Sustained response on sequential anti-FGFR therapy in metastatic gall bladder cancer: a case report and literature review

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Abstract
Purpose Advanced gall bladder cancer (GBC) is an aggressive disease, and there is no consensus on treatment options beyond first-line chemotherapy. We report a case of an elderly male with FGFR2-altered advanced adenocarcinoma of the gallbladder who failed two prior lines of chemotherapy but had sustained response and stable disease on sequential FGFR-directed targeted therapy.

Design We describe a case of FGFR2-altered metastatic adenocarcinoma of the gallbladder who failed two prior lines of chemotherapy. The treatment was based on comprehensive genomic profiling when the patient was found to have FGFR2 single amino acid mutation (S252W) in one of his tissue samples. A novel therapeutic regimen with sequential anti-FGFR tyrosine kinase inhibitors was later initiated.

Result The patient tolerated the sequential targeted therapy very well and had a sustained response and stable disease. He had an overall survival of nearly five years. Unfortunately, GBC is an aggressive disease, and there is no consensus on treatment options beyond first-line chemotherapy.

Conclusion Through this patient, we demonstrate that advanced-metastatic GBC with FGFR alterations can be maintained on anti-FGFR therapy for prolonged periods of time, with improved survival. Therefore, we endorse the need for comprehensive genomic profiling in advanced-metastatic GBC and the need to study the role of FGFR inhibitors as a viable treatment option in these patients.

Keywords Sequential anti-FGFR therapy · Gallbladder cancer · Pathway resistance · Pemigatinib · Futibatinib

Introduction
Gallbladder cancer (GBC) is a rare and aggressive carcinoma, accounting for 1.2% of all cancers according to GLOBOCAN 2018. The incidence was 219,000 of which 122,000 were women. This was consistent with the global estimate that females had a higher incidence of GBC. Incidence also varies based on the geographic locations. Asians demonstrated a higher incidence than north westerners (Rawla et al. 2019). Presently, radical resection remains the only curative option for GBC. However, GBC is almost always diagnosed in later stages due to noticeable symptoms emerging in advanced disease, thus disproportionately having a poor 5-year overall survival when compared to other cancers (Howlader et al. 2018).

The majority of GBCs are adenocarcinomas arising from the secretory cells. On immunohistochemistry (IHC), both GBC and cholangiocarcinoma (CCA) have similar progenitor cells originating from the perihilar glands, thus suggesting a histological crossover among these cancers (Ahn and Bekaii-Saab 2017). Over a span of a few decades, with the advent of advanced diagnostic technologies such as next-generation sequencing (NGS), genetic alterations and signal pathways have been successfully identified and specific targeted therapies have been developed. Here, we present a case of advanced GBC that progressed on multiple lines of
chemotherapies but had sustained response and stable disease on sequential targeted therapy. Through this study, we would like to bring to light the importance of comprehensive genomic profiling (CGP) in advanced GBC patients who have progressed on multiple lines of therapy and the potential clinical benefit of offering sequential targeted therapy in these patients.

**Case**

A 78-year-old gentleman presented to the emergency room with abdomen pain, nausea, distension and constipation in August 2016. CT scan showed a mass at liver segment 5 originating from the gallbladder, porta hepatis and portacaval lymph node (LN) involvement and carcinomatosis. PET/CT scan confirmed diagnosis of GBC with metabolically active gallbladder mass and porta hepatis and portacaval LN. Ultrasound-guided liver biopsy demonstrated moderately differentiated adenocarcinoma with IHC positive for cytokeratin (CK)7 and CK19 and negative for Chromogranin A, Synaptophysin, CDX2, Thyroid Transcription factor (TTF)1, and Napsin. Later, laparoscopic biopsy of the carcinomatosis showed metastatic adenocarcinoma with gallbladder primary. Baseline CA19.9 was 42.4 (Normal < 35 units/ml).

