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Hepatic and Biliary Cancer

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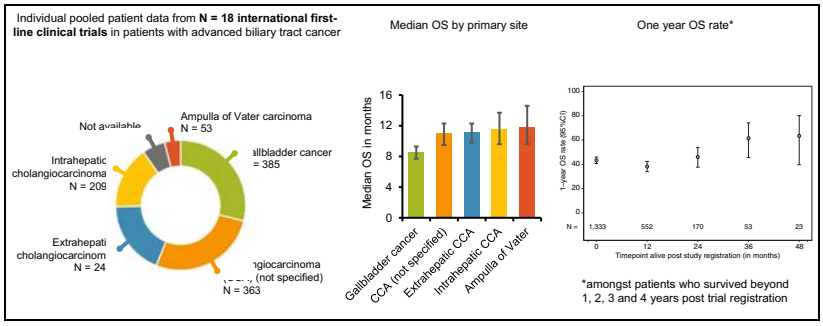
Landmark survival analysis and impact of anatomic site of origin in prospective clinical trials of biliary tract cancer

Graphical abstract



Highlights

- Patients with gallbladder cancer have worse overall survival than those with other primary anatomic origins of biliary tract cancer.
- Reduced risk of death *vs.* gallbladder cancer was maintained in those receiving combination chemotherapy.
- Landmark survival rates provide relevant prognostic information for patients who survive for some time.
- Patients receiving combination therapy have better landmark survival than those receiving monotherapy.
- Patients with intrahepatic cholangiocarcinoma or cholangiocarcinoma-not specified also have better landmark survival.

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Lay summary

Patients with gallbladder cancer have worse overall survival compared to those with biliary tract cancers of different primary origin. Thus, gallbladder cancer should be considered as a stratification factor in future clinical trials. Landmark survival rates enable adjusted prognosis prediction for patients with advanced biliary tract cancer who survive for some time.

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Landmark survival analysis and impact of anatomic site of origin in prospective clinical trials of biliary tract cancer

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Background & Aims: Whether all patients with advanced biliary tract cancer (aBTC) should be included in prospective trials, irrespective of the anatomic site of origin, is debated. Herein, we aimed to assess the survival impact of anatomic site of origin in prospective clinical trials of aBTC using landmark survival analysis.

Methods: Patients enrolled into prospective first-line aBTC clinical trials (Jan 97–Dec 15) were included. Overall survival (OS) was analysed using Cox proportional hazard regression; landmark survival (LS) and 95% CIs were calculated.

Results: Overall, 1,333 patients were included: median age 63 years (range 23–85); 46% male; 84% ECOG-PS0/1; 25% with locally advanced disease, 72% with metastatic, 3% not reported (NR). Patients were treated with mono-chemotherapy (23%), cisplatin/gemcitabine (36%), other combinations (39%), or NR (2%). Median OS was 10.2 months (95% CI 9.6–10.9). All sites (treatment-adjusted) had decreased risk of death *vs.* gallbladder cancer (GBC) (p <0.001). This reduced risk *vs.* GBC was maintained in those receiving cisplatin/gemcitabine for extrahepatic cholangiocarcinoma (p <0.001) and intrahepatic cholangiocarcinoma (IHC, p <0.001), but not in cholangiocarcinoma-not specified (CCA-NS, p = 0.82) or ampullary carcinoma (p = 0.96). One-year OS rates amongst patients who survived beyond 1, 2, 3 and 4 years post-trial registration were 37%, 45%, 61%, and 63%, respectively. For patients who survived 1 year, those receiving combination therapy *vs.* mono (p = 0.008) (acknowledging potential selection bias) and those with IHC and CCA-NS *vs.* GBC had better LS (both p <0.05). Metastatic disease was associated with shorter LS than locally advanced disease (p = 0.002). ECOG-PS and gender were not associated with LS (p >0.05, p = 0.08 respectively).

Conclusions: GBC is associated with worse OS than other BTC sites and should be considered as a stratification factor in clinical trials. LS rates enable adjusted prognostication for aBTC survivors.

Lay summary: Patients with gallbladder cancer have worse overall survival compared to those with biliary tract cancers of different primary origin. Thus, gallbladder cancer should be considered as a stratification factor in future clinical trials. Landmark survival rates enable adjusted prognosis prediction for patients with advanced biliary tract cancer who survive for some time.

