Editorial

The future is here—targeted therapies are coming of age in biliary tract cancers

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Biliary tract cancer (BTC) is a rare human tumor entity comprising intrahepatic, extrahepatic and gallbladder malignancies. The overall prognosis of advanced and metastatic disease stages remains unsatisfactory with a median survival of about 1 year only. While conventional chemotherapy regimens (e.g., gemcitabine or 5-fluorouracil combinations) still remain important treatment options, the broader availability of mutational and genomic analyses via next-generation sequencing technologies provided an opportunity for novel targeted therapies in distinct subpopulations of BTC (*Figure 1*). As summarized by Banales *et al.*, heterogeneous signaling pathways are involved in cholangiocarcinogenesis. These processes are further complicated by the interplay of extracellular ligands within the tumor microenvironment with increased expression and/or aberrant activation of cell surface receptors in combination with deregulated intracellular signaling pathways (such as *KRAS*, *BRAF*, *ARID1*, *PBRM1*, *BAP1*, *IDH1*, and *IDH2*) (4).

LaPelusa *et al.* have comprehensively summarized some of those novel therapeutic approaches and showed that especially *FGFR2*- and *IDH1*-targeting agents achieve clinically meaningful responses in the intrahepatic subtype of BTC (5). The small molecule fibroblast growth factor receptor (FGFR) inhibitor futibatinib recently received Food and Drug Administration (FDA) approval for the treatment of intrahepatic cholangiocarcinomas harboring *FGFR2* gene rearrangements (6). Unfortunately, these compounds work only in a minor subset of patients due to the low prevalence of these alterations, which is highest in intrahepatic cholangiocarcinomas [*FGFR2* fusions: up to 15% (7), *IDH1* mutations: approximately 13% (8)]. Recent comprehensive sequencing analyses revealed that potentially actionable mutations could be found in approximately 27% of extrahepatic cholangiocarcinomas and 50% of intrahepatic cholangiocarcinomas and gallbladder cancers, respectively (9,10). This supports the need to look in more detail into the mode of gene alterations (gene fusions/arrangements, mutations or amplifications) for diagnostic and therapeutic purposes (11). Overall, these numbers underline the importance of identifying novel therapeutic targets and approaches to overcome resistance development (12) and improve the poor overall response rate and prognosis for patients with BTC. Especially, resistance to targeted therapy of BTC is an often observed clinical situation which could be related to different molecular mechanisms of

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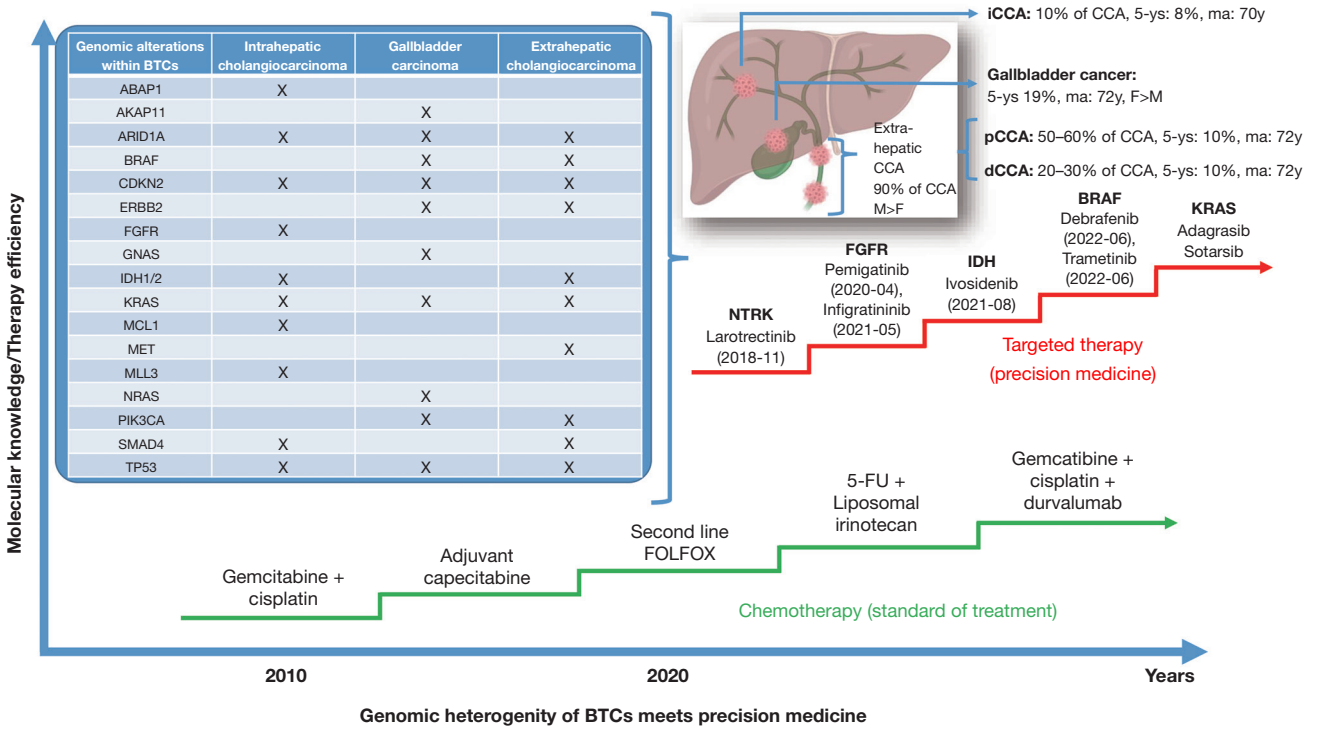