In view of extensive metastasis, the patient was started on first-line chemotherapy with gemcitabine 1000 mg/m² IV day 1 and 8 and cisplatin 60 mg/m² IV day 1 on a 21-day cycle. However, a follow-up scan 3 months later showed progression of the disease, which prompted switching to second-line chemotherapy with mFOLFOX regimen (oxaliplatin 85 mg/m² IV day 1, Leucovorin 400 mg/m² IV day 1 and 5-fluorouracil 400 mg/m² IV bolus on day 1, then 1200 mg/m²/day for 2 days (total 2400 mg/m² over 46–48 h) continuous infusion (mFOLFOX6) regimen in December 2016. He tolerated therapy well with stable disease seen in subsequent scans and consistent CA19.9 levels for approximately 18 months.

In May 2018, the patient presented with progression of disease. CT scans showed increase in size of primary tumor with subjectively enlarged omental nodules. An interim CGP done through Foundation One CDx testing on the tissue sample showed single amino acid mutation (S252W) in FGFR2 and microsatellite stable disease. Based on the CGP results, the patient was started on tab pazopanib, a multi-kinase inhibitor, at 400 mg orally once daily. He tolerated the therapy well and had stable disease for over 2 years. However, in September 2019, a follow-up CT abdomen/pelvis showed mild interval progression of disease, with reappearance of perihepatic fluid and increase in peritoneal metastasis. Given the fact that his tumor carried FGFR 2 alteration and he derived benefit from pazopanib, we decided to offer him a selective FGFR inhibitor tab erdafitinib 8 mg daily in February 2020. He was later switched to 9 mg daily dose on day 15 as his serum phosphate level remained below 5.5 mg/

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**Fig. 1** CT abdomen and pelvis comparing baseline to October 2021. A Baseline scan—hepatic segment 5 mass measuring 5.4 cm appearing to arise from the gallbladder adjacent to an area of abnormal gallbladder wall thickening, small pericholecystic fluid collection, peritoneal carcinomatosis with a small amount of ascites, subcentimeter porta hepatis and portacaval lymph nodes. Findings are suspicious for malignancy. B Intermediate scan (October 2021) while on erdafitinib—partial response to therapy
dl. He had a sustained less than partial treatment response to erdafitinib from March 2020 to March 2021. Figure 1 compares baseline CT to October 2020.

Unfortunately, follow-up surveillance scans done in March 2021 showed interval progression of disease along with rise in CA19.9. In April 2021, the patient presented with transaminitis, hyperbilirubinemia in the setting of worsening intrahepatic ductal dilatation, portal venous thrombosis and hypercalcemia. Erdaftinib was held at this point, a biliary drain was placed and he was started on tab apixaban 5mg every 12 h for portal vein thrombosis. He also developed ascites in May 2021 requiring treatment with diuretics and multiple ultrasound-guided paracentesis. Given his history of resistance to other systemic chemotheraphy options and sustained response to anti-FGFR tyrosine kinase therapy, it was prudent to evaluate another anti-FGFR agent in this setting. We discussed repeating tissue biopsy and a liquid biopsy at this point mainly to assess for drug-resistance mechanisms and the patient opted for a repeat liquid biopsy at this time. He was subsequently switched to pemigatinib 13.5 mg PO daily dose (days 1–14 of a 21-day cycle) in first week of May 2021. We obtained FDA investigational new drug application and institutional review board approval for compassionate drug use.

His Foundation One Liquid Biopsy CDx report was discussed in our molecular tumor board. The patient had developed additional FGFR2 alterations (M537I, N549K, N549D, N549T) and RAF1 S257L apart from the primary FGFR2 S252W alteration, which was considered a sign of evolving resistance to anti-FGFR therapy. With these findings, we discussed switching him to Futibatinib (TAS120) based on a study by Goyal et al. (Goyal et al. 2019) or adding trametinib to pemigatinib (Cristinziano et al. 2021) to cover for downstream RAF1 mutations.

We tried to obtain expanded access to TAS120. Unfortunately, we did not have the luxury of time to get this authorized for use at our cancer center, so we provided him with a list of potential study site locations. However, the patient was unable to travel due to his deteriorating health. We also requested insurance approval for trametinib to be used in conjunction with pemigatinib. He completed second cycle of pemigatinib by second week of June 2021 without any apparent significant drug-related side effects apart from fatigue and paronychia.