Introduction

Biliary tract cancers (BTCs) encompass cancers of the extrahepatic and intrahepatic bile ducts and gallbladder, as well as ampullary carcinoma.[1] The only potentially curative options are complete surgical resection[2] or liver transplantation, which are more often available within a clinical trial setting.[3–5] Recurrence rates are high and the only first-line phase III clinical trial showing a survival benefit for patients with a diagnosis of advanced BTC (aBTC) was the Advanced Biliary Cancer-02 (ABC-02) trial, which demonstrated that cisplatin plus gemcitabine was superior to gemcitabine alone in terms of progression-free survival (PFS) (8.0 *vs.* 5.0 months, respectively) and overall survival (OS) (11.7 *vs.* 8.1 months, respectively).[6] A dilemma surrounds the wisdom of including all patients with aBTC, irrespective of anatomic location, within the assessment of OS in prospective clinical trials, particularly given the reported genomic differences within BTC subtypes.[7]

Additionally, survival projections made at the time of an advanced cancer diagnosis, which are often poor, can be

Keywords: Biliary tract cancer; Primary site; Overall survival; Landmark survival; First-line clinical trials.
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disheartening for patients and so patients may inquire about the likelihood of surviving beyond reported median survival time-points.

However, the estimates of subsequent survival probabilities after a patient has survived for a certain number of years, excluding the patients who died at that point, are not directly available from the standard Kaplan-Meier curve. A useful analysis that addresses this question is landmark survival (LS). Landmark survival analysis, defined as the probability of surviving an additional amount of time after the patient has already survived for a specific period, may provide necessary practical information, as it accounts for the length of survivorship and changes in hazard ratios (HRs) over time, and this can offer more relevant prognostic information, once a patient reaches or exceeds a specific LS time.[8–12]

Landmark analysis for survival has been assessed in retrospective series of patients following resection of perihilar cholangiocarcinoma,[13] intrahepatic cholangiocarcinoma (IHC)[14] and gallbladder carcinoma (GBC)[15], as well as in patients with unresectable perihilar cholangiocarcinoma[16] and patients with GBC who were included within the Surveillance, Epidemiology, and End Results (SEER) database.[17] However, it has never been investigated prospectively in the setting of advanced first-line clinical trials including large numbers of patients from all 5 primary BTC sites (IHC, perihilar, distal bile duct, GBC and ampullary carcinoma).

The aim of this study was thus to assess the impact of anatomic site of BTC origin on traditional survival estimates, including investigation of association with risk of death from any cause by treatment group (monotherapy and combination therapy) and to determine the survival rates of patients with aBTC once they have survived for some time (LS).

Patients and methods

Individual patient data from 18 international first-line clinical trials in aBTC were accessed for analysis (Table S1)[18-32] through a co-operative effort of the International Biliary Tract Cancer Collaborators (IBTCC) who provided approval for the use of these data. All trials were approved by appropriate research ethics committees and regulatory authorities and written informed consent was obtained from each patient included in the study and the trials conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the individual institution's human research committees (See Table S1 for details of trial references).[18-32]

Statistical analysis

All eligible patients were included in the analysis. Baseline characteristics analysed included age, gender, ECOG-PS, disease stage (locally advanced and metastatic), site of primary cancer (IHC, extrahepatic cholangiocarcinoma [EHC: distal bile duct and perihilar], GBC or ampulla of Vater cancer) and systemic therapy received (monotherapy or combination). Where primary site of cholangiocarcinoma was not further defined within the database, the terminology cholangiocarcinoma-not specified (CCA-NS) was utilised (this did not include GBC or ampulla of Vater cancer). Prognostic factors for PFS/OS[33] and the impact of age on outcomes in aBTC[34] were previously explored in 11 and 13 of these trials, respectively.

PFS (time from registration to progression or death, whichever happened first) and OS (time from registration to death) were analysed using Cox proportional hazards regression.

