Current and Future Systemic Therapies in Biliary Tract Cancer

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Abstract
Background: Despite an increasing incidence, biliary tumors are still considered a rare tumor entity. Due to an often long clinically inapparent course and a lack of early detection strategies, surgical resection is often not possible at the time of diagnosis. Since 2010, chemotherapy with gemcitabine and cisplatin is considered the standard of care in the palliative situation. Only recently, first studies have been published or initiated that expand the treatment options in the first line and, for the first time, also suggest valid systemic approaches in the second line. Summary: Molecularly targeted therapies in selected patient subgroups are rapidly changing the field. In addition to IDH1 mutations and FGFR2 fusions in patients with intrahepatic tumors, the therapeutic relevance of rare but targetable alterations such as HER2/neu amplification, NTRK fusions, or BRAF mutations should be considered in patients with biliary tract cancers. Key Message: The current study landscape clearly shows that precision medicine will play an important role in the therapy of biliary malignancies and underlines the importance of early tumor genetic diagnostics. In this article we provide an overview of systemic therapy concepts in the adjuvant and palliative setting.

Introduction
Cancers of the biliary system (BTC) are highly aggressive tumors that either originate within the liver (intrahepatic cholangiocarcinoma [iCCA]), in the perihilar or distal bile ducts (perihilar or distal CCA), or in the gallbladder [1]. In most countries, CCA is considered a “rare” cancer with incidence rates below 6/100,000. However, due to the demographic distribution of different risk factors and probably influenced by ethnic factors, the incidence of CCA ranges from 0.1/100,000 in Australia to more than 110/100,000 in northeast Thailand. In Europe, most biliary tumors occur sporadically after the age of 50, with a slight predominance of male patients. Risk factors include obesity, viral hepatitis B and C, primarily sclerosing cholangitis, and, for gallbladder carcinoma, gallstones. In Asian countries, infestation with parasitic liver flukes is considered an important risk factor. As the only potentially curative therapy, surgical resection should be offered to patients who are diagnosed at an early stage. However, due to the late manifestation of clinical symptoms, most patients suffer from locally advanced or metastatic disease at the time of diagnosis, and even after successful resection early recurrence is frequent. Therefore, most patients are eventually bound to receive palliative treatments. Unfortunately, BTCs are relatively chemoresistant tumors, and the median overall survival (mOS) of 11–13 months under systemic palliative therapy with gemcitabine and cisplatin highlights the urgent need for new therapeutic approaches [2, 3].

In the following, we provide an overview of the treatment strategies that are currently available, or are under clinical consideration, for the systemic treatment of biliary cancers.

Adjuvant Therapy
The high 3-year rate of recurrence that can be up to 80% [4, 5] after curatively intended resection has led to an intensive discussion about the importance of adjuvant
therapy concepts. Until 2017, the use of adjuvant treatment was based on meta-analyses from mostly small retrospective phase II studies, which suggested that specifically two high-risk populations benefit from postoperative chemotherapy in terms of mOS: patients with nodal-positive disease and following R1 resection [6, 7]. A similar trend was also observed in our own patient population in a retrospective matched pair analysis [8].

Recently, three prospective randomized clinical trials have been published in which different adjuvant chemotherapy concepts were investigated: the French PRODIGE-12, the Japanese BCAT, and the British BILCAP study. The French PRODIGE-12/ACCORD-18 study, first published in 2017, showed no benefit of adjuvant gemcitabine/oxaliplatin (GemOx) compared to observation alone in patients with CCA and GBC in terms of RFS (30.4 months vs. 18.5 months in the observation arm; HR 0.88; 95% CI 0.62–1.25; \( p = 0.48 \)) [9]. Similarly, the Japanese BCAT study evaluating gemcitabine as a monotherapy in the adjuvant arm in a 225-patient population was negative for RFS (median 36.0 vs. 39.9 months; HR 0.93; 95% CI 0.66–1.32; \( p = 0.693 \)) and OS (62.3 vs. 63.8 months; HR 1.01; 95% CI 0.70–1.45; \( p = 0.964 \)) [10].

