Robust Response to Futibatinib in a Patient With Metastatic \( \text{FGFR} \)-Addicted Cholangiocarcinoma Previously Treated Using Pemigatinib

Anil K. Rengan, MD,1 and Crystal S. Denlinger, MD1,2

ABSTRACT

Futibatinib is a novel \( \text{FGFR} \) inhibitor currently under investigation as a second-line treatment for locally advanced or metastatic cholangiocarcinoma harboring \( \text{FGFR2} \) gene fusions and rearrangements. As \( \text{FGFR} \)-targeted therapies move into the frontline setting, sequencing of these drugs remains undetermined. To date, no study has investigated the use of futibatinib in the context of pemigatinib resistance. We describe a 50-year-old woman with metastatic \( \text{FGFR} \)-aberrant intrahepatic cholangiocarcinoma who showed a robust response to futibatinib for 23.6 months, having previously benefited from pemigatinib. Futibatinib was safely used despite her history of decompensated cirrhosis and significant cytopenias. We observed a reduction in CA 19-9 level and a partial radiographic response on futibatinib. Serial next-generation sequencing and cell-free DNA testing proved crucial to making appropriate treatment decisions.

Intrahepatic cholangiocarcinoma (iCCA) historically presents with advanced stage and poor prognosis. Although conventional chemotherapy is the mainstay of treatment, targeted therapy has proven effective for patients with specific molecular alterations. The \( \text{FGFR} \) pathway includes 4 tyrosine kinases that control cellular processes ranging from proliferation to cell death. Constitutively active \( \text{FGFR} \) occurs in several cancer types, including iCCA, due to gene fusion and gain-of-function mutations. \( \text{FGFR2} \) fusions occur in up to 15% of patients with iCCA,2–5 with >100 unique \( \text{FGFR2} \) partners identified. The presence of a fusion is thought to have more clinical relevance than the composition of the fusion itself.6 \( \text{FGFR} \)-aberrant iCCA is also associated with significantly longer overall survival (OS) compared with wild-type \( \text{FGFR} \), regardless of whether these patients receive \( \text{FGFR} \)-directed therapy.7

\( \text{FGFR} \) has become a therapeutic target in iCCA with the development of tyrosine kinase inhibitors (TKIs) that successfully abrogate the effects of aberrations in this pathway. Several \( \text{FGFR} \) TKIs are currently being studied in the cytotoxic therapy–refractory and frontline settings.8–9 Pemigatinib, futibatinib, and infgratinib were recently FDA-approved for the treatment of refractory advanced/metastatic \( \text{FGFR2} \)-aberrant iCCA.10–14 Derazantinib has also been shown to have activity in these patients with phase II trial data supporting its use in this setting.15

Patients inevitably acquire resistance to these agents because of single-nucleotide variants in the \( \text{FGFR} \) gene.16–18 This development has highlighted the need for novel approaches to bypass resistance via alternative \( \text{FGFR} \) inhibition. Futibatinib, a third-generation irreversible pan-\( \text{FGFR} \) inhibitor, has been shown to overcome the resistance induced by kinase domain mutations that develop during prior \( \text{FGFR} \)-targeted therapy.18 As \( \text{FGFR} \) TKIs move into the frontline setting, sequencing of these drugs remains undetermined. This case report presents a patient with advanced \( \text{FGFR2} \) fusion–positive iCCA who had significant clinical and radiographic response to futibatinib after progression on pemigatinib.

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Case Report

A 50-year-old woman with a history of ductal carcinoma in situ of the breast 2 years prior presented to her local emergency department with abdominal pain. Hepatomegaly was seen on right upper quadrant ultrasound. CT and MRI of the abdomen showed multiple hepatic lesions concerning for metastatic disease, and an ultrasound-guided liver biopsy confirmed moderately differentiated adenocarcinoma favoring an upper gastrointestinal or pancreaticobiliary primary. Internal pathology review verified that the specimen was histologically distinct from the patient’s prior ductal carcinoma in situ. Further staging established multifocal disease of the liver without extrahepatic spread, consistent with unresectable metastatic iCCA.