The association between treatment and OS was evaluated using Cox regression. The variables carbohydrate associated antigen 19-9 (CA 19-9), ECOG-PS, gender, and disease stage (locally advanced/metastatic) were used to adjust the estimates for the association between treatment and OS. The Cox regression results were reported in terms of unadjusted and adjusted HRs, 95% CIs and p values.

One-year landmark overall survival and progression-free survival

Time-to-event endpoints (PFS and OS) were measured amongst patients event-free at each specific time point post randomisation: 0, 12, 24, 36 and 48 months (0, 1, 2, 3 and 4 years); they were measured as the time from that relevant time point to the time of the event of interest (PFS event or death). Patients who did not experience the event of interest were censored at the date that they were last known to be alive. Survival rates and 95% CIs were calculated.

Due to the exploratory nature of the analysis, no adjustment for multiple testing was performed. Differences were considered to be statistically significant at p values <0.05. Stata, version 15.1, statistical software package (Stata Corporation, College Station, Texas) (See Supplementary CTAT Table) was used to analyse the data.

Results

Baseline demographic information on 1,333 patients included in this study (recruited January 1997–December 2015) is provided in Table 1.

The median age of patients was 63 years and the majority had an ECOG-PS of 0 or 1 (84%), had metastatic disease (72%) and received combination systemic therapy (75%). The predominant BTC primary site was GBC (29%), followed by CCA-NS (27%), EHC (19%) and IHC (16%) (Table 1). Data on treatment received post first-line systemic chemotherapy was only available for ABC-02[6] and -03[35] (n = 534). No surgery with curative intent was recorded; 6 patients (1%) received locoregional therapy: 4 received radiofrequency ablation, 1 radioembolisation and 1 CyberKnife radiotherapy.

Most patients had follow-up until death (1,193/1,333: 89%) and 140 patients did not have a recorded date of death. The median follow-up time amongst the 140 patients who were censored for survival was 25.1 months (range 0–114.6 months).

Progression-free and overall survival

Median PFS for the entire cohort was 5.9 months (95% CI 5.6–6.3); GBC (n = 385), 5.3 months (95% CI 4.4–5.8); EHC (n = 247), 6.6 months (95% CI 5.8–8.2); IHC (n = 209), 6.4 months (95% CI 5.2–7.9); CCA-NS (n = 363), 5.8 months (95% CI 5.3–6.7); ampulla of Vater cancer (n = 53), 6.4 months (95% CI 4.8–8.5). Median OS for the entire cohort was 10.2 months (95% CI 9.6–10.9); GBC (n = 385), 8.5 months (95% CI 7.7–9.3); EHC (n = 247), 11.1 months (95% CI 9.9–12.4); IHC (n = 209), 11.5 months (95% CI 9.3–13.4); CCA-NS (n = 363), 11.0 months (95% CI 9.7–12.5); ampulla of Vater cancer (n = 53), 11.8 months (95% CI 9.7–14.0) (Table 2).

The 1-year OS rates for patients with aBTC enrolled in first-line trials within Europe, North America, Australia and Asia were 43% (95% CI 40–46%), 42% (95% CI 34–51%), 39% (95% CI 29–48%) and 35% (95% CI 25–46%) respectively. The 2-year OS rate for patients enrolled in trials within Europe, North America, Australia and Asia was 15% (95% CI 13–18%), 22% (95% CI 15–29%), 13% (95% CI 6–23%)

Table 1. Baseline information on patients included in study.

Baseline information	n (%) N = 1,333
Median age [years (range)]	63 (23–85)
Gender	
Female	677 (51)
Male	608 (46)
Not available	48 (4)
ECOG performance status	
0	436 (33)
1	685 (51)
2	83 (6)
Not available	129 (10)
Biliary tract cancer primary site	
Gallbladder cancer	385 (29)
Extrahepatic cholangiocarcinoma	247 (19)
Intrahepatic cholangiocarcinoma	209 (16)
Cholangiocarcinoma (not specified)	363 (27)
Ampulla of Vater	53 (4)
Not available	76 (6)
Disease stage	
Locally advanced	335 (25)
Metastatic	964 (72)
Not available	34 (3)
Treatment	
Monotherapy	310 (23)
Cisplatin/Gemcitabine combination	482 (36)
*Other combination therapy	520 (39)
Not available	21 (2)

*For details on combination regimens, please see Table S1.

and 14% (95% CI 8–23%), respectively. There was no evidence of an effect of geographical region on OS ($p = 0.59$).