Cycle 3 of pemigatinib was put on hold in last week of June 2021 due to admission for sepsis, altered mental status, and recurrent ascites in the setting of worsening liver failure. Unfortunately, he could not start trametinib due to his worsening clinical condition. His mental status improved but the hospital course was further complicated by spontaneous bacterial peritonitis and hematochezia due to hemorrhoids. Fevers improved with supportive care and broad-spectrum antibiotics though infectious source was not identified. Overall, his clinical condition continued to decline with worsening liver failure and further disease progression. At this point, we discussed comfort care options with him and his family. Using shared decision-making process, we decided to discontinue all life-prolonging treatments. He later went home on home hospice and died in July 2021. Figure 2 depicts the treatment timeline for this patient.

## Discussion

GBC are often diagnosed in an advanced stage and carry a dismal prognosis. Overall, 5-year survival rate of all GBCs in USA is around 18% with advanced GBC being with less than 2% survival at 5 years. The median survival of GBC for resectable tumors is 12–14 months and unresectable tumors around 6 months (Howlader et al. 2018).

First-line chemotherapy of advanced biliary tract carcinoma (BTC), including GBC, is gemcitabine combined with a platinum usually cisplatin based on ABC-02 trial. Gemcitabine platinum combination has shown superior overall survival (OS) compared to single-agent gemcitabine (Valle et al. 2010). Recently, interim results of the TOPAZ-1 clinical trial presented at ASCO GI 2022 showed a significant improvement in OS and progression-free survival (PFS) with no significant increase in toxicity in advanced BTC and GBC treated with a combination of durvalumab and standard of care chemotherapy when compared to chemotherapy alone (Do-Youn et al. 2022).
5-Flurouracil + oxaliplatin + leucovorin is considered second-line therapy upon progression with gemcitabine–cisplatin combination based on the ABC-06 trial (Lamarca et al. 2021). Previous studies have shown that common genomic alterations associated with GBC are TP53, CDKN2A/B, ERBB2, PI3KCA, ARID1A, KRAS, EGFR, FGFR1-3, BAP1, BRAF, and MET (Mehrotra et al. 2018). Our previous work identified Dickoppf homologue 3 (DKK3), a secreted protein belonging to the Wnt antagonist family, as a potential tumor suppressor in GBC cell lines. In addition, we performed quantitative proteomics and phospho-proteomics analysis on DKK3 overexpression in GBC which showed phosphorylation alteration in 14 kinases (Gondkar et al., 2019, 2021).

FGFR2 or cluster of differentiation 332 (CD332) is a protein encoded by the FGFR2 gene residing on chromosome 10 (Dienstmann et al. 2014). A full-length representative protein consists of an extracellular region, composed of three domains, a single hydrophobic that spans the entire length of the membrane and a cytoplasmic tyrosine kinase domain. The interaction between FGFR and FGF leads to mitogenesis and differentiation through signaling cascade. FGFR2 alterations have been implicated in breast, urinary bladder, gastric, colorectal, uterine, skin (including melanoma and squamous cell carcinoma [SCC]), lung SCC, pancreatic, prostate and BTC (Mehrotra et al. 2018; Houssaint et al. 1990; Katoh 2009; Maruki et al. 2021; Liao et al. 2013). Figure 3 illustrates the FGFR signaling pathway and site of action of treatments mentioned in the above case.

Pazopanib is a multiple kinase inhibitor targeted towards tumor angiogenesis by inhibition of enzymes including vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), c-KIT and FGFR (Zivi et al. 2012). It has received worldwide approval for renal cell carcinoma and soft tissue sarcoma (Que et al. 2018). Erdafitinib, a selective pan-FGFR kinase inhibitor, has been implemented in patients with FGFR altered tumors, one of which is CCA. A phase II open label, multicenter, clinical trial comprising of Asian patients with FGFR altered advanced CCA who progressed on more than 1 line of therapy received erdafitinib. In 10 FGFR2+ patients, objective response rate (ORR) was 60.0%; disease control rate (DCR) was 100%; median PFS was 12.35 months (Park et al. 2019).

