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Review

Pemigatinib for adults with previously treated, locally advanced or metastatic cholangiocarcinoma with FGFR2 fusions/rearrangements

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***Abstract*:** Biliary tract cancers are a diverse and aggressive malignancy that carry a poor chance for curative treatment and significant associated mortality. Current first-line treatment only extends median overall survival to roughly 1 year and is associated with a significant adverse event profile. Recently, advancements in genetic sequencing have opened new avenues of targeted treatment. In cholangiocarcinoma, FGFR2 alterations have been shown to be present in roughly 10–15% of intrahepatic cholangiocarcinoma. Pemigatinib, a FGFR1–4 inhibitor, has been shown to significantly extend survival in the second-line setting to over 20 months in patients who harbor FGFR2 fusions. Here, we outline the development and future direction of pemigatinib and other FGFR2 inhibitors in the field of advanced biliary tract cancers.

Keywords: cholangiocarcinoma, FGFR, FGFR inhibitor, fusion, pemigatinib

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Background

Biliary tract cancers represent a diverse group of epithelial cancers characterized by aggressive and chemoresistant tumors with poor long-term survival.[1] Surgery remains the only curative treatment; however, only roughly 35% of patients can undergo curative surgery and of surgically resected patients, 35% have clinical relapse in 2 years.[2,3] Often limiting surgical resection includes the presence of vascular involvement and the presence of metastatic spread to regional lymph nodes, which are often evident at time of diagnosis given the frequent asymptomatic status of early disease. Systemic therapy for cholangiocarcinoma represents the only feasible option for patients with locally advanced or metastatic cholangiocarcinoma. Results of the multicenter ABC-02 trial showed superior results of gemcitabine-based chemotherapy combined with cisplatin when compared to gemcitabine alone. However, this regimen is associated with significant toxicity, limited to patients with adequate renal function, and achieves only limited efficacy with median overall survival (OS) of 11.7 months.[4] Outside of the United States, a commonly used regimen includes gemcitabine plus S-1 (tegafur/gimeracil/oteracil). Both gemcitabine/cisplatin and gemcitabine/S-1 showed similar results with regard to median OS (15.1 *versus* 13.4 months) and median PFS (6.8 *versus* 5.8 months) with gemcitabine plus S-1 compared to gemcitabine plus cisplatin.[5]

Following first-line treatment, only 15–25% of patients are candidates for salvage therapy due to morbidity of the disease and rapid decline in performance status.[6] Prognostic tools to determine clinical response in second-line treatment are not established; however, three studies suggest that patients with ECOG 0-1, disease control to first-line therapy, low CA 19-9, and absence of peritoneal carcinomatosis confer the best response in the second line.[7–9] Patients who progress on first-line treatment have limited treatment options with dismal OS and progression-free survival benefit compared to active symptom control

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(ASC). The recently published ABC-06 trial reported an OS benefit of just 4 weeks with the addition of 5-fluoruracil, oxaliplatin, and leucovorin (FOLFOX) compared to ASC alone (6.2 months *versus* 5.3 months).[10] Furthermore, the recent results from the NIFTY trial suggest added efficacy of liposomal irinotecan with fluorouracil when compared to fluorouracil and leucovorin in the second-line setting with an OS of 8.6 months versus 5.5 months ($p = 0.035$), highlighting the need for additional therapies.[11]