The percentages of patients alive and at risk at 1, 2, 3, and 4 years post randomisation were 41%, 13%, 4% and 2%, respectively. For a 1-month extension in the time to progression, there was a 5% reduction in risk of death post-progression (HR 0.95; 95% CI 0.94–0.96; p <0.001).

All sites, adjusted for treatment, had decreased risk of death when compared to GBC: EHC (p <0.001), IHC (p <0.002), CCA-NS (p <0.003), and ampulla of Vater cancer ($p = 0.003$) (Table 2).

This reduced risk *vs.* GBC was maintained in those receiving cisplatin/gemcitabine combination therapy in EHC (HR 0.64; 95% CI 0.5–0.82; p <0.001) and IHC (HR 0.54; 95% CI 0.41–0.72; p <0.001), but not in CCA-NS (HR 1.04; 95% CI 0.71–1.53; $p = 0.82$) or ampulla of Vater cancer (HR 0.99; 95% CI 0.64–1.54; $p = 0.96$), acknowledging smaller patient numbers in the latter 2 groups (Table 2).

For patients that received "other combination" therapy (see Table S1 for details on regimens), there was a reduced risk of death *vs.* GBC in all sites: EHC (HR 0.63; 95% CI 0.4–0.99; $p = 0.043$), IHC (HR 0.62; 95% CI 0.41–0.95; $p = 0.026$), CCA-NS (HR 0.65; 95% CI 0.53–0.8; p <0.001) and ampulla of Vater cancer (HR 0.37; 95% CI 0.2–0.7; $p = 0.002$).

In patients who received monotherapy, only the CCA-NS group had a reduced risk of death *vs.* GBC (HR 0.67; 95% CI 0.46–0.96; $p = 0.03$).

Association between treatment and overall survival adjusted for potential confounding factors

Baseline CA 19-9 (μg/l) was only available for 254 patients in ABC-02 (measurement was not mandated on initiation of ABC-02)[6] and was not available for the other studies included in this manuscript. The median baseline CA 19-9 in ABC-02 was 175 μg/L (range 1–862,480). In ABC-02, when adjusted for the

Table 2. Median overall survival by biliary tract tumour primary site and association with risk of death from any cause by treatment group (gallbladder cancer as reference group).*

Primary tumour site**	Median OS (months) (95% CI)	Treatment-adjusted HR (95% CI; p value)	Monotherapy HR (95% CI; p value) (n)	Cis/Gem combination HR (95% CI; p value) (n)	***Other combination HR (95% CI; p value)
Gallbladder cancer (n = 385)	8.5 (7.7–9.3)	Reference	Reference (n = 87)	Reference (n = 140)	Reference (n = 156)
Extrahepatic CCA (n = 247)	11.1 (9.9–12.4)	0.67 (0.56–0.79, p <0.001)	0.78 (0.57–1.05, p = 0.104) (n = 87)	0.64 (0.50–0.82, p <0.001) (n = 135)	0.63 (0.40–0.99, p = 0.043) (n = 23)
Intrahepatic CCA (n = 209)	11.5 (9.3–13.4)	0.60 (0.50–0.73, p <0.002)	0.74 (0.54–1.02, p = 0.063) (n = 73)	0.54 (0.41–0.72, p <0.001) (n = 95)	0.62 (0.41–0.95, p = 0.026) (n = 28)
CCA (not specified) (n = 363)	11.0 (9.7–12.5)	0.70 (0.60–0.83, p <0.003)	0.67 (0.46–0.96, p = 0.03) (n = 46)	1.04 (0.71–1.53, p = 0.824) (n = 35)	0.65 (0.53–0.80, p <0.001) (n = 280)
Ampulla of Vater (n = 53)	11.8 (9.0–14.0)	0.63 (0.47–0.86, p = 0.003)	0.62 (0.35–1.12, p = 0.112) (n = 14)	0.99 (0.64–1.54, p = 0.96) (n = 24)	0.37 (0.20–0.70, p = 0.002) (n = 15)

CCA, cholangiocarcinoma; Cis/Gem, Cisplatin/Gemcitabine; HR, hazard ratio.
*Cox proportional hazards regression.
**Primary tumour site not available in 76 patients; where data was not available, numbers in treatment groups may not align with overall numbers.
***For details on combination regimens, please see Table S1.

