Outcomes in patients receiving palliative chemotherapy for advanced biliary tract cancer

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Graphical abstract

| Background | Findings | Findings |
|------------|----------|----------|
| Real world data depicting the outcome of biliary tract cancer remains scarce | Undergoing sequential chemotherapy lines may confer a survival benefit | The use of FOLFIRINOX was associated with a promising overall survival of 23.8 months. |
| although it would be extremely important, as it can critically inform clinical decision making. | Prognostic factors such as pre-therapeutic albumin levels | can increase the precision of the prognosis. |
| 1 line; 2 lines; 3 lines; ≥4 lines | OS 6.7; 15.2; 18.2; 24.6 months | of 23.8 months. |

Highlights
- This study provides important real-world data on the clinical outcomes of patients with ABTC.
- Patients may benefit from later lines of chemotherapy beyond second line.
- The use of FOLFIRINOX was associated with a promising overall survival of 23.8 months in our study.
- Many prognostically relevant factors, such as pre-therapeutic albumin, bilirubin or CA19-9 levels, were identified.
- Targeted therapies will become an integral part of the standard of care for patients with ABTC.

Lay summary
Real-world data depicting the outcome of patients with advanced biliary tract cancer outside the framework of controlled trials remain rare despite being extremely important for clinical decision-making. This study therefore provides important real-world data on the established first- and second-line treatments with gemcitabine + cisplatin and FOLFOX, as well as on other chemotherapy regimens or later lines of chemotherapy. It further demonstrates that the use of FOLFIRINOX is associated with promising survival and that there is an association between various clinical parameters such as pre-therapeutic albumin, bilirubin or carbohydrate antigen 19-9 levels and survival.

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Background & Aims: Advanced biliary tract cancer (ABTC) is associated with a poor prognosis. Real-world data on the outcome of patients with ABTC undergoing sequential chemotherapies remain scarce, and little is known about treatment options beyond the established first- and second-line treatments with gemcitabine + cisplatin and FOLFOX. This study aimed to evaluate the outcome of patients with regard to different oncological therapies and to identify prognostic factors.

Methods: From January 2010 until December 2019, 142 patients started palliative chemotherapy at our tertiary care liver center. Overall survival (OS) was calculated using Kaplan-Meier plots. Prognostic factors were evaluated using cox proportional-hazards.

Results: Patients received a median number of 2 lines of chemotherapy. Median OS was 6.7, 15.2 and 18.2 months for patients who received 1, 2 and 3 lines of chemotherapy, respectively. Patients treated with FOLFIRINOX had a significantly extended OS of 23.8 months (log-rank test: \( p = 0.018 \)). The univariate cox regression analysis identified several clinical parameters associated with survival (e.g. albumin, bilirubin, carcinoembryonic antigen, carbohydrate antigen 19-9 levels).

Conclusions: Our study provides real-world data on the prognosis of ABTC including survival times for patients receiving third and later lines of chemotherapy.

Lay summary: Real-world data depicting the outcome of patients with advanced biliary tract cancer outside the framework of controlled trials remain rare despite being extremely important for clinical decision-making. This study therefore provides important real-world data on the established first- and second-line treatments with gemcitabine + cisplatin and FOLFOX, as well as on other chemotherapy regimens or later lines of chemotherapy. It further demonstrates that the use of FOLFIRINOX is associated with promising survival and that there is an association between various clinical parameters such as pre-therapeutic albumin, bilirubin or carbohydrate antigen 19-9 levels and survival.