In recent years, advancements in gene sequencing have better highlighted the genetic landscape of BTC and have shown that molecular profiles segregate with anatomical location [perihilar/distal *versus* intrahepatic cholangiocarcinoma (iCCA)]. A recent analysis which reviewed next generation sequencing of 1200 patients with cholangiocarcinoma revealed that patients harbor an average of 4.6 genomic alterations with the most frequent being altered genes in p53 (40%), CDKN2A (29.0%), KRAS (22.6%), CDKN2B (19.7%), ARID1A (16.0%), SMAD4 (11.7%), IDH1 (10.2%), and BAP1 (10.2%).[12] Mutations harboring potential actionable mutations were reported at 44% with most being IDH1 mutations (10.2%), ERBB2 mutations/amplifications (8.0%), FGFR2 mutations/rearrangements (7.1%), PIK3CA mutations (7.0%), and BRAF mutations (4.7%). Better definition of potential actionable mutations in BTC has led to numerous trials evaluating the efficacy of blockade of such driver mutations including IDH1/2, FGFR2/4, EGFR, HER2, and PIK3 (NCT02631590).[13–17] Of these trials, the most promising has been through inhibition of the FGFR receptor.

Numerous agents have been developed to target FGFR inhibition in this clinical context. Initial agents acquiring FDA approval included pemigatinib in April 2020 and shortly followed by infigratinib in May 2021. Third-generation FGFR inhibitors including futibatinib (TAS-120) have recently been FDA approved which have been shown to overcome the gatekeeper mutation, V565F, that exemplifies resistance to pemigatinib and infigratinib.[18]

FGFR2 alterations in cholangiocarcinoma

The prevalence of FGFR2 alterations including fusions, translocations, and rearrangements in cholangiocarcinoma ranges from 10 to 15% and are almost exclusively confined to iCCA.[19,20] FGFR2 is a part of a larger FGFR family of four transmembrane receptors (FGFR1–5) and has been shown to be critical in physiologic proliferation, survival, migration, and angiogenesis.[21] Notable downstream substrates include activation of PKC, Pi3K, MAPK as well as c-JUN and STAT.[22] The FGFR2 gene most commonly undergoes a rearrangement/fusion with other genes resulting in dimerization and subsequent constitutive activation, promoting oncogenesis. The most common translocations include FGFR2 to periphilin 1, adenosyl-homocysteinase, and bicaudal-C family RNA-binding protein (BICC1)[23]; however, over 150 fusion partners have been identified.[23,24] FGFR2 gene fusions may represent a distinct molecular subtype of iCCA with a predominance toward younger age of onset, less aggressive clinical course with female predominance.[23] Since the discovery of these aberrant signaling domains in iCCA, numerous trials have emerged to discover mechanisms to block this constitutive signaling leading to carcinogenesis.

Pemigatinib preclinical studies

Pemigatinib (Pemazyre™) is a potent ATP-competitive selective inhibitor of FGFR1, FGFR2, and FGFR3 with half maximal inhibitor concentration (IC50) values of 0.4, 0.4, and 1 nmol/l, respectively, with weaker inhibition of FGFR4. Pemigatinib is highly selective for FGFR but has been shown to have mild inhibitor effects on vascular endothelial growth factor receptor 2 (IC50 182 nM and c-kit (IC50 266 nM).[25] *In vitro* studies showed reduction in phosphorylation of FGFR to basal levels at a concentration of just 5 nM of pemigatinib with concurrent downstream suppression of phospho-ERK and phospho-STAT5 in concentration-dependent manner. *In vivo* studies revealed significant tumor suppression in mice xenograph models with oral doses of 0.3 mg/kg in AML (FGFR1), cholangiocarcinoma (FGFR2), and urothelial carcinoma (FGFR3).[25] By sparing FGFR4, the effects on bile acid metabolism and subsequent hepatotoxicity can be mitigated.[26]

Phase 1 trials with pemigatinib

FGFR inhibitor therapy in oncology and hematology trial (FIGHT)-101 was a phase I/II, open label, three-part, dose escalation trial in patients

with pretreated advanced solid tumors with and without FGF/FGFR alterations who progressed after prior therapy with no effective standard therapy available.[27] In part 1, FGF/FGFR mutations were not required, and patients were enrolled into cohorts 1–3 (1–4 mg QD) with escalation following a 3+3 design (6–20 mg QD). Part 2 followed a dose expansion protocol for which FGF/FGFR mutations were required and additional patients were dosed at 13.5 mg or 20 mg QD. Part 3 included pemigatinib in combination with standard therapies. The most frequent all-cause, all-grade adverse events (AEs) were hyperphosphatemia (74%) and fatigue (40%) for 9/13.5 mg QD dose. Similar AEs were noted for the 20 mg dose. No dose-limiting toxicities were observed and recommended phase 2 dose was 13.5 mg QD.