The BILCAP study was conducted in the UK over a period of 11 years and is the largest study involving both CCC and GBC patients. The study did not meet its primary endpoint in terms of mOS in the ITT population; however, a pre-specified ITT sensitivity analysis adjusted for prognostic factors (lymphonodal status, tumor grading, and sex) revealed a significantly longer mOS in the capecitabine arm compared to the observation arm (53 months vs. 36 months; HR 0.75; 95% CI 0.58–0.97; \( p = 0.028 \)) [11]. In the ITT analysis, there was also a trend for a longer median RFS in the capecitabine arm compared to observation (24.4 months vs. 17.5 months; HR 0.81; 95% CI 0.63–1.04; \( p = 0.097 \)). Based on the available results, the control arm was adjusted in the currently recruiting German ACTICCA study (NCT02170090): gemcitabine and cisplatin are now compared to capecitabine (Xeloda) rather than to observation.

Despite the lack of a formally positive prospective study, we believe that, based on the published data, adjuvant treatment with capecitabine for 6 months should be discussed with patients following resection. To what extent an intensification of the adjuvant therapy with gemcitabine and cisplatin is necessary or meaningful cannot yet be decided. Adjuvant and/or neoadjuvant therapy concepts may be especially beneficial in patients with a high risk of very early relapse. A recent study showed that very early recurrence within 6 months after surgery occurs in almost 25% of iCCA patients and is associated with a dismal mOS of 13.8 months and a 5-year OS of 8.9%, compared to 59.7 months and 49.8% (\( p < 0.001 \)) in patients without very early recurrence [5]. Not surprisingly, tumor size (OR 1.11), number of tumors (OR 1.36), microvascular invasion (OR 1.55), N1 or Nx status (OR 1.94), and R1 resection (OR 2.14) were associated with a higher probability of early recurrence. Complementing these clinical parameters, the detection of circulating tumor DNA will most likely help in the future to identify patients with a high risk of relapse, who should receive either adjuvant therapy or at least a close follow-up.

**Palliative Therapy**

**First Line**

The ABC-02 phase-III study, published in 2010, and the Japanese BT22 phase II study established the combination of gemcitabine and cisplatin in the first-line treatment of BTC [3, 12, 13]. As an alternative platinum-based regimen, the combination of gemcitabine with oxaliplatin has been investigated in several phase II trials and showed comparable efficacy and safety [14]. In addition, a South Korean phase III trial recently confirmed the non-inferiority of oxaliplatin and capecitabine (XelOx) compared to GemOx [15]. Similar to pancreatic cancer, a phase II trial tested gemcitabine/nab-paclitaxel in the first-line setting and showed comparable efficacy to Gem-Cis, although a direct randomized comparison of the two therapies has not yet been performed [16]. The phase Ib ABC-08 trial investigated cisplatin in combination with NUC-1031, a phosphoramidate variant of gemcitabine that bypasses basic resistance mechanisms to the nucleoside analogue. Based on a remarkable ORR of 63.6%, the combination is currently pursued in a phase III trial (NCT04163900) [17].

The extent to which a further intensification of chemotherapy with a triplet is possible and useful has been addressed in various studies, including a trial in which nab-paclitaxel was combined with cisplatin and gemcitabine [18]. Despite a toxicity-related reduction of the gemcitabine dose, the study reached a mPFS of 11.8 months (95% CI 6.0–15.6 months) with a DCR of 84%, and an impressive mOS of 19.2 months. This combination is currently being compared directly with the standard of care (GemOx) in the first-line setting and showed comparable efficacy to Gem-Cis, although a direct randomized comparison of the two therapies has not yet been performed [16]. The phase Ib ABC-08 trial investigated cisplatin in combination with NUC-1031, a phosphoramidate variant of gemcitabine that bypasses basic resistance mechanisms to the nucleoside analogue. Based on a remarkable ORR of 63.6%, the combination is currently pursued in a phase III trial (NCT04163900) [17].
versus 14.3 months in the standard therapy arm (95% CI 11.3–16.5). Based on these data, this triplet will not be further investigated in the originally planned phase III study.

In all studies on BTC, the composition of the trial populations should be taken into account, as the prognostic significance of tumor localization is becoming increasingly apparent. A recent combined post-hoc analysis of the ABC-01/02/03 studies revealed that the mOS of patients with intrahepatic CCAs was approximately 4 months longer than that of patients with biliary tumors that originated in other locations, suggesting a more prolonged course of disease especially in patients with liver-limited iCCA [20].

**Second Line**

Until recently, the efficacy of second-line therapy in patients with advanced biliary tumors was not proven. In a systematic analysis involving nearly 700 patients from 14 phase II studies and several retrospective analyses and case reports, the mPFS and mOS were 3.2 and 7.2 months, respectively, after the start of second-line chemotherapy [21].