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Introduction

Advanced biliary tract cancer (ABTC) is a clinically challenging cancer that is associated with a poor prognosis (reviewed in1–3). The term ABTC encompasses various cancer entities that originate in the bile ducts, the gallbladder (GBC) and the ampulla of Vater. Bile duct carcinomas are also termed cholangiocarcinoma (CCA) and are categorized as intrahepatic (iCCA), perihilar (pCCA) and distal CCA depending on their primary site of origin.4,6 Although ABTC represents a heterogenous group of neoplasms, they are currently treated consistently.5,7 Recurrences are frequent even after successful surgical resection, which makes the use of adjuvant chemotherapy a subject of current research (reviewed in8). In the advanced stage, palliative chemotherapy is the main pillar of oncological treatment.1–11 In the first-line setting, gemcitabine + cisplatin (GemCis) has become the standard-of-care.12–14 After failure of GemCis, recent studies recommend the use of FOLFOX as second-line treatment of ABTC.2,15 In addition, triple therapies such as gemcitabine + cisplatin + nab-paclitaxel16 or FOLFIRINOX17–19, novel regimens such as liposomal irinotecan + fluorouracil + leucovorin,20 checkpoint inhibitors alone or in combination with chemotherapy,21 and molecular targeted therapies such as the inhibition of fibroblast growth factor receptor (FGFR) 1–422–26 or isocitrate dehydrogenase (IDH) 127 are currently being investigated in clinical trials.
Patients and methods

Patients
We performed a retrospective analysis of 142 patients with histologically confirmed malignancies who started treatment with palliative chemotherapy at our center between January 01, 2010 and December 31, 2019. Data were retrieved from our institution’s electronic clinical information system and prepared for analysis. Patients were followed up until December 31, 2020. All patients provided informed consent.

Ethical statement
The study was conducted according to the guidelines of the Declaration of Helsinki 1975 and approved by the Ethics Committee of the state of Rhineland-Palatinate (permit number 2018-13618, October 15th, 2018).

Statistical analysis
Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) version 27.0.1.0 (SPSS, Chicago, IL, USA). Categorical variables were tested for statistical significance using the chi-square test. Kaplan-Meier plots were generated to estimate OS from either the time of diagnosis or the time of unresectability until the time of death or last follow-up. The log-rank test was used to assess the statistical significance of the difference between strata. Univariate Cox proportional-hazards regression models assessing hazard ratios (HRs) and corresponding 95% CIs were employed to determine the relationship between several risk factors and OS (HR >1: potentially harmful; HR <1: potentially protective). p values <0.05 were considered statistically significant. A significance-adjusting Bonferroni correction was not applied despite the multiple testing as the objective of this study was to retrospectively evaluate the outcome of patients with ABTC undergoing palliative chemotherapy at our institution to identify prognostic factors.

Results

Baseline characteristics
Baseline clinical, laboratory and treatment characteristics are summarized in Table 1. The median age at diagnosis was 63.8 years and the sex distribution was balanced. The most frequent subtype was iCCA (51.4%), followed by GBC (21.1%) and pCCA (13.4%). Carcinomas originating from the distal bile duct (8.5%) or the Vateri ampulla (4.2%) were rarely observed. The majority of patients (63.2%) had Union for International Cancer Control (UICC)-stage 3 (14.8%) or 4 (48.4%) disease at diagnosis. Over half of the patients (54.5%) had lymph node metastases and over a third had distant metastases (39.1%). Histopathological grading was available for 92 patients with the majority being moderately (G2 = 55.4%) or poorly (G3 = 43.5%) differentiated. More than half (59.3%) of patients presented with an Eastern Cooperative Oncology Group – performance status (ECOG PS) of 0 at the start of palliative chemotherapy and 34.5% had an ECOG PS of 1. Only a minority (6.2%) had an ECOG PS of 2 or 3. Median baseline carbohydrate antigen 19-9 (CA19-9) and carcinoembryonic antigen (CEA) levels were 122 U/ml and 2.6 ng/ml, respectively. CA19-9 and CEA levels over 1,000 U/ml and 4.5 ng/ml, respectively, could be detected in a third of patients (34.6% and 37.9%). Median bilirubin and albumin levels were 0.7 mg/dl and 33 mg/dl.