Phase 2 trials with pemigatinib

The FIGHT-202 trial was a multicenter, open-label, single arm, multicohort phase 2 trial in patients aged >18 years old who developed disease progression following first-line treatment with an Eastern Cooperative Oncology Group (ECOG) of 0–2 from the United States, Europe, Middle East, and Asia.[17] Patients were enrolled to one of three cohorts: patients with FGFR2 fusions or rearrangements, patients with other FGF/FGFR mutations including mutations, amplifications, or deletions, or patients without FGF/FGFR mutations. All patients received 13.5 mg of oral pemigatinib daily (21-day cycles, 2 weeks on, 1 week off). Treatment was continued until disease progression or intolerable side effects. Tumor response was assessed by independent review according to RECIST 1.1. The primary end point was overall response rate (ORR). A total of 146 patients were included, 107 with FGFR2 fusions or rearrangements, 20 with other FGF/FGFR aberrations, and 18 without FGFR alterations. The most common FGFR2 partner was BICC1 (29%).

Overall median follow-up was 17.8 months with a median duration of treatment of 7.2 months (3.9–10.9) in patients with FGFR2 fusions or rearrangements and only 1.4 months (1.0–6.0) in patients with other FGF/FGFR fusions or rearrangements and 1.3 months (0.7–1.9) in patients without FGF/FGFR alterations. Across all cohorts, 57 patients (39%) had received two or more previous systemic therapies, representing a relatively heavily pretreated population. Of the 107 patients with *FGFR2* fusions or rearrangements, 105 (98%) had iCCA. This cohort represented a greater proportion of women, patients aged younger than 65 years, and patients with disease confined to the liver and included a smaller proportion of patients with an ECOG performance status of 2 than patients in the other cohorts.

Thirty eight (35.5%) of the 107 patients with confirmed FGFR2 fusions/rearrangements achieved a centrally confirmed objective response with 3 patients (2.8%) achieving a complete response. Eighty eight (82%) patients achieved disease control. The median time to first response was 2.7 months (IQR 1.4–3.9) with a median duration of response of responders was 7.5 months (95% CI 5.7–14.5). The median progression-free survival (PFS) was 6.9 months (95% CI 6.2–9.6) and median OS reported at 21.1 months (95% CI 14.8–NR). None of the patients with other FGF/FGFR alterations or without FGF/FGFR alterations had an objective response. Median PFS of patients with other FGF/FGFR fusions or rearrangements and without FGF/FGFR mutations was 2.1 and 1.7 months with OS of 6.7 and 4.0 months, respectively.

The most common AE across all three cohorts was hyperphosphatemia (60%); however, no grade 3–4 hyperphosphatemia was reported. Grade 3 hypophosphatemia was noted in 7% of patients. Additional common grade 1–2 AE included alopecia (46%), dysgeusia (38%), diarrhea (34%), fatigue (31%), stomatitis (27%), nausea (23%), arthralgia (11%), and palmar-plantar erythrodysesthesia (11%).