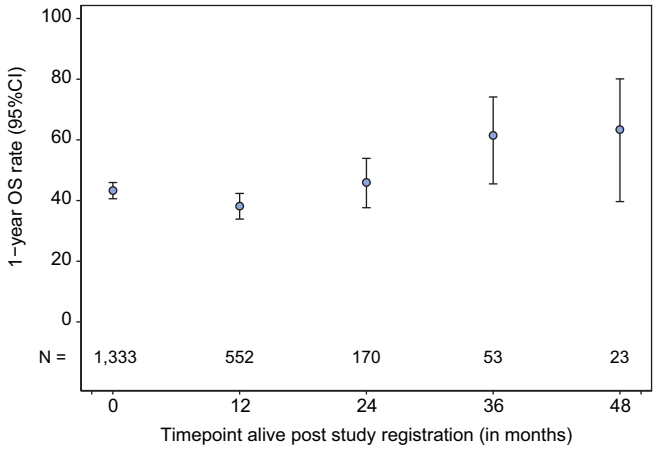

Fig. 1. One-year OS rate amongst patients who survived beyond 1, 2, 3 and 4 years following trial registration. If one measures survival from 3 years after trial registration and restricts the analysis to only those alive 3 years post registration, the 1-year survival rate is 61% amongst patients with advanced biliary tract cancer. OS, overall survival.

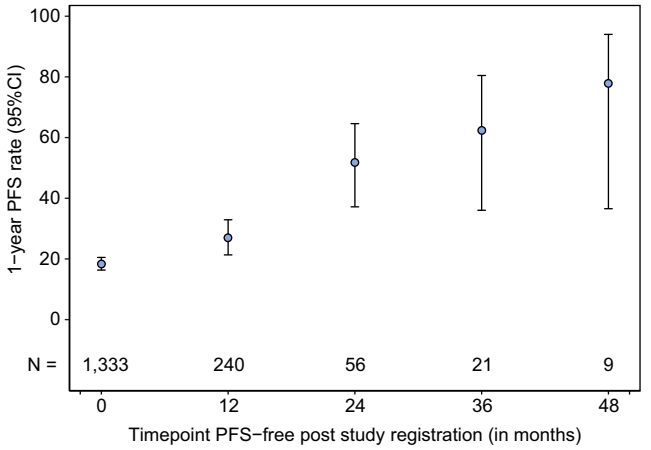

Fig. 2. One-year PFS rate amongst patients who were alive and free from disease beyond 1, 2, 3 and 4 years following trial registration. If one measures PFS from 3-years post registration and restricts the analysis to only those alive and free from progression 3 years post registration, the 1-year PFS rate is 62% amongst patients with advanced biliary tract cancer. PFS, progression-free survival.

variables CA 19-9, ECOG-PS, gender, and disease stage (locally advanced/metastatic), the HR for OS for combination *vs.* monotherapy was 0.66 (95% CI 0.51–0.85; p = 0.001). In ABC-02, the unadjusted HR for OS for combination *vs.* monotherapy was 0.64 (95% CI 0.52–0.80; p <0.001), therefore there is little evidence of a confounding effect associated with these variables.

In the entire cohort included within this study, where data was available (n = 1,312), the unadjusted HR for OS for combination *vs.* monotherapy was 0.70 (95% CI 0.61–0.79; p <0.001). When adjusting for ECOG-PS, gender, and disease stage (locally advanced/metastatic), where data was available, the HR for OS for combination *vs.* monotherapy was 0.67 (95% CI 0.58–0.77; p <0.001; n = 1,128), and therefore there is no evidence of possible confounding.