Table 1. Baseline characteristics.

| Baseline characteristics | Patients |
|--------------------------|---------|
| Age at diagnosis (years) | 63.8 (54.5-73.1) |
| Age at start of CT1 (years) | 64.8 (55.5-73.5) |
| Male sex | 71 (50%) |
| BMI (kg/m²) | 25.1 (22.5-28.6) |
| Underweight (<18.5) | 4 (3%) |
| Normal weight (18.5-24.9) | 62 (46.6%) |
| Overweight (25-29.9) | 42 (31.6%) |
| Obese (>30) | 25 (18.8%) |
| ECOG PS | 1 39 (34.5%) |
| 2 or 3 | 7 (6.2%) |
| CA19-9 (U/ml) | 122 (18.0-1600.2) |
| CEA (ng/ml) | 2.6 (1.6-8.7) |
| Albumin (mg/dl) | 33 (26.0-37.5) |
| Tumor grading | |
| G1 | 1 (1.1%) |
| G2 | 51 (35.4%) |
| G3 | 40 (28.5%) |
| UICC-stage | |
| I | 12 (9.4%) |
| II | 35 (25.3%) |
| III | 19 (14.8%) |
| IV | 62 (44.8%) |
| T-stage | |
| T1 | 11 (9.2%) |
| T2 | 69 (50.0%) |
| T3 | 34 (24.6%) |
| T4 | 5 (4.2%) |
| Lymph node metastases | 55 (54.5%) |
| Distant metastases | 45 (39.1%) |
| Serum markers | |
| CEA (ng/ml) | 2.6 (1.6-8.7) |
| CA19-9 (U/ml) | 122 (18.0-1600.2) |
| Bilirubin (mg/dl) | 0.73 (0.5-1.27) |
| Albumin (mg/dl) | 33 (26.0-37.5) |
| Clinical parameters | |
| Initially resectable | 60 (42.3%) |
| Recurrence after resection | 60 (100%) |
| Neoadjuvant chemotherapy | 2 (1.4%) |
| Adjuvant chemotherapy | 13 (9.2%) |
| Recurrence localization | |
| Lymph node | 3 (3%) |
| Intrahepatic | 29 (48.3%) |
| Peritoneal metastases | 13 (21.7%) |
| Distant metastases | 15 (25%) |
| Resectable recurrence | 5 (6.3%) |

Continuous variables are expressed as median (IQR), categorical variables as n (%).

ABTC, advanced biliary tract cancer; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; CT1, first-line chemotherapy; dCCA, distal cholangiocarcinoma; ECOG PS, Eastern Cooperative Oncology Group performance status; GBC, gallbladder cancer; iCCA, intrahepatic cholangiocarcinoma; pCCA, perihilar cholangiocarcinoma; UICC, Union for International Cancer Control.

Treatment outcome
42.3% of patients were initially treated with curative surgical resection. Of these 21.6% (13/60) also received adjuvant chemotherapy (in most cases GemCis or capecitabine). Recurrence of
ABTC occurred 10.5 months after surgery (median; Table 2). Patients whose malignancy was resected had superior OS of 27.9 months compared with 11.7 months in patients whose malignancy was not resected (log-rank test \( p < 0.001; \text{ Fig. 1A} \)). After recurrence, OS in patients who received an initial tumor resection was comparable to that of initially unresectable patients (log-rank test \( p = 0.130; \text{ Fig. 1B} \)). Median time from unresectability until the start of first-line chemotherapy (CT1) was 1.1 months. In the palliative setting, 50.7% of patients received GemCis or gemcitabine/oxaliplatin (GemOx) as CT1. Gemcitabine monotherapy (13.4%), FOLFIRI/CAPOX (10.6%) or FOLFIRINOX (7.7%) were used less frequently. More than half of patients (57%) were treated with a second-line chemotherapy (CT2) following disease progression. Regarding second-line therapy, most patients received FOLFIRI/CAPOX (30.5%), followed by gemcitabine monotherapy (18.3%), GemCis/GemOx (17.1%), other capectabine-based therapies (9.8%), FOLFI4 (4.9%) or FOLFIRINOX (4.9%). 25.1% received \( \geq 3 \) lines of chemotherapy, while a 4th or 5th line could only be employed in 6.6% of patients. As third-line chemotherapy (CT3), FOLFI4 (18.4%), FOLFOX (18.4%), S1-based therapies (15.8%) and docetaxel (15.8%) were most commonly used. 27.5% of patients received additional locoregional therapy (transarterial chemoembolization [10.6%]), selective internal radiation therapy [9.2%), radiotherapy [7.7%]).