Future directions of pemigatinib in cholangiocarcinoma

Based on the results of the FIGHT-202, pemigatinib was granted accelerated FDA approval for the treatment of adults with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with a FGFR2 fusion or rearrangement in April 2020. This further led to the development of the phase III FIGHT-302 trial which is currently actively recruiting patients to evaluate the efficacy of pemigatinib versus standard chemotherapy in the first-line setting in unresectable or metastatic cholangiocarcinoma (NCT03656536). The trial is estimated to complete accrual in 2023 with estimated completion in 2026. The phase 1 trial, "A Phase I, Multi-Center, Open Label, Dose De-Escalation and Expansion

Study of Gemcitabine and Cisplatin with AG120 or pemigatinib for Advanced Cholangiocarcinoma," is actively recruiting patients and is set to determine the efficacy of pemigatinib in conjunction with gemcitabine and cisplatin in the first-line setting with an estimated completion date of 2025 (NCT04088188). Numerous other phase 2 and phase 3 studies are evaluating novel FGFR inhibitors in cholangiocarcinoma including Infigratinib (NCT02150967), Erdafitinib (NCT02699606), Derazantinib (NCT03230318), and Futibatinib (TAS-120) (NCT04093362). The overall response rates for these agents vary slightly in the second-line setting. The phase 2 trial evaluating Infigratinib in metastatic CCA has published an ORR of 23.1% with an mPFS of 7.3 months and mOS of 12.2 months. Notably, in their trial, 81% of patients have FGFR2 fusions and 19% had other FGFR2 rearrangements.[28] The phase 2 FOENIX-CCA2 study evaluated Futibatinib, an irreversible FGFR1–4 inhibitor in a similar patient population of metastatic CCA following systemic chemotherapy. They reported an ORR of 35.5% with an mPFS of 6.9 months and OS of 21.1 mo.[29] Derazanatinib, a potent FGFR1–3 kinase inhibitor with additional activity against colony stimulating factor-1 receptor, has reported ORR of 20.7% with an mPFS of 5.7 months.[30]

A subset of patients in both the FIGHT 101 and FIGHT 202 trials had rapid disease progression shortly after initiation of pemigatinib, suggesting the development of resistance to FGFR inhibition. Numerous mechanisms of acquired resistance have been demonstrated including activation of MET, PI3K/AKT/mTOR, Ephrin 3B, or EGFR.[31–33] A study evaluating genomic alterations in cell-free circulating DNA (ctDNA) in patients who recently progressed on FGFR2 inhibitor, infigratinib, revealed V565F gatekeeper point mutations in the FGFR2 kinase domain as well as significant inter and intralesional genetic heterogeneity.[30] Ongoing studies have shown that covalent binding of the ATP-binding pocket for FGFR with irreversible FGFR inhibitors may represent a mechanism to overcome such mutations; however, ongoing clinical efficacy data is needed.[34,35].

Expert opinion

Over the past 5 years, there has been tremendous growth in the area of FGFR inhibition in cholangiocarcinoma. We have seen the development of highly specific agents which has allowed for ongoing clinical efficacy despite the development of resistance through gatekeeper (V565) and molecular break (N550) mutations. Given the predictability in the development of these mutations in response to FGFR blockade, the use of ctDNA to monitor for the development of such mutations and subsequent adjustment in treatment may become mainstay. These resistant mutations have also been shown to be present in de novo disease, which would direct treatment decisions, further highlighting the need for genomic monitoring. In the landmark paper by Goyal, we observed the profound inter and intralesional genetic mutational heterogeneity that develops in response to FGFR inhibition, so direct biopsy of one metastatic lesion is likely inadequate for mutational monitoring.[36]