Fig. 3  Fibroblast growth factor receptor signaling pathway and FGFR inhibitors mechanism of action

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Table 1  Summary of studies included in this article

| Study name                                             | Patient demographic                                                                 | Therapy                                         | Response (median)       | Toxicity                                                                 |
|--------------------------------------------------------|--------------------------------------------------------------------------------------|------------------------------------------------|-------------------------|-------------------------------------------------------------------------|
| Phase 1 clinical trial (Goyal et al. 2019)             | Advanced FGFR2 fusion-positive CCA                                                   | TAS120/futibatinib                              | ORR: 4/4 (100%)         | PFS: 5.1–17.4 months                                                   |
| ABC-02 trial (Valle et al. 2010)                       | Locally advanced or metastatic cholangiocarcinoma, gallbladder cancer, or ampullary cancer | Cisplatin 25 mg/m² of body-surface area followed by gemcitabine 1000 mg/m², each administered on days 1 and 8, every 3 weeks for eight cycles vs. gemcitabine alone 1000 mg/m² on days 1, 8, and 15, every 4 weeks for six cycles | OS: 11.7 vs 8.1 months  | HR: 0.68  PFS: 8 vs 5 months DCR: 81.4 vs 71.8%                        |
| TOPAZ-1 (Do-Youn et al. 2022)                          | Chemotherapy naïve unresectable locally advanced, recurrent, or metastatic BTC       | Durvalumab (1500 mg every 3 weeks) or placebo + gemcitabine cisplatin (gemcitabine 1000 mg/m² and Cisplatin 25 mg/m² on Days 1 and 8) for up to 8 cycles, followed by durvalumab (1500 mg) vs. placebo + gemcitabine cisplatin (gemcitabine 1000 mg/m² and Cisplatin 25 mg/m² on Days 1 and 8) for up to 8 cycles | OS: 12.8 vs 11.5 months | HR: 0.8  PFS: 7.2 vs 5.7 months ORR: 26.7% vs 18.7%                    |
| ABC-06 trial (Lamarca et al. 2021)                     | Advanced BTC that progressed after first-line therapy                               | FOLFOX—oxaliplatin 85 mg/m², L-folinic acid 175 mg [or folic acid 350 mg], fluorouracil 400 mg/m² [bolus], and fluorouracil 2400 mg/m² as a 46-h continuous intravenous infusion] vs. active symptom control (ASC) | 6 month OSR: 50.6 vs 35.5% 12 month OSR: 25.9 vs 11.4% | Grade 3–5 FOLFOX-related adverse events—neutropenia 12%, fatigue or lethargy 11%, and infection 10% |
| LUC2001 (Park et al. 2019)                             | Asian patients with FGFR altered advanced CCA who progressed after ≥ 1 prior treatment | Erdafitinib 8 mg once daily                     | ORR: 60%                | DCR: 100% PFS: 12.35 months                                           |
| FIGHT-202 (Abou-Alfa et al. 2020)                      | Locally advanced or metastatic cholangiocarcinoma with FGFR2 fusions or rearrangements with disease progression after ≥ 1 prior treatment and an ECOG performance status of 0–2 | Pemigatinib 13.5 mg once daily                 | ORR: 35.5%              | DOR: 9.1 months                                                       |
| Phase I Dose-Expansion Study (Meric-Bernstam et al. 2022) | CCA was the most common tumor type represented (37.6%), followed by primary CNS tumors (21.2%), urothelial cancer (11.2%), breast cancer (6.5%), and gastric cancer (5.3%); 18.2% of patients had other tumors with FGFR alterations | Futibatinib 20 mg once daily                   | ORR: 13.7% FGFR2 fusion/rearrangement—positive intrahepatic cholangiocarcinoma ORR: 25.4% | Overall adverse events: 58.2% Grade 3 or higher: 6.5% Hyperphosphatemia (81.2%), diarrhea (33.5%), and nausea (30.4%) |
Pemigatinib, a small molecule kinase inhibitor, is the first FDA-approved (April 2020) FGFR inhibitor for advanced CCA with FGFR 2 fusion or rearrangement in patients who progressed on 1 or more lines of therapy (https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-pemigatinib-cholangiocarcinoma-fgfr2-rearrangement-or-fusion). This decision was based on the FLIGHT 202 trial, a multicenter open-label single-arm trial, which included 107 patients with advanced CCA. The study demonstrated an ORR of 36% with 3 patients having complete metabolic response and a median duration of response (DOR) of 9.1 months. Those that did develop response, 63% had a ≥ 6 months’ response and 18% had a ≥ 12 months’ response (Abou-Alfa et al. 2020).

