Editorial Commentary

Futibatinib: new targeted therapy in intrahepatic cholangiocarcinoma

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Biliary tract tumors are a heterogenous group of cancers that includes extrahepatic cholangiocarcinoma, hilar cholangiocarcinoma, gallbladder tumor as well as intrahepatic cholangiocarcinoma (ICCA) (1). Biliary tract tumors are uncommon tumors representing 2% of all newly diagnosed cancers in the United States. The incidence of ICCA is increasing worldwide and associated with a dismal prognosis, and the 5-year overall survival (OS) rate is not exceeding 8% (1). Surgery remains the main curative treatment. However, nearly two thirds of patients experienced disease relapse (1). Systemic treatment is considered in patients with unresectable recurrent and/or metastatic cholangiocarcinoma. The standard first-line treatment consists of the combination of durvalumab, a programmed death ligand-1 (PD-L1) inhibitor, in combination with gemcitabine and platinum according to the phase III TOPAZ-1 trial (2). The phase III KEYNOTE-966 trial that added pembrolizumab to gemcitabine and platinum chemotherapy also found a significant improvement of OS (3). Fluoropyrimidine [5-fluorouracil (5-FU)]-based chemotherapy is recommended as second-line treatment and associated with a response rate of around 5%. In the TOPAZ-1 and KEYNOTE-966 trials, the median OS does not exceed 13 months suggesting that novel therapeutic approaches are needed (2,3).

In fact, genetic alterations, including *FGFR2*, *BRAF* V660E, *HER2*, *NTRK*, *IDH1*, and *RET* are found in nearly 80% of patients with ICCAs. The fibroblast growth factor receptor (FGFR) family consists of four transmembrane receptors, FGFR1–4. These receptors are activated in 10% to 30% of tumors. Notably, *FGFR2* fusions or rearrangements are found in 10% to 20% ICCAs (4,5).

Pemigatinib and infigratinib are two selective, reversible FGFR1–3 inhibitors that have been approved by the Food and Drug Administration (FDA) for the treatment of patients with unresectable or metastatic cholangiocarcinomas harboring *FGFR2* fusions or rearrangements. The overall response rates (ORR) were 35.5% with pemigatinib and 23.1% with infigratinib in the two phase II trials (6,7). However, the production of infigratinib was interrupted by the manufacturer. The PROOF trial, a phase III trial that aimed to randomize and compare infigratinib with standard gemcitabine-cisplatin chemotherapy was terminated by the sponsor (NCT03773302). Moreover, the ongoing FIGHT-302 phase III trial is comparing pemigatinib with gemcitabine plus cisplatin in the first-line treatment in advanced and/or metastatic cholangiocarcinoma harboring FGFR2 rearrangements (NCT03656536).

Futibatinib, previously called TAS-120, is a new drug that has been evaluated for the treatment of ICCAs. Futibatinib is a highly selective, potent FGFR1–4 inhibitor binding covalently and irreversibly to a conserved cysteine residue

of the kinase domain P-loop structure. The irreversible binding and the different binding site render TAS-120 less susceptible to on-target drug resistance mutations than other reversible adenosine triphosphate (ATP)-competitive inhibitors such as infigratinib and pemigatinib. In fact, preclinical data demonstrated that futibatinib is active against several mutations of the FGFR2 kinase domain (8).

Futibatinib was investigated in two phase I trials. The first one was the Japanese JapicCTI-142552 that evaluated the efficacy and safety of futibatinib in patients with solid tumors harboring FGFR or FGF/FGFR abnormalities with no remaining standard treatment available. Futibatinib was associated with an ORR of 11.5%. There were no dose-limiting toxicities and the maximum-tolerated dose (MTD) was not reached. The dosage of 20 mg once daily was chosen as the recommended dose for phase II studies. Futibatinib was well tolerated. Hyperphosphatemia was the most frequent adverse event which is an on-target effect related to decreased FGF23-FGFR1 signaling leading to increased phosphate reabsorption and hyperphosphatemia in proximal tubules (9). In parallel, the FOENIX-101 is a multicenter phase I trial that also evaluated futibatinib in previously treated solid tumors with FGF/FGFR aberrations. This trial investigated the safety and tolerability of futibatinib when given three times a week versus a continuous daily usage. The MTD was 20 mg once daily and associated with an acceptable safety profile. Hyperphosphatemia was also the most common adverse event. The activity of futibatinib was mainly seen in ICCAs with an ORR of 25.4% in the dose expansion cohort (10).