Highly selective and irreversible FGFR inhibitors are slowly coming to market. Most notably, futibatinib, a pan-FGFR irreversible antagonist, has been shown to produce clinical and radiographic responses in patients who had progression on prior FGFR inhibitors pemigatinib and infirgratinb.[29] Pemigatinib and infigratinib are not irreversible inhibitors and thus mutations in the FGFR binding site can lead to allosteric hindrance, preventing drug interaction and efficacy. The phase 2 FOENIX-CCA2 trial recently reported their updated results at the 2022 ASCO conference and report an ORR of 41.7% with a median OS of 20.0 months with hyperphosphatemia being the most common treatment-related AE at 85%. Data presented at ASCO 2022 suggest that futibatinib continues to have efficacy against gatekeeper mutations V565L; however, preliminary data may suggest that the V565F may continue to confer resistance. We anticipate the phase 3 FOENIX-CCA3 trial comparing futibatinib versus cisplatin plus gemcitabine in the first-line setting (NCT04093362). The most recent development in FGFR inhibitors comes out of the phase 1 data presented on drug RLY-4008, an oral, highly selective FGFR2 inhibitor to target both FGFR2 driver and resistance mutations. Most interestingly their preliminary data revealed that 100% of the previous FGFR inhibitor treated patients had stable disease with 9/16 patients with tumor reduction from −12 to −35%. Furthermore, 78% of the patients with detectable FGFR2 resistance mutation on ctDNA at baseline became undetected after one cycle of treatment.[37] Furthermore, given RLY-4008's highly specific target of FGFR2, the common side effects of hyperphosphatemia are mitigated significantly.

Given the existing evidence to suggest that targeted FGFR inhibitor therapy may be superior to chemotherapy in cholangiocarcinoma harboring FGFR2 fusions (mOS 6.2 months with FOLFOX *versus* 17.5 months with pemigatinib in second line), ongoing studies evaluating the efficacy of adjuvant or neoadjuvant FGFR inhibition in stages I–III cholangiocarcinoma is warranted. Clinical data to suggest benefit of adjuvant capecitabine is uncertain, given the absence of statistical significance of capecitabine in the intention to treat population of the BILCAP trial when compared to placebo (51.1 months *versus* 35.4 months), thus additional adjuvant treatments are needed.[38] Evaluating the use of targeted therapy in the adjuvant and neoadjuvant space is undoubtedly an area of growing interest and clinical need.

Declarations

Ethics approval and consent to participate

None.

Consent for publication

Not applicable.

Author contributions

Daniel Walden: Conceptualization; Investigation; Methodology; Writing – original draft; Writing – review & editing.

Cody Eslinger: Visualization; Writing – original draft; Writing – review & editing.

Tanios Bekaii-Saab: Conceptualization; Methodology; Supervision.

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Competing Interests

The authors declare that there is no conflict of interest.

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References

1. de Groen PC, Gores GJ, LaRusso NF, *et al.* Biliary tract cancers. *N Engl J Med* 1999; 341: 1368–1378.
2. Khan SA, Davidson BR, Goldin RD, *et al.* Guidelines for the diagnosis and treatment of cholangiocarcinoma: an update. *Gut* 2012; 61: 1657–1669.
3. Yamamoto M, Takasaki K, Otsubo T, *et al.* Recurrence after surgical resection of intrahepatic cholangiocarcinoma. *J Hepatobiliary Pancreat Surg* 2001; 8: 154–157.
4. Valle J, Wasan H, Palmer DH, *et al.* Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. *N Engl J Med* 2010; 362: 1273–1281.
5. Morizane C, Okusaka T, Mizusawa J, *et al.* Combination gemcitabine plus S-1 versus gemcitabine plus cisplatin for advanced/recurrent biliary tract cancer: the FUGA-BT (JCOG1113) randomized phase III clinical trial. *Ann Oncol* 2019; 30: 1950–1958.
6. Lamarca A, Hubner RA, David Ryder W, *et al.* Second-line chemotherapy in advanced biliary cancer: a systematic review. *Ann Oncol* 2014; 25: 2328–2338.
7. Fornaro L, Cereda S, Aprile G, *et al.* Multivariate prognostic factors analysis for second-line chemotherapy in advanced biliary tract cancer. *Br J Cancer* 2014; 110: 2165–2169.
8. Brieau B, Dahan L, De Rycke Y, *et al.* Second-line chemotherapy for advanced biliary tract cancer after failure of the gemcitabine-platinum combination: a large multicenter study by the Association des Gastro-Entérologues Oncologues. *Cancer* 2015; 121: 3290–3297.
9. Neuzillet C, Casadei Gardini A, Brieau B, *et al.* Prediction of survival with second-line therapy in biliary tract cancer: actualisation of the AGEO CT2BIL cohort and European multicentre validations. *Eur J Cancer* 2019; 111: 94–106.
10. Lamarca A, Palmer DH, Wasan HS, *et al.* Second-line FOLFOX chemotherapy versus active symptom control for advanced biliary tract cancer (ABC-06): a phase 3, open-label, randomised, controlled trial. *Lancet Oncol* 2021; 22: 690–701.
11. Yoo C, Kim KP, Jeong JH, *et al.* Liposomal irinotecan plus fluorouracil and leucovorin versus fluorouracil and leucovorin for metastatic biliary tract cancer after progression on gemcitabine plus cisplatin (NIFTY): a multicentre, open-label,