The caveat to selective FGFR inhibitor is that only a limited number of patients respond to therapy in the first place suggesting a primary resistance. In addition, those who do respond, the median DOR is around 7–9 months suggesting a secondary resistance. Other mechanisms of resistance include gatekeeper mutations, activation of alternate signaling pathways, polyclonal secondary FGFR mutations, cooccurring tumor suppressor gene alterations such as BAP1, CDKN2A/B, PBRM1, and TP53 (King and Javle 2021; Goyal et al. 2017, 2021). A number of FGFR2-point mutations (N549H, N549K, E565A, K641R, or K659M) and gatekeeper mutation (V565F and V565I) were seen in patients who developed progression on reversible ATP-competitive FGFR inhibitor. King et al. and Goyal et al. suggested combination therapy with mTOR/PI3K targeted therapy, immune checkpoint inhibitor, vascular endothelial growth factor (VEGF) inhibitor, chemotherapy or sequential FGFR targeted therapy as a possible direction towards overcoming resistance (King and Javle 2021; Goyal et al. 2017, 2021). Prevention of treatment resistance relies heavily on the understanding of tumor heterogeneity. Goyal et al. suggest tracing genetic alterations that emerge upon disease progression through serial circulating tumor DNA (ctDNA) analysis and, based on those findings, recommends sequential treatment with various FGFR inhibitors depending upon their spectrum of activity. This could potentially extend the efficacy of FGFR inhibitors (Goyal et al. 2017, 2021).

In our case, the patient progressed on multiple lines of cytotoxic chemotherapy but later responded to sequential anti-FGFR therapy. Previously, published data point towards the potential role of sequential anti-FGFR therapy in CCA (Goyal et al. 2017, 2021; Kasi 2020). As gallbladder cancer shares several clinical and pathological characteristics of CCA, it is reasonable to assume that a similar effect would likely be seen in these patients.

