of FGF receptor. For instance, FGFR1 pathway plays a key role in regulating the phosphate metabolism and the drugs

Table 3
Key clinical trials of selective small molecule tyrosine kinase inhibitors targeting FGFR pathway.

Targeted therapy agents	Study	Significance/outcome						Ongoing clinical trials
		Complete response	Partial response	Stable disease	Progressive disease	DCR	PFS	
BGJ398 (Infigratinib)	Javle M et al., Phase II (n = 61)	0%	15% 19%*	61%	24%	75% 83%*	5.8 months	NCT02150967
ARQ087 (Derazantinib)	Mazzaferro V et al., (n = 29)	0%	21%	62%	17%	83%	5.7 months	NCT03230318
	Papadopoulos KP et al., (n = 12; 3 with FGFR aberrations)	–	67%*	–	33%*	–	–	
JNJ-42756493 (Erdafitinib)	Soria JC et al., (n = 11)	0%	27%	27%	45%	55%	5.1 months	NCT02699606
TAS120	Meric-Bernstam F et al., (n = 45)	0%	25%*	53%*	7%*	79%*		NCT02052778
INCB054828 (Pemigatinib)	Hollebecque A et al., (n = 45)*	0%#	18%#	58%#	24%#	76%#	6.8 months	NCT02924376
		0%^	0%^	0%^	0%^	0%^	1.4 months	NCT03656536
		0%**	0%**	0%**	0%**	0%**	1.5 months	NCT02393248

* Represent percentage in patients harboring FGFR2 fusions.
\# Represent percentage in patients with FGFR2 translocations.
^ Represent percentage change in patients with other FGF/FGFR genetic alterations.
** Represent percentage in patients with no FGF/FGFR genetic alterations.

Table 4
Common adverse events reported in key clinical trials that evaluated the drugs targeting the FGFR pathway.

Targeted therapy agents	Major targeted receptors	Study	Common side effects							
			Hyper-phosphatemia	Diarrhea	Fatigue	stomatitis	Elevated AST	Alopecia	Nausea/Vomiting	constipation
BGJ398 (Infigratinib)	FGFR 1–3	Nogova et al., Phase I (n = 3)	82.5%			46%				51%
		Javle et al., Phase II (n = 61)	72%	15%	36%	29.5%	–	26%	15%	18%
ARQ087 (Derazantinib)	FGFR 1–3	Mazzaferro et al., Phase I/II open label trial (n = 29)	76%	21%	69%	–	17%	24%	45%	–
JNJ-42756493 (Erdafitinib)	FGFR 1–4	Soria et al., (n = 11)	64%	–	45%	82%	–	–	–	–
TAS120	FGFR 1–4	Meric-Bernstam et al., (n = 45) Phase I	80%	31%	–	22%	36%	–	24%	38%
INCB054828 (Pemigatinib)	FGFR 1–3	Hollebecque et al., Phase II (n = 87)	56%	32%	–	–	–	36%	–	–
Pazopanib + Trametinib	VEGF and MEK	Shroff et al., (n = 25)	–	56%	64%	8%	44%	–	72%	12%

having more affinity to block FGFR1 receptor (i.e., having low IC50 values in FGFR1) such as infigratinib may be contributing to hyperphosphatemia as predominant side effect [41]. Similarly, FGFR4 has been implicated in the physiology of bile acid synthesis [42,43]. Prior pre-clinical and translational studies demonstrated the disruption of the bile acid synthesis with the agents that target FGF19-FGFR4 pathway. Moreover, a phase I clinical trial by Meric-Bernstam et al., that evaluated TAS-120 found that a significant number of patients (31%) had diarrhea as one of the side effects [34]. TAS-120 has low IC50 (8.3 nM) towards FGFR4 receptor as compared to that of other agents such as infigratinib (IC50 on FGFR4: 60 nM), CH5183284 (IC50 on FGFR4: 290 nM), and Derazantinib (IC50 on FGFR4: 34 nM). Future clinical trials focusing on the side effects based on the affinity to individual FGF receptors would help in better understanding and management of side effects of FGFR inhibitors.