Median OS was 6.7, 15.2, 18.2 and 24.6 months for patients receiving 1, 2, 3, or \( \geq 4 \) lines of chemotherapy, respectively (log-rank test \( p < 0.001; \text{ Fig. 1C} \)). The median number of received therapy lines was 2 (range 1-5). The duration of CT1, CT2 and CT3 was 2.9, 2.8 and 2.0 months, respectively.

In patients receiving FOLFOX/CAPOX as CT1, median OS was significantly lower than in patients receiving GemCis/GemOx with a difference of approximately 8 months (12.3 vs. 4.8 months; log-rank test \( p = 0.007; \text{ Fig. 1D-F} \)). In contrast, a comparison of patients who had received FOLFIRINOX at some point with those who never did revealed a significantly prolonged survival for the FOLFIRINOX group (11.9 vs. 23.8 months; log-rank test \( p = 0.018; \text{ Fig. 1G} \)). A comparison of prognostically relevant factors revealed that patients treated with FOLFIRINOX received more lines of chemotherapy and had lower bilirubin levels than those who never did.

Regardless of the chemotherapy regimen received, median OS after the start of CT1, CT2 and CT3 was 11.4, 8.0 and 6.2 months, respectively. Time from the last administration of chemotherapy until death was 1.8 months (median). At the end of follow-up, 127 patients (90.1%) had died.

Reported treatment outcomes and palliative chemotherapy regimens are summarized in Table 2 and Fig. 2. The fractions of patients who received 1, 2, 3 or \( \geq 4 \) chemotherapy lines and their associated OS are illustrated in Fig. 3.

### Prognostic factors
In the log-rank tests and univariate cox regression analyses, increasing age, gallbladder cancer, lymph node metastases, distant metastases, UICC-stage 3 or 4, poor differentiation (G3) and a poor ECOG PS were associated with a shorter OS (Table 3). The greatest differences in OS were found for ECOG PS (17.2 months OS for ECOG PS 0, 12.1 for ECOG PS 1 and 5.2 for ECOG PS \( \geq 2 \); log-rank test \( p = 0.036; \text{ Fig. 4A} \)), age at diagnosis (10 vs. 18.0 months OS for patients <65 years; log-rank test \( p = 0.001 \)), distant metastases (10.8 vs. 17.6 months OS for patients without metastatic disease; log-rank test \( p = 0.003 \)), tumor cell differentiation (10.3 vs. 16.5 months OS for patients with well or moderately differentiated tumor cells [G1, G2] compared with poorly differentiated tumor cells [G3]; log-rank test \( p = 0.005 \)) and CBC (11.5 vs. 14.7 months OS for patients with other primary anatomic origins; log-rank test \( p = 0.006; \text{ Fig. 4B} \)). In addition, serological markers such as elevated CEA, CA19-9 or bilirubin levels were found to be associated with poor OS. In patients with CEA <4.5 ng/dl, CA19-9 <1,000 U/ml and bilirubin <1.2 mg/dl, OS was extended by 6.9, 3.8 and 7.3 months, respectively, in comparison to patients with higher levels (Fig. 4C-E). In contrast, an albumin level >33 mg/dl was associated with a 7.5 month extension in OS (Fig. 4F).

Finally, no significant correlation with OS was found for BMI, T-stage and sex.

### Discussion
GemCis/GemOx as CT1 and FOLFIRI as CT2 have been established for patients with ABTC.12-15,26 The survival times reported here are comparable to the OS of 9.5-11.7 months after CT111,14 and 6.7-7.2 months after CT230-32 obtained in previous studies. In our analysis, OS was significantly dependent on the number of received therapy lines. It is worth noting that in our cohort almost twice as many patients received CT2 (57% vs. 32.5%) and CT3 (25.1% vs. 13.9%) as reported in a meta-analysis by Brieau et al., which could be a reason for the prolonged survival times observed in our study.30 Therefore, our data suggest that patients