Foundation One CDx performed on tissue sample showed development of FGFR2 alterations apart from S252W resistance through secondary FGFR mutations. Addition of MEK inhibitor to the ongoing pemigatinib to overcome resistance...
| Study name | Patient demographic | Therapy |
|------------|---------------------|---------|
| The PROOF trial (NCT03773302) (Makawita et al. 2020) | Advanced/metastatic or inoperable cholangiocarcinoma with FGFR2 gene fusions/translocations | Infigratinib (BGJ398) 125 mg orally once daily, 3 weeks on, 1 week off vs. Gemcitabine 1000 mg/m² D1 and D8 + Cisplatin 25 mg/m² D1 and D8 for a 21-day cycle |
| A Multicenter, Open-Label, Phase II Trial (NCT04238715) (https://clinicaltrials.gov/ct2/show/NCT04238715) | Unresectable advanced or metastatic cholangiocarcinoma with FGFR2 gene fusion | E7090 140 mg orally once daily |
| Phase I clinical trial (NCT04526106) (https://clinicaltrials.gov/ct2/show/study/NCT04526106) | Unresectable or metastatic cholangiocarcinoma and other unresectable or metastatic solid tumors with FGFR2 alteration | Multiple doses of RLY-4008 for oral administration |
| FIGHT 302 (NCT01656536) (Bekaii-Saab et al. 2020) | Chemotherapy-naïve unresectable/metastatic cholangiocarcinoma with FGFR2 rearrangements | Pemigatinib 13.5 mg once daily for a 21-day cycle vs. Gemcitabine 1000 mg/m² D1 and D8 + Cisplatin 25 mg/m² D1 and D8 for a 21-day cycle |
| Phase II, Open Label, Multicenter Study (NCT04919642) (https://clinicaltrials.gov/ct2/show/NCT04919642) | Advanced/metastatic and surgically unresectable cholangiocarcinoma with 1) FGFR 2 fusions who failed prior FGFR inhibitor treatment, 2) FGFR2 fusions who responded on prior FGFR inhibitor treatment, 3) with other FGFR alterations, or 4) whose tumors do not contain a detectable FGFR alteration | TT-0042 orally once daily |
| Phase II Study (NCT04233367) (https://clinicaltrials.gov/ct2/show/NCT04233367) | Advanced or metastatic solid tumors (including cholangiocarcinoma) with FGFR1-3 gene fusions or other FGFR Genetic alterations | Infigratinib (BGJ398) 125 mg orally daily, 3 weeks on, 1 week off vs. Gemcitabine 1000 mg/m² D1 and D8 + Cisplatin 25 mg/m² D1 and D8 for a 21-day cycle |
| FOENIX-CCA3 (NCT04093362) (https://clinicaltrials.gov/ct2/show/NCT04093362) | Chemotherapy-naïve advanced cholangiocarcinoma harboring FGFR2 gene rearrangements | TAS120 orally once daily for a 21-day cycle vs. Gemcitabine 1000 mg/m² D1 and D8 + Cisplatin 25 mg/m² D1 and D8 for a 21-day cycle |
| FIDES-01 (NCT03230318) (Mazzaferrro et al. 2019) | FGFR2 gene fusion-, mutation-, or amplification-positive inoperable or advanced intrahepatic cholangiocarcinoma | Derazantinib 300 mg orally once daily |
| Single-arm, Multicenter, Open-label Phase II Study (NCT04353375) (https://clinicaltrials.gov/ct2/show/NCT04353375) | Metastatic or local advanced intrahepatic cholangiocarcinoma with FGFR2 fusion, who have failed at least one systemic therapy | HMPL-453 150 mg orally once daily |
| Phase II Single-arm, Open-label Study (NCT05174650) (https://clinicaltrials.gov/ct2/show/NCT05174650) | Advanced intrahepatic cholangiocarcinoma | Atezolizumab 1200 mg IV for a 21-day cycle + Derazantinib 300 mg orally once daily |
| Open-label, Single Arm, Multicenter Phase 2 Study (NCT05039892) (https://clinicaltrials.gov/ct2/show/NCT05039892) | Advanced/metastatic cholangiocarcinoma with FGFR2 gene alterations who have failed at least 1 previous treatment | 3D185 |
| Phase I/II, Open-label, Multicenter Study (NCT05242282) (https://clinicaltrials.gov/ct2/show/NCT05039892) | Advanced tumors (includes cholangiocarcinoma) harboring FGFR2 and/or FGFR3 gene alterations | KIN-3248 orally once daily for a 28-day cycles |
| Phase II Study (NCT02699606) (https://clinicaltrials.gov/ct2/show/NCT05242282) | Asian patients with advanced tumors (includes cholangiocarcinoma) | Erdafitinib 8 mg starting dose orally once daily with option to up-titrate to 9 mg for a 28-day cycle |
| Multi-center Open-label, Phase I/II Clinical Trial (NCT04565275) (https://clinicaltrials.gov/ct2/show/NCT04565275) | Advanced solid tumors (includes cholangiocarcinoma) with FGFR gene alterations | ICP-192 |

**BTC** biliary tract cancer, **CCA** cholangiocarcinoma, **CNS** central nervous system, **DCR** disease control rate, **DFS** disease free survival, **DOR** duration of response, **HR** hazard ration, **ORR** overall response rate, **OS** overall survival, **OSR** overall survival rate, **PFS** progression-free survival
mutation would be a viable option to consider in this scenario. A study by Cristianziano et al. demonstrated that dual blockade of FGFR2 fusion proteins and MEK 1/2 with a combination of BGJ398/infigratinib and trametinib was superior to single-agent FGFR2 fusion or MEK1/2 inhibitors in vitro and in vivo, thus indicating a promising clinical benefit of dual FGFR2-MEK1/2 blockade in patients with CCA (Cristianziano et al. 2021).