The British ABC-06 study presented at ASCO 2019 was the first phase III study that evaluated a second-line approach after first-line therapy with GemCis: mFOLFOX led to a 15% improvement of both the 6- and 12-month survival in ECOG 0/1 patients compared to observation. The chemotherapy arm had a moderately improved mOS of 6.2 months, compared to 5.3 months in the control arm (HR = 0.69; 95% CI 0.5–0.97; \( p = 0.031 \)). As a note of caution it should be mentioned that, according to the recommendations in the United Kingdom, the majority of patients receive a predetermined number of treatments in first line (8 cycles of GemCis), whereas patients in most other countries, including Germany, are more frequently treated until disease progression. The extent to which oxaliplatin-based chemotherapy after cisplatin actually leads to a clinically significant prolongation of survival in patients who progressed under GemCis is not proven. In a Dutch single-arm phase II trial, promising results were shown for the use of FOLFIRINOX in fit patients with a DCR of 67%, a PFS of 6.2 months (95% CI 5.5–15.4) [22]. The mOS for sequential GemCis, followed by FOLFOX, was 18.5 months (95% CI 13.5–21.4). In daily clinical life, an escalation from doubled to triplet chemotherapy should be considered until disease progression. The extent to which oxaliplatin-based chemotherapy after cisplatin actually leads to a clinically significant prolongation of survival in patients who progressed under GemCis is not proven. In a Dutch single-arm phase II trial, promising results were shown for the use of FOLFIRINOX in fit patients with a DCR of 67%, a PFS of 6.2 months (95% CI 5.5–15.4) [22]. The mOS for sequential GemCis, followed by FOLFOX, was 18.5 months (95% CI 13.5–21.4). In daily clinical life, an escalation from doubled to triplet chemotherapy is, however, highly unlikely, and the triplet may – if at all – be considered in the first-line setting. In Germany, the AIO NALIRICC study currently investigates the efficacy of Nal-IRI in combination with 5-FU versus 5-FU alone (NCT03043547) in the second-line setting.

In summary, based on the currently available data, second-line chemotherapy should be offered to fit patients who progress on first-line therapy. We usually recommend a 5-FU-based combination with irinotecan or oxaliplatin, alternatively 5-FU or capecitabine monotherapy may be considered.

**Targeted Therapies**

To date, all studies that employed molecular therapies in unselected BTC cohorts were negative, including antiangiogenetic agents [2, 23]. Even in RAS WT patients, epidermal growth factor receptor (EGFR)-directed therapy failed to show added value over the chemotherapeutic backbone GemCis [24]. In recent years, a detailed characterization of the molecular landscape of biliary tumors has been conducted and revealed that BTCs are a genetically heterogeneous group of malignancies. However, these studies also identified a subset of recurrent and treatable alterations. Especially in patients with iCCA, nearly 40% of patients harbor genetic alterations which are potential targets for precision medicine [25–27]. If tumor tissue is available, we recommend that molecular analysis should be performed preferentially already before or during first-line therapy in order to evaluate options for second and higher lines early during the course of treatment. In particular, the following genetic alterations should be considered:

**IDH1/2**

The neomorphic activity of the mutant IDH1/2 enzymes results in an increased production of the oncometabolite 2-hydroxyglutarate (2-HG) from α-ketoglutarate. In preclinical models, 2-HG leads to a number of protumorigenic changes in multiple tumors including BTC. The most common, clinically relevant mutations in IDH1 and -2 occur at amino acid positions 132 (R132) and 172 (R172), respectively. These mutations are found in about 10–20% of iCCA patients but are likely without prognostic significance.

Ivosidenib is an oral inhibitor of the mutant IDH1 enzyme and thus far the only targeted agent that has successfully completed a phase III trial in CCA. In the ClarIDHy phase III study, the efficacy of ivosidenib was evaluated in comparison to placebo in 185 IDH1 mutant CCA patients who progressed on first-line therapy [28]. Patients were randomized to ivosidenib or placebo at a 2:1 ratio and crossover to ivosidenib was permitted in the placebo arm after progression. The primary endpoint – an improvement in PFS – was achieved with an impressive HR of 0.37 (95% CI 0.25–0.54; \( p < 0.001 \)) but with a mPFS of only 2.7 months for ivosidenib compared to 1.4 months for placebo. Regardless of the minor absolute PFS difference and the low radiological response rate of 2.4%, PFS rates at 6 and 12 months were clinically relevant (32.0 and 21.9% in the ivosidenib arm at 6 and 12 months, re-
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FGFR2
FGF receptor alterations in malignant tumors include amplifications and mutations as well as oncogenic fusions. These FGFR2 fusions occur in up to 15% of ICCa patients and are caused by a translocation between the 5' portion of FGFR2 and the 3' end of one of more than 150 fusion partners identified thus far. While the FGFR2 portion contains the intact extracellular and kinase domains, the fusion partners are characterized by a protein dimerization domain, which leads to constitutive dimerization and ligand-independent kinase activation [29].