Non-selective small molecule TKIs

Ponatinib is a non-selective TKI that is Food and Drug Administration (FDA) approved for use in refractory BCR-ABL positive chronic myeloid leukemia. Given its non-selective tyrosine kinase blocking activity and notable *in vitro* IC50 of 8 nM on *FGFR2*, the drug was evaluated in a patient with intrahepatic cholangiocarcinoma harboring *FGFR2* fusion (*FGFR-MGEA5*) [26]. The patient had a tumor progression on gemcitabine + cisplatin and ponatinib was initiated as a salvage therapy. Ponatinib resulted in necrosis of the tumor mass with 14% decrease in largest tumor diameter, shrinkage of lymph node metastasis, and reduction of carbohydrate antigen (CA) 19–9 levels by 90%. Pazopanib is another non-selective tyrosine kinase inhibitor of FGFR (*in vitro FGFR2* IC50 of 350 nM), platelet derived growth factor receptor (PDGFR), MEK, and *KIT* protooncogene. Pazopanib was evaluated in a patient with intrahepatic cholangiocarcinoma harboring *FGFR2-TACC3* fusion. After a 4-month therapy with pazopanib 800 mg once daily, the drug resulted in partial response. Later, due to disease progression, pazopanib was replaced with ponatinib, which resulted in stable disease after 2 months of therapy [26]. Ponatinib is currently being evaluated in a phase II trial involving patients with solid malignancies harboring *FGFR (1–4), RET, or KIT* mutations (NCT02272998). Another multi-center pilot study evaluating the efficacy and safety of ponatinib in cholangiocarcinoma patients with FGFR2 fusions [44]. In addition, pazopanib 800 mg was also evaluated in combination with *MEK* inhibitor, trametinib 2 mg in an open-label multicenter trial involving 25 advanced, inoperable cholangiocarcinoma patients. Though there was a trend towards increased progression-free-survival, it did not reach statistical significance. However, the study did not detail *FGFR* mutation status in the patients enrolled [45].

Monoclonal antibody therapies against FGFR

Gastric tumor xenograft models have shown that *FGFR* gene has variable isoforms such as FGFR2- IIIb, FGFR2-IIIc isoforms, based on the tissue-specific mitochondrial Ribonucleic acid (RNA) splicing [46]. A genomic analysis (RNA sequencing) study on cholangiocarcinoma tumors identified the presence of FGFR2-IIIb isoform (having binding specificity to FGF7 and 10 ligands) in all the tumors that harbored *FGFR2* fusion [26]. Monoclonal antibody, FPA144 demonstrated excellent efficacy in targeting FGFR2-IIIb isoform in a preclinical gastric cancer xenograft model [46]. The drug is currently being evaluated in a phase I clinical trial involving patients with advanced solid tumors (NCT02318329). These monoclonal antibodies selectively targeting FGFR2-IIIb isoform theoretically looks promising in cholangiocarcinoma tumors harboring *FGFR2* fusion. Preclinical models and clinical trials that evaluate the drug class in cholangiocarcinoma are much awaited.

Heat shock protein (Hsp90) inhibitors

Hsp90, a chaperon protein to FGFR family seems to be an attractive target especially in the tumors harboring *FGFR* aberrations [47,48]. Prior studies have shown that targeting Hsp90 along with kinase inhibitors resulted in encouraging outcomes in ALK-positive non-small cell lung cancer and *FGFR3-TACC3* fusion positive bladder cancer [49,50]. Promising results from these two cases suggest that Hsp90 inhibitors may be used as complimentary agents along with TKIs in cholangiocarcinoma with *FGFR* aberrations.

Resistance mechanisms to FGFR inhibition

FGFR inhibitors have demonstrated clinically meaningful responses in phase II trials. However, majority of the patients with *FGFR2* fusions did not achieve overall response. Moreover, the median duration of response is only 5–6 months. Goyal et al., evaluated the mechanism of resistance by targeted genomic sequencing of cell free DNA in circulating tumor cells and tumor tissue from the primary/metastatic sites in 3 patients with progressive disease after initial documented response [51]. Authors identified that the development of new point mutations (p.N549H [2 patients], p.N549K, p.V564F [2 patients], p.L617V, p.E565A [2 patients], p.K641R, and p.K659M) is one of the plausible causes of developing resistance to FGFR2 inhibitors [51]. It was shown that the acquired point mutations destabilize the interaction of BGJ398 to FGFR tyrosine kinases. Another hypothesis is non-FGFR2 mediated resistance through Phosphatase and tensin homolog (PTEN)/PI3K pathway alterations (truncations, frame shift, and non-sense mutations) [51]. Authors have identified inter and intra-lesional variability in point mutations. Evaluation of an autopsy specimens (one from BGJ398 responsive lesion and the other from resistance site) have shown that the lesion that showed resistance to BGJ398 harbored new *FGFR2* point mutation (p.K641R), whereas responsive lesion had loss of function *PTEN* mutations.