She began therapy using cisplatin and gemcitabine, which was complicated by leukopenia and thrombocytopenia, resulting in dose reduction and treatment delays. Given the severity of her cytopenias, she underwent bone marrow biopsy that revealed mild myelodysplasia, which, in combination with chemotherapy, explained her hematologic abnormalities. Limited by low blood counts, the patient received bilobar radioembolization of the liver for local disease control to allow for a treatment-free interval, having completed 7 months of cisplatin and gemcitabine.

FoundationOne (Foundation Medicine, Inc.) next-generation sequencing (NGS) of the patient’s diagnostic liver biopsy showed an FGFR2-CORO2B gene fusion. Upon disease progression 6 months later, she enrolled in a clinical trial of pemigatinib and attained a durable partial response lasting 23 months. Just before enrollment, she developed decompensated cirrhosis with esophageal varices and ascites, considered secondary to radioembolization-induced liver injury and scarring from previous treatment response. Her CA 19-9 level was initially elevated but normalized within 2 months of starting therapy (Figure 1). Upon progression, she underwent repeat liver biopsy using (Caris Life Sciences) NGS, confirming the continued presence of the FGFR2-CORO2B fusion and the development of a new FGFR2 point mutation, N549D (Table 1). While awaiting NGS results, the patient received dose-reduced capecitabine because she was ineligible for standard-of-care FOLFOX (fluorouracil/leucovorin/oxaliplatin) due to cytopenias. She showed disease progression at her first evaluation after 2 months of capecitabine with significant increase in hepatic tumor burden.

The patient was then treated using futibatinib, a novel irreversible pan-FGFR inhibitor, under a single-patient investigational new drug application from Taiho Oncology. This decision was based on her N549D point mutation, which was shown to confer resistance to infgratinib in vitro, and data from a case series indicating that futibatinib was effective against several FGFR2 mutations that promote resistance to infgratinib and zoligratinib.\textsuperscript{17,18} At initiation, the patient’s CA 19-9 level was 109 U/mL and her hepatic function was stable with a Child-Pugh score of A5. Treatment was complicated by anticipated anti-FGFR2 adverse effects, including grade 2 hyperphosphatemia (managed by diet and phosphate binders), grade 1 hand-foot syndrome (treated using moisturizers), and grade 1 fatigue, requiring one dose reduction from 20 mg to 16 mg within the first month. Her cytopenias remained stable, her CA 19-9 level reached a nadir at 10.6 U/mL, and she achieved a partial radiographic response at her first disease evaluation 2 months into treatment (Figure 2).

The patient’s course was complicated by SARS-CoV-2 infection, resulting in a 25-day treatment hiatus. During this time, her CA 19-9 level increased to 91 U/mL. She also developed an acute portal vein thrombosis with hepatic decompensation that was managed using dose-reduced apixaban and diuretics. Disease was radiologically stable. Upon resumption of futibatinib, the patient’s CA 19-9 level decreased to 27.9 U/mL. In anticipation of disease progression, Guardant360 (Guardant Health, Inc.) cell-free DNA (cfDNA) was obtained, which revealed a new FGFR2 N549K point mutation. The prior FGFR fusion and N549D mutation were not seen. She remained on futibatinib for 23.6 months with long-term clinical and radiographic response. At progression, her CA 19-9 level was 96.9 U/mL. Additional molecular profiling was not performed. Figure 1 illustrates the CA 19-9 trend during treatment using pemigatinib, capecitabine, and futibatinib.