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**Table 2. Treatment outcomes.**

| Outcome | Deceased \( (90.1%) \) |
|---|---|
| Number of received chemotherapy lines | \( (43.0%) \) |
| \( 1 \) | 58 (43.0%) |
| \( 2 \) | 43 (31.9%) |
| \( 3 \) | 25 (18.5%) |
| \( \geq 4 \) | 9 (6.6%) |
| Number of received cycles | \( (2-8) \) |
| Cycles of CT1 | 4.5 (2-8) |
| Cycles of CT2 | 4 (2-6) |
| Cycles of CT3 | 3 (2-5.25) |
| Cycles of CT4 | 4 (1.75-5.25) |
| Palliative oncological treatments | \( (17.1%) \) |
| FOLFIRINOX as CT1 | 11 (7.7%) |
| FOLFOX in any line | 25 (14.7%) |
| FOLFOX/CAPOX as CT1 | 14 (9.9%) |
| Targeted therapy | 17 (12%) |
| Treatment with TACE | 15 (10.6%) |
| Treatment with SIRT | 13 (9.2%) |
| Treatment with radiotherapy | 11 (7.7%) |
| Ongoing oncological treatment at data cut-off | 6 (4.2%) |

**Survival times**

- OS since diagnosis of ABTC: \( 18.4 (8.1-31.9) \) months
- OS since resection (in case of resectability): \( 27.9 (19.5-45.7) \) months
- Recurrence-free survival: \( 10.5 (4.9-15.4) \) months
- OS since unresectability: \( 14.5 (7.1-23.1) \) months
- Time from unresectability until the start of CT1: \( 11.1 (0.7-2.0) \) months
- OS since start of CT1: \( 11.4 (4.8-21.0) \) months
- OS since start of CT2: \( 8.0 (4.1-17.3) \) months
- OS since start of CT3: \( 6.2 (4.2-12.2) \) months
- Duration of CT1: \( 2.9 (1.1-6.4) \) months
- Duration of CT2: \( 2.8 (1.4-5.2) \) months
- Duration of CT3: \( 2.0 (1.0-2.8) \) months
- OS since last CTX application: \( 1.8 (1.1-4.1) \) months

Continuous variables are expressed as median (IQR), categorical variables as \( n (\%) \). Survival times are given in months and expressed as median (IQR).

ABTC, advanced biliary tract cancer; CT1, first-line chemotherapy; CT2, second-line chemotherapy; CT3, third-line chemotherapy; OS, overall survival; SIRT, selective internal radiation therapy; TACE, transarterial chemoembolization.
OS initially resectable = 27.9 months (median)
OS initially unresectable = 11.7 months (median)
Log-rank test: p value < 0.001

OS FOLFOX/CAPOX = 4.8 months (median)
OS others = 12.8 months (median)
Log-rank test: p value = 0.003

OS FOLFIRINOX = 23.8 months (median)
OS without FOLFIRINOX = 11.9 months (median)
Log-rank test: p value = 0.018

N° at risk
60 45 17 2 1 1
82 21 6 3 1

Fig. 1. Kaplan-Meier plots comparing OS. (A) OS since diagnosis with regard to initial resectability; (B) OS since unresectability with regard to initial resectability; (C) OS since unresectability with regard to the number of received chemotherapy lines; (D) OS since the start of CT1 with regard to the chosen CT1 regimen; (E) OS since the start of CT2 with regard to the chosen CT2 regimen; (F) OS after unresectability with regard to a treatment with FOLFOX / CAPOX as CT1; (G) OS after unresectability with regard to a treatment with FOLFIRINOX at any point. P values were generated by using log-rank tests. CT1, first-line chemotherapy; CT2, second-line chemotherapy; CT3, third-line chemotherapy; OS, overall survival.
with ABTC who are still fit for chemotherapy might benefit from later lines of therapy, which should lead to further investigation and consideration in clinical decision-making.