Based on the encouraging results of futibatinib in patients with cholangiocarcinoma in the phase I trials, the registrational FOENIX-CCA2 phase II trial was launched. Patients with unresectable or metastatic cholangiocarcinoma, harboring *FGFR2* fusion or rearrangement, previously treated with gemcitabine and platinum-based chemotherapy were included. Previous treatment with FGFR inhibitor was an exclusion criterion. Oral futibatinib was given at a dosage of 20 mg of once daily in a continuous dosing schedule over a 21-day cycle. Primary endpoint was objective response. The study enrolled 103 of pretreated patients of whom 53% had received two or more prior treatment lines. Of the entire cohort, 78% of patients (80/103) had *FGFR2* fusions, while 20% had rearrangements with unidentified partner genes. The ORR was 42% (43/103 patients) as assessed by an independent center radiology review and the disease control rate (DCR) was 82.5%. The median time to response was 2.5 months and the median duration of response was 9.7 months. Interestingly, responses were observed among patient subgroups especially heavily pretreated patients, older adults, and notably patients with co-occurring *TP53* mutations. At a median follow-up of 17.1 months, the median progression-free survival (PFS) was 9 months and the median OS was 21.7 months. Moreover, the authors evaluated the impact of the fusion partner and co-occurring mutations on the response to futibatinib. The median PFS did not differ among patients with or without *BAP1* alterations as well as among patients with and those without *TP53* mutations (8).

Concerning the safety of futibatinib, all enrolled patients presented one or more adverse event and the safety profile was comparable to that observed with other FGFR inhibitors. The most frequent treatment-related adverse events (TRAEs) were hyperphosphatemia as expected and reported in 85% of patients followed by alopecia (33%), dry mouth (30%) and diarrhea (28%). The most common grade 3 TRAEs was hyperphosphatemia (30% of patients) and no treatment-related death occurred. To be noted that only two patients permanently discontinued treatment due to TREAs (8).

Overall, futibatinib contributed to durable responses and survival that was higher than those reported with historical data The promising activity of futibatinib and its acceptable safety profile in the FEONIX-CCA2 phase II trial led to accelerated approval by the US FDA of futibatinib for the treatment of adult patients with previously treated, unresectable, locally advanced or metastatic ICCA harboring *FGFR2* gene fusions or other rearrangements. Futibatinib is currently under investigation in first-line setting in a randomized phase III trial (FOENIX-CCA3, NCT04093362) in comparison with gemcitabine plus cisplatin in cholangiocarcinoma harboring *FGFR2* fusion or rearrangement.

The efficacy of FGFR inhibitors is counterbalanced by the appearance of primary or secondary resistance. Primary resistance is seen in specific genetic alterations with other co-occurring tumor-suppressing genes. Recently, Silverman and colleagues reported a tendency towards lower PFS among patients with cholangiocarcinoma harboring *FGFR2* fusions with *BAP1*, *CDKN2A/B*, *PBRM1* and *TP53* (11). Concerning acquired resistance, Goyal *et al.* described the genetic mechanisms of acquired resistance to FGFR inhibitors in patients with ICCA harboring *FGFR2* fusions. The most common mutation was V565F gatekeeper mutation and two patients presented secondary mutations

in the FGFR2 kinase domain (12). Goyal and colleagues also demonstrated that futibatinib was effective in patients with acquired resistance to infigratinib or Debio 1347 and overcomes several *FGFR2* mutations in ICCA models (13).

Recent reports reported that the most common acquired resistance mutations to pan-FGFR inhibitors include mutations in the kinase domain at the gatekeeper residue (FGFR2$^{V564F/L/I}$) as well as FGFR2$^{N549K/D/H}$ and FGFR2$^{K6549N/M}$ mutations that contribute to ligand-independent kinase activation. These mutations were found in nearly 50% of patients treated with pan-FGFR inhibitors at progression (14). RLY-4008 is a highly selective, irreversible, small-molecule FGFR2 inhibitor that was designed to overcome pan-FGFR inhibitors limitations via targeting of FGFR2 alterations as well as resistance mutations. ReFocus is a first-in-human phase I/II trial evaluating RLY-4008 in patients with cholangiocarcinoma and other solid tumors harboring *FGFR2* fusion or rearrangement. The recommended phase II dose is 70 mg daily. The ORR in patients with FGFR inhibitor-naïve patients with *FGFR2* fusion-positive cholangiocarcinoma was 73% (n=11). Moreover, the ORR was 21% in FGFR inhibitor-pretreated patients (n=14) in the dose-escalation portion (15). These data suggest that RLY-4008 is effective in both FGFR inhibitor-naïve and pretreated patients with cholangiocarcinoma.

The above data are just another step in the new era for the treatment of patients with cholangiocarcinoma. However, multiple questions remain to be answered: are we moving towards a strategy similar to non-small cell lung cancer? Should we hold back on the use of chemo-immunotherapy at earlier lines and switch to sequencing several lines of FGFR inhibitors? And if so, what is the best FGFR inhibitors sequence? Should immunotherapy be used in combination with FGFR inhibitors in first-line setting or kept for later lines?

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