One-year landmark overall survival and progression-free survival

One year OS rate amongst patients who survived beyond 1 (n = 552), 2 (n = 170), 3 (n = 53), and 4 (n = 23) years following trial registration were 37% (95% CI 33–42), 45% (95% CI 37–53), 61% (95% CI 45–73), and 63% (95% CI 39–79), respectively (Fig. 1). The landmark PFS rates at 1 year, given that a PFS event was not experienced at 1, 2, 3 and 4 years following trial registration were 27% (95% CI 21–33), 52% (95% CI 37–65), 62% (95% CI 36–80) and 78% (95% CI 37–94), respectively (Fig. 2). The landmark PFS rates at 1 year, given that the PFS event was not experienced at 3- and 6-months following trial registration are presented in Table 3.

Assessment of prognostic factors at 1-year after trial registration

For patients who survived 1 year, those receiving combination therapy *vs.* monotherapy (HR 0.73; 95% CI 0.59–0.92; p = 0.008), and those with IHC (HR 0.68; 95% CI 0.51–0.92; p = 0.01) and CCA-NS (HR 0.75; 95% CI 0.58–0.97; p = 0.003) *vs.* GBC had better survival. Those receiving combination cisplatin/gemcitabine (p = 0.022) or another combination (p = 0.011) (for details of regimens, see Table S1) had better LS than those receiving monotherapy 1-year after trial registration. Metastatic stage *vs.* locally advanced was associated with shorter survival (HR 1.40; 95% CI 1.14–1.73; p = 0.002), and age, ECOG-PS and gender had no effect on LS (p = 0.34, p >0.05, p = 0.08, respectively) (Table 4).

Discussion

Inclusion of patients with aBTC, without stratification by anatomical primary sites, within clinical trials is debated,[36] due primarily to emerging knowledge on the genomic and transcriptomic heterogeneity in this disease group.[7]

In the current study, patients with GBC, who made up approximately one-third of those included, had numerically worse OS compared to other anatomic BTC sites. The median OS for these patients (8.5 months) was not dissimilar to the median OS of 8.1 months for those who received gemcitabine alone in the ABC-02 trial.[6] This is surprising given that those with GBC (n = 149) had similar benefit from cisplatin/gemcitabine in ABC-02 to other aBTC subtypes with a reduced HR for death (HR 0.61; 95% CI 0.42–0.89).[6] In the current study, patients with tumours from all other included aBTC primary sites, adjusted for treatment, had a decreased risk of death *vs.* GBC. This reduced risk of death *vs.* GBC was maintained in those receiving combination therapy (cisplatin/gemcitabine or other combination therapy), with the exception of those with a CCA-NS or ampulla of Vater primary tumour location who received cisplatin/gemcitabine, which may be attributable to smaller numbers included in these 2 groups.

The study of Nakamura *et al.*[7] demonstrated that the molecular spectra of GBC (n = 29) differs from that of cholangiocarcinoma, and this may contribute to the worse outcomes seen in patients with GBC. For example, the apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like (APOBEC)-mediated somatic mutational signature, which was associated with APOBEC3B expression and higher mutational number, was preferentially expressed in GBC rather than cholangiocarcinoma. Similarly, Javle *et al.* performed hybrid capture-based comprehensive genomic profiling on GBC tumour tissue (n = 85) (stage III and IV: 94%) and reported that the most frequent genetic aberrations observed were in *TP53* (59%), cyclin-dependent

Table 3. The landmark PFS rate at 1 year, given that the PFS event was not experienced at 3 and 6 months following trial registration for each BTC primary site.*

BTC primary site	n	1-year PFS rate (%) (95% CI)
Landmark PFS at 3 months		
GBC	264	11.4 (7.9–15.5)
EHC	187	19.0 (13.7–24.9)
IHC	148	18.6 (12.8–25.3)
CCA-NS	256	19.2 (14.6–24.3)
Ampulla of Vater	39	21.1 (9.9–35.1)
Landmark PFS at 6 months**		
GBC	167	13.8 (9.1–19.5)
EHC	134	20.2 (13.9–27.3)
IHC	106	17.9 (11.3–25.8)
CCA-NS	175	19.1 (13.5–25.4)
Ampulla of Vater	26	26.9 (11.9–44.5)

BTC, biliary tract cancer; CCA-NS, cholangiocarcinoma-not specified; EHC, extrahepatic cholangiocarcinoma; GBC, gallbladder cancer; HR, hazard ratio; IHC, intrahepatic cholangiocarcinoma; PFS, progression-free survival.
*Survival rates and 95% CIs were calculated.
**If one measures PFS from 6 months following trial registration and restricts the analysis to only those patients alive and free from progression at 6 months post registration, the 1-year progression-free survival rate was 17.9% for patients with intrahepatic cholangiocarcinoma and 13.8% for patients with a gallbladder cancer primary.