Discussion

In our patient with FGFR-addicted unresectable iCCA, we documented a robust response to sequential FGFR inhibitor

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**Figure 1.** CA 19-9 trend during treatment using pemigatinib, capecitabine, and futibatinib.
therapy after first-line chemotherapy. Upon discovery of her FGFR2 fusion, she was treated successfully using pemigatinib for nearly 2 years, far exceeding the median progression-free survival (PFS) of 6.9 months observed in the FIGHT-202 trial. After a short-interval therapy using capecitabine, she then received futibatinib for almost 2 years as well, having experienced an early dose reduction for anticipated adverse effects. Futibatinib was safely used despite this patient’s history of decompensated cirrhosis and significant treatment-limiting cytopenias, suggesting the potential for safe use in higher-risk patients.

FGFR gene fusions keep the FGFR pathway constitutively active, thus promoting oncogenicity. The sensitivity of FGFR gene fusions to FGFR inhibition is a recognized area of clinical interest across various cancer types. FGFR2 fusions tend to form via translocation, and several common fusion partners have been reported (eg, AHCYL, BICC1, PPHLN1, and TACC3) although numerous others have been described. The FGFR2 fusion partner in our patient was CORO2B, an actin-regulating protein normally expressed by neuronal cells not previously observed in iCCA. Although there is no known direct link between CORO2B and iCCA pathogenesis, the actin-positive expression of cancer-associated fibroblasts (CAFs) in iCCA has been suggested to predict unfavorable prognosis and lymph node metastasis. An investigation of the role of CAFs in 12 tumor samples of patients with iCCA showed marked CAF content in the stroma surrounding neoplastic cholangiocytes. The isolated CAFs were shown to promote iCCA growth in vitro and in vivo in mice. Although the presence of a fusion is thought to have more clinical relevance than the composition of the fusion itself, the extent to which these genetic alterations may impact oncogenesis is yet to be fully understood.

Nevertheless, the FGFR2 domain mutations that develop during treatment ultimately drive resistance to FGFR inhibition, thereby dictating progression and prognosis. In a study assessing resistance mechanisms in FGFR fusion–positive iCCA, 3 patients receiving infigratinib were found to have an FGFR2 V564F point mutation in cfDNA at the time of disease progression. Two of these patients were also found to have N549H mutations, with 1 patient also having an N549K mutation. Of the 2 patients with available tumor tissue, both had at least 1 FGFR2 point mutation identified in the tumor in addition to the persistent FGFR fusion.

While receiving pemigatinib, our patient acquired a secondary FGFR2 N549D point mutation. Although the N549D mutation did not disappear while she was on futibatinib, cfDNA testing detected an N549K point mutation in cfDNA at the time of disease progression. Two of these patients were also found to have N549H mutations, with 1 patient also having an N549K mutation. Of the 2 patients with available tumor tissue, both had at least 1 FGFR2 point mutation identified in the tumor in addition to the persistent FGFR fusion.

Table 1. FGFR-Related Events and Treatment Course

<table>
<thead>
<tr>
<th>Liver Biopsy</th>
<th>1st FGFRi PFS (mo)</th>
<th>Intervening Therapy Between 1st and 2nd FGFRi</th>
<th>Interval Between 1st and 2nd FGFRi (mo)</th>
<th>2nd FGFRi PFS (mo)</th>
<th>cfDNA (Guardant360)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FGFR-CORO2B fusion</td>
<td>Pemigatinib 23.0</td>
<td>Capecitabine 3</td>
<td></td>
<td>Futibatinib 23.6</td>
<td>N549K point mutation</td>
</tr>
</tbody>
</table>

Abbreviations: cfDNA, cell-free DNA; FGFRi, FGFR inhibitor; PFS, progression-free survival.