To date, several phase II studies in patients with ICCa and FGFR2 fusions have revealed a very consistent efficacy of FGFR-targeted therapies in higher lines with a response rate between 20 and 36% [30, 31]. The FIGHT-202 trial investigated the efficacy of the FGFR inhibitor pemigatinib in progressed fusion-positive ICCa patients and was the largest study conducted in this genetically selected population thus far. Disease control was 85.1% with an ORR of 36%, and an impressive mPFS and mOS of 9.2 and 15 months, respectively [32]. Based on these results, pemigatinib has received FDA approval for pretreated ICCa patients with FGFR2 fusions.

Currently, several FGFR inhibitors have been entered into phase III trials. Since early 2019, the randomized trial “PROOF” has been recruiting patients in the first line for treatment with infgratinib versus GemCis (and possible crossover into the infgratinib arm) [33]. In addition, pemigatinib is further developed in first line in comparison to standard of care (GemCis) in the FIGHT-302 study (NCT03656536) [34], whereas derazantinib is evaluated in the FIDES-01 study in second line (NCT03230318).

In summary, it appears highly likely that FGFR2 inhibitors will soon become an integral component of the standard systemic therapy for FGFR2 fusion-positive iCCa patients and are being used in Europe. Considering the imminent therapeutic relevance of FGFR2 fusions, it appears mandatory that all patients with iCCA problems receive molecular testing that is capable of detecting FGFR2 fusions independent of the fusion partner.

HER2
In an increasing number of solid tumors, HER2/neu (ERBB2) is being recognized as a predictive biomarker and promising target for molecular therapy [35]. While genetic amplification is the most frequent HER2 alteration, activating HER2 mutations are particularly common in biliary tumors. In CCA, HER2 alterations occur in approximately 8–10% of patients, and nearly 40% of these are classified as HER2 mutations. In patients with gallbladder carcinoma, the proportion of HER2 amplifications/over-expression is estimated to exceed 10% [36], and, in addition, almost 10% of cases harbor active mutations in ERBB2 or ERBB3 (11%) [37].

The recently published MyPathway basket study investigated the efficacy of dual receptor inhibition using trastuzumab and pertuzumab in heavily pre-treated patients with various solid tumors. In CCA, disease control was achieved in 5 out of 7 patients with HER2-amplified CCA and in 1 out of 3 patients with HER2-mutated CCA [38, 39].

The SUMMIT phase II basket study specifically investigated the response to targeted therapy in patients with HER2- and HER3-mutated, but not -amplified, tumors. By the beginning of 2019, a total of 19 patients with HER2-mutant biliary tract tumors had received the pan-HER kinase inhibitor neratinib in higher therapy lines. Treatment was well tolerated with an ORR of 10.5% (95% CI 1.3–33.1) and a median PFS of 1.8 months (95% CI 1.0–3.7) [40]. Overall, these results suggest that although selected patients seem to benefit, the response in HER2-mutant CCA patients is inferior to the response observed in HER2-amplified tumors [38, 39].

Due to the small number and frequently heavily pretreated patients, data on chemotherapy-free, HER2-directed therapies need to be interpreted with caution. Nevertheless, the available information overall supports the use of these substances in patients who lack other therapeutic options.

BRAF
Activating BRAF V600E mutations are found in 3–5% of patients with CCA [27]. In contrast to melanoma, no convincing efficacy could be achieved in GI tumors with anti-BRAF directed monotherapy [41]. However, recent data support the sequential inhibition of the EGFR pathway using a combination of EGFR and BRAF or BRAF and MEK inhibitors. In CCA, co-treatment with BRAF and MEK inhibitors yielded highly promising results.