randomised, phase 2b study. *Lancet Oncol* 2021; 22: 1560–1572.

12. Silverman IM, Hollebecque A, Friboulet L, *et al.* Clinicogenomic analysis of FGFR2-rearranged cholangiocarcinoma identifies correlates of response and mechanisms of resistance to pemigatinib. *Cancer Discov* 2021; 11: 326–339.
13. Javle M, Churi C, Kang HC, *et al.* HER2/neu-directed therapy for biliary tract cancer. *J Hematol Oncol* 2015; 8: 58.
14. Zhu AX, Macarulla T, Javle MM, *et al.* Final overall survival efficacy results of ivosidenib for patients with advanced cholangiocarcinoma with IDH1 mutation: the phase 3 randomized clinical ClarIDHy trial. *JAMA Oncol* 2021; 7: 1669–1677.
15. Hezel AF, Noel MS, Allen JN, *et al.* Phase II study of gemcitabine, oxaliplatin in combination with panitumumab in KRAS wild-type unresectable or metastatic biliary tract and gallbladder cancer. *Br J Cancer* 2014; 111: 430–436.
16. Malka D, Cervera P, Foulon S, *et al.* Gemcitabine and oxaliplatin with or without cetuximab in advanced biliary-tract cancer (BINGO): a randomised, open-label, non-comparative phase 2 trial. *Lancet Oncol* 2014; 15: 819–828.
17. Abou-Alfa GK, Sahai V, Hollebecque A, *et al.* Pemigatinib for previously treated, locally advanced or metastatic cholangiocarcinoma: a multicentre, open-label, phase 2 study. *Lancet Oncol* 2020; 21: 671–684.
18. Rizzo A, Ricci AD and Brandi G. Futibatinib, an investigational agent for the treatment of intrahepatic cholangiocarcinoma: evidence to date and future perspectives. *Expert Opin Investig Drugs* 2021; 30: 317–324.
19. Javle MM, Murugesan K, Shroff RT, *et al.* Profiling of 3,634 cholangiocarcinomas (CCA) to identify genomic alterations (GA), tumor mutational burden (TMB), and genomic loss of heterozygosity (gLOH). J Clin Oncol 2019; 37: 4087.
20. Lowery MA, Ptashkin R, Jordan E, *et al.* Comprehensive molecular profiling of intrahepatic and extrahepatic cholangiocarcinomas: potential targets for intervention. *Clin Cancer Res* 2018; 24: 4154–4161.
21. Hallinan N, Finn S, Cuffe S, *et al.* Targeting the fibroblast growth factor receptor family in cancer. *Cancer Treat Rev* 2016; 46: 51–62.
22. Gallo LH, Nelson KN, Meyer AN, *et al.* Functions of fibroblast growth factor receptors in cancer defined by novel translocations and mutations. *Cytokine Growth Factor Rev* 2015; 26: 425–449.
23. Arai Y, Totoki Y, Hosoda F, *et al.* Fibroblast growth factor receptor 2 tyrosine kinase fusions define a unique molecular subtype of cholangiocarcinoma. *Hepatology* 2014; 59: 1427–1434.
24. Zou S, Li J, Zhou H, *et al.* Mutational landscape of intrahepatic cholangiocarcinoma. *Nat Commun* 2014; 5: 5696.
25. Liu PCC, Koblish H, Wu L, *et al.* INCB054828 (pemigatinib), a potent and selective inhibitor of fibroblast growth factor receptors 1, 2, and 3, displays activity against genetically defined tumor models. *PLoS One* 2020; 15: e0231877.
26. Mellor HR. Targeted inhibition of the FGF19-FGFR4 pathway in hepatocellular carcinoma; translational safety considerations. *Liver Int* 2014; 34: e1–e9.
27. Saleh M, Gutierrez M, Subbiah V, *et al.* *Preliminary results from a phase I/II study of INCB054828, a highly selective fibroblast growth factor receptor (FGFR) inhibitor, in patients (pts) with advanced malignancies. Paper presented at the AACR-NCI-EORTC International Conference: Molecular Targets and Cancer Therapeutics*, 26–30 October 2017, Philadelphia, PA.
28. Javle M, Roychowdhury S, Kelley RK, *et al.* Infigratinib (BGJ398) in previously treated patients with advanced or metastatic cholangiocarcinoma with FGFR2 fusions or rearrangements: mature results from a multicentre, open-label, single-arm, phase 2 study. *Lancet Gastroenterol Hepatol* 2021; 6: 803–815.
29. Golay L, MericBernstam F, Hollebecque A, *et al.* FOENIX-CCA2: a phase II, open-label, multicenter study of futibatinib in patients (pts) with intrahepatic cholangiocarcinoma (iCCA) harboring FGFR2 gene fusions or other rearrangements. *J Clin Oncol* 2020; 38: 108.
30. Mazzaferro V, El-Rayes BF, Droz Dit Busset M, *et al.* Derazantinib (ARQ 087) in advanced or inoperable FGFR2 gene fusion-positive intrahepatic cholangiocarcinoma. *Br J Cancer* 2019; 120: 165–171.
31. Kim SM, Kim H, Yun MR, *et al.* Activation of the Met kinase confers acquired drug resistance in FGFR-targeted lung cancer therapy. *Oncogenesis* 2016; 5: e241.