Figure 2. CT images at (A) treatment initiation, (B) CA 19-9 nadir, (C) treatment hold for COVID-19, and (D) disease progression.
although futibatinib has shown antiproliferative effect against N549K-mutated cholangiocarcinoma and endometrial carcinoma in vitro.25-26 We hypothesize that the population of cells harboring this point mutation at the time of cfDNA testing was small given the radiographic disease stability despite the slight increase in CA 19-9 level. This finding is indicative of tumor heterogeneity, a concept regarded as a negative predictor of treatment response and contributor to drug resistance. Tumor heterogeneity is a result of genetic, epigenetic, and tumor microenvironment variation. Goyal et al17 described a patient who developed resistance to infiratinib but whose tumor samples lacked a secondary FGFR2 mutation in 8 of 12 biopsy specimens. A separate study observed the variability of in vitro sensitivity to different FGFR inhibitors in a patient with FGFR fusion–positive iCCA who experienced disease progression on pemigatinib after the development of an N549H point mutation.27 Tumor heterogeneity highlights the need for FGFR-directed agents capable of bypassing multiple secondary mutations associated with TKI resistance. cfDNA was not repeated when our patient experienced progression on futibatinib; therefore, it is unknown whether the N549K subclone persisted or whether new FGFR2 point mutations arose.

The potential for the development of such single-nucleotide polymorphisms suggests the need for serial genomic monitoring in patients treated using FGFR TKIs, especially when resistance is suspected. It emphasizes the utility of NGS and cfDNA testing as a guide for future therapy decision-making, although each is not without its limitations. Tissue biopsy is invasive and may be difficult if lesions are anatomically inaccessible. Tumor heterogeneity can also cause subclonal cell populations to go unnoticed, especially in metastasis where obtaining multiple biopsies is impractical. This type of situation is where cfDNA is advantageous, allowing for the real-time detection of mutations throughout a patient’s disease course. cfDNA can also identify variation between the primary tumor and metastatic lesions, because tissue-based molecular profiling can yield varying results depending on the biopsy site. For example, in gastric cancer, whole-exome sequencing has revealed significant heterogeneity in somatic mutations between the primary tumor and metastatic lymph nodes.28 However, subclones may still fall below the level of detection and go overlooked. In addition, cfDNA may not be able to distinguish between somatic tumor mutations, somatic hematopoietic mutations, and germline variants. Furthermore, certain biomarkers (eg, PD-L1) require immunohistochemistry of the tumor specimen, thus requiring tissue biopsy. NGS and cfDNA platforms may be disease-specific, assist with cancer screening or guiding treatment selection, vary in the number of genes tested and the types of alterations present, and use different technologies to detect molecular alterations. Therefore, the platform to be used for any given patient should be appropriate for that tumor type and the potential actionable molecular alterations.

Futibatinib is a highly selective irreversible inhibitor of FGFR1-4 that covalently binds to the P-loop cysteine residue in the ATP binding pocket of FGFR, retaining permanent activity irrespective of kinase conformation.18,29 This mechanism of action is distinct from that of reversible FGFR inhibitors, such as infiratinib, zoligratinib, and pemigatinib. Futibatinib displayed efficacy in a phase I basket trial of advanced solid tumors, particularly in patients with FGFR-aberrant iCCA.30 A total of 83 patients with iCCA were treated, 64 of whom received the 20-mg dose of futibatinib and 19 of whom received the 16-mg dose. Most patients (n=59; 71.1%) harbored an FGFR2 fusion or rearrangement. Among those who received the 20-mg dose, 9 had a partial response (PR). The overall response rate (ORR) was 15.6%, the disease control rate was 71.9%, the median duration of response (DoR) was 5.3 months with 50% of responses lasting ≥6 months, and the median PFS was 5.1 months. Within the subset of patients with FGFR2 fusions or rearrangements, the ORR was 16.7%, with a disease control rate of 78.6%, a median DoR of 6.9 months, and a median PFS of 6 months. Among the 19 patients who received the 16-mg dose, the ORR was 33.3% and 8 individuals had a PR. Overall, 28 patients had been previously treated using FGFR inhibitors, 5 of whom had a PR. Notably, pre-enrollment tumor or liquid biopsy was not required. Therefore, acquired resistance to prior FGFR-directed therapy was not evaluated in this study.