The ROAR basket trial included 43 partly intensively pretreated patients with BRAFV600E mutations. The combination of trametinib (MEK inhibitor) and dabrafenib (BRAF inhibitor) achieved a convincing ORR of 51% (95% CI 36–67, investigator-assessed) with a clinically significant mPFS of 9 months (95% CI 5–10) and a mOS of 14 months (95% CI 10–33). Similar positive signals were also reported from the NCI Match study, likewise a precision medicine basket trial, in which 3 out of 4 patients with BRAF V600E mutant biliary tumors treated...
with trametinib/dabrafenib achieved a partial response. We believe that these data highlight the benefits of molecular targeted therapy in patients with biliary tumors, and that BTC patients should be screened for the presence of BRAF mutations.

**NTRK**

Additional rare targetable events include fusions of the neurotrophic tyrosine kinase receptor (NTRK) genes that code for the tropomyosin receptor kinase receptors. The NAVIGATE phase II study included patients suffering from one of 17 different NTRK fusion-positive cancers, but only two patients with CCA [42]. In the overall population, the NTRK inhibitor larotrectinib achieved an impressive ORR of 80% with long-lasting tumor control. These results led to a tumor agnostic approval of the substance. A major challenge in the identification of NTRK fusion-positive cases is their very low prevalence. Due to the high therapeutic relevance and the tumor agnostic approval of larotrectinib and entrectinib, patients should be screened for NTRK fusion at least by immunohistochemistry.

**Immunotherapy**

Immunotherapeutic approaches are also under active investigation in patients with BTC. In contrast to the promising results in hepatocellular carcinoma, which have recently been confirmed in phase III studies, no convincing data are available yet for biliary tumors. In an early study that involved 24 patients with PD-L1-positive CCAs, the response rates of 20% in patients who received the PD-1 antibody pembrolizumab was comparable to other solid tumors [11]. However, Keynote-158, the largest immune-oncology study in CCA to date, reported disappointing results with a low response rate of 5.8% [43]. These initial data suggest that clinically significant benefits can only be achieved in a small subset of patients with advanced BTC. As expected, high response rates were observed for pembrolizumab in BTC with microsatellite instability (MSI); however, MSI-high tumors account for less than 2% of the patient population [44].

For patients with microsatellite-stable tumors, combination therapies may be more effective. A first analysis for the combination of GemCis with the PD-L1 antibody durvalumab and with and without the CTLA-4 antibody tremelimumab was presented at ASCO 2020. In this Korean patient population, the combination of dual checkpoint inhibition with GemCis demonstrated a very promising efficacy with a DCR of 98% and a mPFS of 11.9 (95% CI 10.1–13.7) and a mOS of 20.7 (95% CI 13.8–27.6) months. Interestingly, the tumor mutational burden did not correlate with mPFS or mOS. Whether these data can be confirmed in Caucasian patients needs to be determined in ongoing studies such as TOPAZ-1 and KEY-NOTE-966, in which patients are treated with GemCis alone or in combination with durvalumab or pembrolizumab. Overall, however, there are no sufficiently convincing data thus far that justify the use of immunotherapy outside of clinical trials in microsatellite-stable BTC.

**Conclusion**

After several years without significant progress in the treatment of BTC, a number of important studies have been successfully completed or initiated in the field that will generate meaningful insights for future systemic therapy concepts. Already today, for the first time, evidence-based approaches can be offered in the second line. The importance of immunotherapy is subject to ongoing investigation and should, at present, only be recommended to MSI patients.

A better understanding of the mutational spectrum of BTC has not only helped to realize the promise of targeted therapies in these cancers, but also to recognize the fundamental importance of patient stratification. In order to ensure that valid therapeutic options are not withheld from BTC patients, molecular testing should be performed at an early stage in the palliative setting and include MSI, BRAF and IDH1/2 mutations, FGFR2 and NTRK fusions, HER2/neu amplifications, and mutations. Several treatment decisions, especially in second and higher line, will remain individualized approaches, and we recommend that BTC patients are treated in specialized centers with a long-standing expertise in hepatobiliary surgery, loco-regional therapies, as well as systemic therapies.

**Conflict of Interest Statement**

Honoraria for Speaker, consultancy and advisory role to A.V.: Roche, Bayer, Sanofi, BMS, Lilly, Novartis, Eisai, AstraZeneca, Merck, Medac, Ipsen, PierreFabre, MSD. Honoraria for Speaker, consultancy and advisory role to A.S.: none.

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**Author Contributions**

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