In light of the survival times reported by us and others, there is still an urgent and unmet medical need for more efficacious treatments for ABTC. In this regard, several previous studies have failed to identify new and more effective therapies. Therefore, a variety of new treatment regimens, such as triple therapies like FOLFIRINOX (NCT02591030) or gemcitabine/cisplatin/nab-paclitaxel (NCT03768414) are currently being investigated in clinical trials.16,20,40

In a recent study, FOLFIRINOX appeared to be a valid alternative for CT1 reaching an OS of 15 months.17 Furthermore, even when FOLFIRINOX was used as salvage treatment after GemCis failure, an OS of 13.2 months was achieved.18 These observations support our finding of a significantly prolonged OS in patients who received FOLFIRINOX at some point. However, AMEBICA PRODIGE 38, a randomized controlled trial, which compared treatment with FOLFIRINOX against GemCis did not meet its primary endpoint,\textsuperscript{19} which should be taken into account when considering our study results and the role of selection bias in our study. In addition to survival, the quality of life should not be neglected in the evaluation of novel triple therapies, as increased toxicity can lead to a higher rate of adverse events. Recent studies, however, have not reported abnormalities in this regard.\textsuperscript{17–19,41}

Molecular targeted therapies hold great promise for the treatment of ABTC (reviewed in\textsuperscript{42}). One novel mechanism of action is the inhibition of FGFR1-4. In this line, the FGFR inhibitor pemigatinib has demonstrated a survival benefit as second-line treatment in a phase II study in patients with advanced iCCA and a FGFR gene rearrangement which led to its approval by the Food and Drug Administration.\textsuperscript{22} Consequently, results from the FIGHT-302 phase III trial (NCT03656536) investigating the efficacy of pemigatinib as first-line treatment in patients with FGFR2 fusions are highly awaited.\textsuperscript{26} In addition to pemigatinib, various

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{flow_chart.png}
\caption{Flow chart illustrating first-, second- and third-line palliative chemotherapies. CT1, first-line chemotherapy; CT2, second-line chemotherapy; CT3, third-line chemotherapy; GemCis, gemcitabine + cisplatin; GemOx, gemcitabine + oxaliplatin.}
\end{figure}
other FGFR inhibitors, such as derazantinib (FIDES-01 phase II trial, NCT03230318), futibatinib (FOENIX-CCA3 phase III trial, NCT04093362) and infigratinib (PROOF study, NCT03773302), are being tested in clinical trials.23–25 Another target for personalized therapies involves mutations in the IDH gene. In this regard, the ClarIDHy phase III trial (NCT02989857) reported a significantly longer progression-free survival for pretreated patients with icca who received ivode- 

Table 3. Univariate cox proportional-hazards of death for selected factors.

| Factor                  | Hazard ratio (95% CI) | p value |
|-------------------------|-----------------------|---------|
| Age at diagnosis (years)| 1.017 (1.002-1.033)   | 0.029   |
| Age over 65 years at diagnosis| 1.756 (1.236-2.496)   | 0.002   |
| Gallbladder cancer       | 1.797 (1.174-2.749)   | 0.007   |
| T-stage                 | 1.181 (0.788-1.771)   | 0.421   |
| T1+T2 vs. T3+T4         | 1.627 (1.067-2.482)   | 0.024   |
| Lymph node metastases   | 1.817 (1.213-2.723)   | 0.004   |
| UICC-stage              | 1.580 (1.069-2.337)   | 0.022   |
| H1 vs. III+V            |                       |         |
| Tumor grading           | 1.853 (1.192-2.882)   | 0.006   |
| G1+G2 vs. G3            |                       |         |
| Number of received chemotherapy lines|              | <0.001  |
| 1                       | Reference             |         |
| 2                       | 0.444 (0.294-0.671)   | <0.001  |
| 3                       | 0.334 (0.202-0.553)   | <0.001  |
| ≥4                      | 0.285 (0.126-0.530)   | <0.001  |
| Treatment with FOLFIRINOX| 0.574 (0.360-0.914)   | 0.019   |
| ECOG PS                 |                       |         |
| 0                       | Reference             |         |
| 1                       | 1.516 (0.981-2.383)   | 0.061   |
| 2 or 3                  | 2.443 (1.047-5.841)   | 0.039   |
| Serological markers     |                       |         |
| CEA >4.5 ng/ml          | 1.859 (1.167-2.962)   | 0.009   |
| CA19-9 >1,000 U/ml      | 1.580 (1.030-2.425)   | 0.036   |
| Bilirubin >1.2 mg/dl    | 1.649 (1.059-2.566)   | 0.027   |
| Albumin >33 mg/dl       | 0.456 (0.281-0.738)   | 0.001   |
| Initially resectable    | 0.760 (0.532-1.086)   | 0.132   |