Another option to overcome resistance would be to consider irreversible FGFR kinase inhibitors. Futibatinib is an irreversible FGFR 1–4 tyrosine kinase inhibitor which had shown activity in a number of solid tumors CCA and gastric, urothelial, central nervous system, head and neck, and breast cancers, most significantly in FGFR2 fusion/rearrangement-positive intrahepatic CCA (Meric-Bernstam et al. 2022). An article by Sootome et al summarizing the preclinical significance of TAS120 strongly suggests the use of futibatinib in patients who have developed resistance to prior tyrosine kinase inhibitors (Sootome et al. 2020). In contrast to reversible FGFR inhibitors, very few resistant clones were observed with prolonged futibatinib treatment, and in the FGFR2 kinase domain, no mutations were observed. Futibatinib was found to be effective in tumors with FGFR mutations known to be resistant to irreversible inhibitors. Goyal et al. reported 4 advanced CCA cases which initially progressed on selective FGFR2 inhibitor showing efficacy to pan-FGFR futibatinib inhibitor (Goyal et al. 2019). A recent update from the FOENIX-CCA2 trial reported a median PFS and OS of 8.9 and 20 months, respectively, with a good safety profile suggesting durable efficacy and sustained tolerability of futibatinib in advanced CCA with FGFR alterations (Goyal et al. 2022). Other irreversible FGFR tyrosine kinase inhibitor under investigation include PRN1371, FINN-2, FINN-3, BLU9931 and fisogatinib/BLU554 (Venetsanakos et al. 2017; Tan et al. 2014; Lu et al. 2020). Tables 1 and 2 describe the all the BLU554 (Venetsanakos et al. 2017; Tan et al. 2014; Lu et al. 2020) and breast cancers, most significantly in FGFR2 fusion/rearrangement-positive intrahepatic CCA (Meric-Bernstam et al. 2022). An article by Sootome et al summarizing the preclinical significance of TAS120 strongly suggests the use of futibatinib in patients who have developed resistance to prior tyrosine kinase inhibitors (Sootome et al. 2020). In contrast to reversible FGFR inhibitors, very few resistant clones were observed with prolonged futibatinib treatment, and in the FGFR2 kinase domain, no mutations were observed. Futibatinib was found to be effective in tumors with FGFR mutations known to be resistant to irreversible inhibitors. Goyal et al. reported 4 advanced CCA cases which initially progressed on selective FGFR2 inhibitor showing efficacy to pan-FGFR futibatinib inhibitor (Goyal et al. 2019). A recent update from the FOENIX-CCA2 trial reported a median PFS and OS of 8.9 and 20 months, respectively, with a good safety profile suggesting durable efficacy and sustained tolerability of futibatinib in advanced CCA with FGFR alterations (Goyal et al. 2022). Other irreversible FGFR tyrosine kinase inhibitor under investigation include PRN1371, FINN-2, FINN-3, BLU9931 and fisogatinib/BLU554 (Venetsanakos et al. 2017; Tan et al. 2014; Lu et al. 2019; Kim et al. 2019). Tables 1 and 2 describe all the studies referenced in this article along with ongoing clinical trials involving CCA with FGFR alteration (Makawita et al. 2020; https://clinicaltrials.gov/ct2/show/NCT04238715; https://clinicaltrials.gov/ct2/show/NCT04526106; Bekaii-Saab et al. 2020; https://clinicaltrials.gov/ct2/show/NCT04919642; https://clinicaltrials.gov/ct2/show/NCT04233567; https://clinicaltrials.gov/ct2/show/NCT04093362; Mazzaferrro et al. 2019; https://clinicaltrials.gov/ct2/show/NCT04353375; https://clinicaltrials.gov/ct2/show/NCT05174650; https://clinicaltrials.gov/ct2/show/NCT05039892; https://clinicaltrials.gov/ct2/show/NCT05242822; https://clinicaltrials.gov/ct2/show/NCT02699606; https://clinicaltrials.gov/ct2/show/NCT04565275).

Options of switching to futibatinib or adding trametinib to pemigatinib to target downstream pathways were explored but the patient could not travel to be enrolled in clinical trials and eventually developed progression of disease and worsening liver failure. Metastatic GBC with FGFR alterations can be maintained on sequential anti-FGFR therapy for durable periods of time, which is truly remarkable in this case. GBC is an aggressive disease and there is no consensus on treatment options beyond first-line chemotherapy. Our study further underpins the value of CGP and the need to further study the role of sequential FGFR inhibitors as a viable treatment option in FGFR altered advanced GBC that failed multiple lines of therapy.

**Author contributions** Conceived and designed by A.S. and H.S. Patient care and follow up by A.S. Original draft preparation by H.S. and A.S. All authors contributed to manuscript revisions and approved the final version of the manuscript.

**Funding** The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

**Declarations**

**Conflict of interest** The authors have no relevant financial or non-financial interests to disclose.

**Consent to participate** Written informed consent was obtained from the individual included in the study.

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