Goyal et al., further compared five FGFR inhibitors against these resistant point mutations. The authors found that TKI, LY2874455 showed more potent activity against all point mutations, where as non-selective TKIs (dovitinib, ponatinib) showed potent activity against the point mutations p.N540 and p.549 K. This shows that FGFR inhibitors have distinctive capabilities to incapacitate the newly developed resistant FGFR point mutations.

Prognostic importance of FGFR fusion aberrations

Though early clinical trials evaluating the potential role of FGFR inhibitors yielded in modest benefit, promising results were seen in the studies that specifically enrolled patients with FGFR genetic aberrations [52]. Encouraging results were seen in intrahepatic cholangiocarcinoma with *FGFR2* fusions, muscle invasive urothelial/bladder cancer harboring *FGFR3* fusions, and gliomas harboring *FGFR2/3* fusions [53]. It is important to note that not all clinical trials mention the number of gains/degree of amplification of FGFR pathway, which may have contributed to variable results. This was evident on the low-level of amplifications 8p11-12 genomic locus seen in hormone receptor positive breast cancer raising the possibility FGFR1 genetic aberration may not be accountable for tumorigenesis and the resultant phenotype [52,54]. Targeting FGFR1 pathway in such cases may not yield fruitful results. Furthermore, AZD4547 showed promising results in patients harboring tumors with high-level of *FGFR2* amplifications as opposed to the counterparts [55]. Hence, development of universal techniques identifying such alterations and degree of amplifications may help in identifying tumors that respond to FGFR inhibitors. In this era of precision oncology, identification of intrahepatic cholangiocarcinoma patients that most likely harbor *FGFR2* aberrations and targeting such tumors with FGFR inhibitors would be beneficial. Nonetheless, ongoing phase III clinical trials that provide details on degree of FGFR amplification will more likely provide more information on FGFR inhibition in cholangiocarcinoma.

Future directions

Systemic therapy with gemcitabine and cisplatin has been traditionally used in unresectable, advanced cholangiocarcinoma. A better understanding of biomarker profile with the advent of state of art genomic profiling assays opened doors for precision oncology in this dismal cancer. A number of targeted and immunotherapeutic agents such as FGFR inhibitors, anti-PD-1 inhibitors (in mismatch repair deficient cholangiocarcinoma), and IDH inhibitors are currently being evaluated in clinical trials with encouraging results [51,56]. As genomic studies showed the presence of *FGFR2* fusion genes in approximately 15% of cholangiocarcinoma cases (predominantly in the intrahepatic subtype), FGFR inhibition emerged as a worthwhile option in patients with advanced, unresectable disease, especially in the patients harboring the *FGFR2* mutations. FGFR inhibitors are now being evaluated as first line therapy options for patients with unresectable disease potentially replacing chemotherapy. Another approach would be to use them as maintenance therapy after chemotherapy. These approaches may provide alternative therapeutic approaches leading to maximal tumor control while preserving quality of life for the patients. Though the future looks bright with the advent of these drugs, one has to be cautious about development of resistance to the targeted therapy, which was evident in phase II trial of BGJ398 [29,51]. A better understanding on the resistance mechanisms may help us in better use of targeted therapy based on their action on newly developed point mutations. Moreover, identifying the agents that have higher affinity and potency on FGFR2 would improve the tolerance by minimizing the side effect profile that may result from pan-FGFR inhibition.

Another approach would be developing the downstream FGFR pathway inhibitors that target PI3KAkt- mTOR pathway and others involved in tumorigenesis. Given the heterogenous nature of the disease, targeting multiple pathways simultaneously is a viable option. Future trials evaluating the combination regimens such as FGFR inhibitors plus systemic therapy or with other targeted therapies that target EGFR, mitogen-activated protein kinase (MEK)/ERK, tyrosine-protein kinase Met (MET), VEGF pathways. In short, genomic analysis that identifies tumor biomarkers at the time of diagnosis helps in choosing appropriate enrollment onto clinical trials that evaluate targeted therapy either alone or in combination.

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