The calculated p values and hazard ratios including a 95% CI are given. P values and hazard ratios were generated by using univariate cox proportional-hazards. CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; ECOG PS, Eastern Cooperative Oncology Group performance status; UICC, Union for International Cancer Control.

Another target for personalized therapies involves mutations in the IDH gene. In this regard, the ClarIDHy phase III trial (NCT02989857) reported a significantly longer progression-free survival for pretreated patients with icca who received ivode-sinib in comparison to placebo.43 Moreover, cancer immunotherapy will continue to be explored for the treatment of ABTC despite disappointing results from the first clinical trials testing checkpoint inhibitors as monotherapy.44 Currently, checkpoint inhibitors are evaluated in combination with established chemotherapies such as GemCis (EORTC–1607-GITCG [NCT03260712], Keynote-966 [NCT04003636] or TOPAZ-1[NCT03875235])45,46 and other targeted agents.21 In this regard, the TOPAZ-1 trial, investigating a combination therapy with the PD-L1 inhibitor durvalumab and GemCis already showed promising results in an interim analysis in which it met its primary endpoint of a prolonged OS compared to GemCis. However, it remains to be seen how all these novel treatments will affect the overall outcome and management of patients with ABTC.

Regarding prognostic factors, ECOG PS has been identified previously and is used in the current ESMO guidelines to select patients for an appropriate CT1 therapy regimen. Thus, patients with an ECOG PS of 0-1 should receive treatment with GemCis, while patients with an ECOG PS >2 should instead receive gemcitabine monotherapy.9,47 In addition to ECOG PS,48–51 several other factors such as old age at diagnosis,52 lymph node metastases,53 distant metastases,50 poor tumor cell differenti-
ation,54 gallbladder cancer,54,55 or levels of bilirubin,56 albumin, or CA19-9 have previously been reported to be associated with survival in ABTC and can therefore inform clinical decision-making. Our findings lend further support to their prognostic value. Taking these parameters one step further, prognostic scores can be employed to predict the outcome of patients, as has already been shown for the ALAN and Glasgow score.57,58
Regarding the limitations of our study, one major limitation is its retrospective and monocentric design. In addition, the possibility of selection bias must be considered. Thus, the superior OS of patients who received sequential therapy lines and those who received FOLFIRINOX at some point may have been due to a selection bias (patients in a generally better condition are more likely to receive both more lines of chemotherapy as well as FOLFIRINOX). Furthermore, the number of patients who received
Abbreviations
ABT, advanced biliary tract cancer; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; CT1, first-line chemotherapy; CT2, second-line chemotherapy; CT3, third-line chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; FGF, fibroblast growth factor receptor; GBC, gallbladder cancer; GemCis, gemcitabine + cisplatin; GemOx, gemcitabine + oxaliplatin; IDH, isocitrate dehydrogenase; iCCA, intrahepatic cholangiocarcinoma; OS, overall survival; pCCA, perihilar cholangiocarcinoma; UICC, Union for International Cancer Control.

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Conflicts of Interest
The authors declare no conflict of interest.

Authors’ contributions
FF: conceptualization, methodology, project administration, supervision. FT, SJG and FF: writing-original draft preparation, validation. FT: formal analysis, visualization. FT, SJG, CC, TT, YH, JV, JJ, MMi, FB, LM, RK, PRG, MAW, JUM, MMo, AW and FF: writing-review and editing, data collection. All authors have read and agreed to the published version of the manuscript. This manuscript contains parts of the doctoral thesis of FT at the ‘Johannes Gutenberg-Universität Mainz’.

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Supplementary data
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Author names in bold designate shared co-first authorship

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