32. Lee SY, Na YJ, Jeong YA, *et al*. Upregulation of EphB3 in gastric cancer with acquired resistance to a FGFR inhibitor. *Int J Biochem Cell Biol* 2018; 102: 128–137.
33. Datta J, Damodaran S, Parks H, *et al*. Akt activation mediates acquired resistance to fibroblast growth factor receptor inhibitor BGJ398. *Mol Cancer Ther* 2017; 16: 614–624.
34. Javle M, Lowery M, Shroff RT, *et al*. Phase II study of BGJ398 in patients with FGFR-altered advanced cholangiocarcinoma. *J Clin Oncol* 2018; 36: 276–282.
35. Kalyukina M, Yosaatmadja Y, Middleditch MJ, *et al*. TAS-120 cancer target binding: defining reactivity and revealing the first fibroblast growth factor receptor 1 (FGFR1) irreversible structure. *ChemMedChem* 2019; 14: 494–500.
36. Goyal L, Saha SK, Liu LY, *et al*. Polyclonal secondary FGFR2 mutations drive acquired resistance to FGFR inhibition in patients with FGFR2 fusion-positive cholangiocarcinoma. *Cancer Discov* 2017; 7: 252–263.
37. Goyal L, Borad M, Subbiah V, *et al*. Abstract P02-02: first results of RLY-4008, a potent and highly selective FGFR2 inhibitor in a first-in-human study in patients with FGFR2-altered cholangiocarcinoma and multiple solid tumors. *Mol Cancer Ther* 2021; 20: P02-02.
38. Primrose JN, Fox RP, Palmer DH, *et al*. Capecitabine compared with observation in resected biliary tract cancer (BILCAP): a randomised, controlled, multicentre, phase 3 study. *Lancet Oncol* 2019; 20: 663–673.