The phase II FOENIX-iCCA2 trial evaluated futibatinib in patients with FGFR-aberrant unresectable or metastatic iCCA who had received prior gemcitabine and platinum-based chemotherapy but no prior FGFR TKI.11-13 The

### Table 2. FGFR-Related Events and Associated Therapies

<table>
<thead>
<tr>
<th>FGFR2 Aberrancy</th>
<th>Source</th>
<th>Associated Therapies</th>
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<tbody>
<tr>
<td>FGFR2-CORO28 fusion</td>
<td>First liver biopsy (FoundationOne)</td>
<td>Pazopanib, ponatinib, AZD4547, infiratinib, Debio 1347, dovitinib, erdafitinib, futibatinib</td>
</tr>
<tr>
<td>N549D point mutation</td>
<td>Second liver biopsy (Caris)</td>
<td>Ponatinib, derazantinib, infiratinib, Debio 1347, erdafitinib, futibatinib, sulfatinib</td>
</tr>
<tr>
<td>N549K point mutation</td>
<td>cfDNA (Guardant360)</td>
<td>Erdafitinib, lenvatinib, nintedanib, pazopanib, pemigatinib, ponatinib</td>
</tr>
</tbody>
</table>

Abbreviation: cfDNA, cell-free DNA.
fused iCCA have been retrospectively shown to live longer than their untreated counterparts. However, our patient has survived beyond the expected median OS of 31.3 months in this study.

Futibatinib has a manageable adverse effect profile similar to that of other FGFR inhibitors. Hyperphosphatemia and gastrointestinal toxicity are most common. Hyperphosphatemia affects approximately 80% of patients and is attributed to FGFR1 inhibition of renal tubule function. Management typically includes phosphate binder therapy, decreased dietary phosphorus intake, and/or TKI dose adjustment. Our patient underwent treatment without worsening hepatic function, and her hyperphosphatemia was managed using the interventions noted earlier.

Although several phase II trials have reported similar activity among various FGFR inhibitors in previously treated iCCA, data are lacking to guide the sequencing of these agents. This is the first case report to describe clinical benefit from futibatinib in a patient with resistance to pemigatinib, with treatment decisions responsive to serial molecular and cfDNA testing. Futibatinib has previously been shown to have in vivo and in vitro activity in patients with iCCA who developed resistance to iniflitratinib or zolifliritinib in a case series by Goyal et al. This result was perhaps attributable to the unique covalent bond that futibatinib forms with the ATP-binding pocket of FGFR1-4. Findings were consistent with our own, supporting the use of futibatinib and cfDNA to track resistance mechanisms in patients with FGFR-altered iCCA who previously received FGFR TKI therapy. However, it is evident that only a subset of patients who develop resistance to prior ATP-competitive FGFR inhibitor treatment respond to futibatinib, likely due to resistance mechanisms other than acquired kinase domain mutations. Our patient’s robust response to successive FGFR inhibitor therapy was therefore remarkable. As was observed in EGFR-mutated non–small cell lung cancer, we must gain an understanding of which FGFR2 fusions and mutations affect acquired resistance and time to treatment failure. Further investigation on a larger scale is also critical to delineating the optimal sequence of FGFR TKIs in patients with FGFR-aberrant iCCA.

Conclusions

Our patient’s experience reflects the importance of serial monitoring of FGFR aberrations for sequential TKI administration. We found marked durability and response with pemigatinib and futibatinib in an individual with otherwise treatment-limiting comorbidities. For FGFR-addicted tumors, outcomes with sequential FGFR TKIs seem beneficial. Our patient achieved a DoR of approximately 2 years using both pemigatinib and futibatinib. Concurrent serial NGS and cfDNA testing proved essential in making treatment decisions at diagnosis and at each stage of progression. As these modalities become more widely accessible, using them throughout TKI treatment may reveal potential mechanisms of resistance and new avenues of therapy. As FGFR inhibitors advance into the frontline setting and newer drugs emerge, we hope to achieve a more complete understanding of the complex molecular landscape in cholangiocarcinoma and sequence these agents for patients such as our own.

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References

Futibatinib After Pemigatinib in iCCA

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