Figure 1 The figure gives an overview of the time (FDA approval date in brackets) of classical chemotherapy and targeted therapy of BTCs, on the one hand, and a view of genomic alterations (most frequent genetic aberrations) and basic clinico-pathological findings of BTCs (created with BioRender), information taken from (1-3), on the other hand. BTC, biliary tract cancer; ABAP1, armadillo BTB Arabidopsis protein 1; AKAP11, A-kinase anchoring protein 11; ARID1A, AT-rich interactive domain-containing protein 1A; BRAF, proto-oncogene B-Raf; CDKN2, cyclin-dependent kinase inhibitor 2A; ERBB2, V-erb-b2 erythroblastic leukemia viral oncogene homolog 2; FGFR, fibroblast growth factor receptor; GNAS, guanine nucleotide binding protein, alpha stimulating activity polypeptide; IDH1/2, isocitrate dehydrogenase 1/2; KRAS, Kirsten rat sarcoma viral oncogene; MCL1, myeloid cell leukemia-1; MET, mesenchymal epithelial transition; MLL3, mixed-lineage leukemia protein 3; NRAS, neuroblastoma RAS viral oncogene homolog; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; SMAD4, SMA- and MAD-regulated protein 4; TP53, tumor protein p53; iCCA, intrahepatic cholangiocarcinoma; CCA, cholangiocarcinoma; 5-ys, 5-year survival; ma, median age; F, female; M, male; pCCA, perihilar cholangiocarcinoma; dCCA, distal cholangiocarcinoma; NTRK, neurotrophic tyrosine receptor kinase; FOLFOX, folinic acid, fluorouracil and oxaliplatin; 5-FU, 5-fluorouracil; FDA, Food and Drug Administration.

chemoresistance (MOC) like changes of drug transporters (MOC 1a), changes in drug molecular targets (MOC 3a), activation of alternative signaling pathways through other growth receptors (MOC 3b), drug-induced selection of tumor cell subclones (MOC 3c) or changes in the balance between pro- and anti-apoptotic proteins (MOC 5a/b) indicating the complexity of such targeted therapies in BTCs (12).

Immune checkpoint inhibitors have become a mainstay of modern oncology. LaPelusa *et al.* also highlight recent studies using immune checkpoint inhibitor antibodies alone or in combination with chemotherapy or targeted agents in BTC. Similar to other solid tumors, overall response rates do not exceed 40% although some responses are durable (5). The combination of durvalumab, gemcitabine and cisplatin received FDA approval based on the phase 3 TOPAZ-1 study. Although objective response rate was 26.7% in the triple combination *vs.* 18.7% for chemotherapy only, addition of durvalumab to the chemotherapy backbone more than doubled overall survival at 24 months, reaching 24.9% *vs.* 10.4% without significantly increasing toxicity (13).

In BTC, too, there still is debate on predictivity of tumor mutational burden (TMB), programmed death ligand 1 (PD-L1) expression level and DNA mismatch repair/

microsatellite stability, which overall show low expression or positivity in BTC (10,14). Novel targets regulating the tumor-immune microenvironment include *LAG3*, *TIGIT*, or *CD47/SIRPα* are currently explored in early clinical studies but no clinical data for BTC is available yet (15-17).

mRNA based cancer vaccines are considered the next step in immuno-oncology and several early clinical studies explore various tumor-antigens like carcinoembryonic antigen (CEA), modified *KRAS*, tyrosinase or novel antigens like *CD247*, *FCGR1A*, or *TRAP* in BTC (18,19). Other novel experimental approaches include the use of antibody-drug conjugates, e.g., targeting anti-glypican-1 or FGFR2 (20,21), or enhancing the efficacy of photodynamic therapy by coupling a photosensitizer to a TROP2-targeting antibody (22). Also, several approaches using chimeric antigen receptor (CAR)-T cells have been explored that included BTC patients (23) but data on their clinical efficacy are still pending.

LaPelusa *et al.* also highlight the importance of non-invasive detection and monitoring of alterations in BTC (5). This is crucial for early detection but also to understand the mode of action and potential mechanisms of resistance against these novel therapies. Driver alterations like *IDH1* mutation or *FGFR2* fusions can already be reliably detected from circulating DNA samples (24,25). Further technical refinements and broader availability of such technologies will increase the number of patients who can actually benefit from these novel therapies.

Finally, an important aspect of all targeted therapies, especially in BTC, is a tissue-based problem: With the exception of most intrahepatic BTCs, all other forms of BTC are anatomically difficult for radiologists, endoscopists or surgeons to obtain diagnostically relevant and sufficient tumor tissue. As a result, the time between diagnosis and the start of any targeted therapy is too long, and the amount of BTC tissue available is usually minimal. The small amount of tumor tissue raises the question which next step of biomarker analysis (immunohistochemistry, *in situ* hybridization, panel or whole genome sequencing) should be performed. Therefore, an intensive interaction of all clinical and molecular stakeholders in the care process of patients with BTCs is necessary to get deep and detailed molecular information as soon as possible.

In summary, several promising novel targets and therapeutic modalities are currently investigated in the various subtypes of BTCs. The increasing use of molecular diagnostics like next-generation sequencing panels or the development of circulating DNA technologies increases the probability to find an actionable alteration that could lead to improved overall survival for patients with BTC. The field is quickly moving away from unselected chemotherapy combinations into the era of advanced precision medicine in a real-world scenario.

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