Table 4. Landmark survival estimates at 1-year following trial registration by gender, ECOG-PS, primary site, stage (metastatic stage *vs.* locally advanced), and therapy received (combination therapy *vs.* monotherapy).*

Variable	Landmark overall survival rate at 1 year (%) (95% CI)	HR (95% CI) [*p* value]
Gender		
Female	38.5 (32.5–44.5)	Reference
Male	35.2 (29.2–41.2)	1.18 (0.98–1.43) [0.084]
ECOG-PS		
0	41.6 (34.5–48.6)	Reference
1	33.5 (27.8–39.3)	1.09 (0.89–1.34) [0.402]
2	31.3 (11.4–53.6)	1.36 (0.80–2.31) [0.263]
BTC primary site		
GBC	27.2 (19.9–36)	Reference
EHC	36.5 (27.7–45.3)	0.78 (0.59–1.03) [0.074]
IHC	41.9 (32–51.6)	0.68 (0.51–0.92) [0.011]
CCA-NS	42.1 (33.9–50.2)	0.75 (0.58–0.97) [0.03]
Ampulla of Vater	39.7 (20.3–58.6)	0.73 (0.45–1.18) [0.199]
Disease stage		
Locally advanced	43.5 (35.6–51.1)	Reference
Metastatic	33.2 (28.1–38.3)	1.40 (1.14–1.73) [0.002]
Treatment		
Monotherapy	25.9 (17.8–34.8)	Reference
Combination	40.2 (35.4–45)	0.73 (0.59–0.92) [0.008]

BTC, biliary tract cancer; CCA-NS, cholangiocarcinoma-not specified; EHC, extrahepatic cholangiocarcinoma; GBC, gallbladder cancer; HR, hazard ratio; IHC, intrahepatic cholangiocarcinoma; PFS, progression-free survival. Time-to-event endpoints (overall survival) were measured amongst patients event-free at each specific time point post randomisation: 0, 12, 24, 36 and 48 months (0, 1, 2, 3 and 4 years); they were measured as the time from that relevant time point to the time of the event of interest (death). Patients who did not experience the event of interest were censored at the date that they were last known to be alive. Survival rates and 95% CIs were calculated. Due to the exploratory nature of the analysis, no adjustment for multiple testing was performed. Differences were considered to be statistically significant at p value <0.05.
*Survival rates and 95% CIs were calculated.

kinase inhibitor 2A/B (*CDKN2A/B*) (19%), AT-rich interactive domain-containing protein 1A (*ARID1A*) (13%), and *ERBB2* (16%).[37] In addition, Li *et al.* identified, through exome and ultra-deep sequencing of cancer-related genes in 57 tumour/normal pairs (GBC), that ErbB signalling pathways (including epidermal growth factor receptor, ERBB2, ERBB3, ERBB4 and their downstream genes) were the most extensively mutated (reported in 36.8% of GBC samples), and patients with ErbB pathway mutations had a worse outcome.[38]

In patients with multiple myeloma, the APOBEC signature results in an increased mutational load and a poor prognosis,[39] and similarly in non-small cell lung cancer, APOBEC3B has been reported to be upregulated and predicts bad prognosis, but durable clinical benefit after immunotherapy.[40] Two on-going first-line aBTC clinical trials of cisplatin/gemcitabine ± immunotherapy (NCT03875235 [TOPAZ-1] and NCT04003636 [Keynote-966]) may provide insight as to whether patients with GBC, compared to other aBTC subtypes, actually derive more clinical benefit from immunotherapy.

There is emerging data that specific genomic subtypes can have major responses to targeted therapy such as tumours that harbour fibroblast growth factor receptor 2 (*FGFR2*) gene rearrangements/fusions,[41] or with an isocitrate dehydrogenase 1 *(IDH1)* mutation.[42] These alterations are predominantly found in patients with IHC; in the phase II trial of pemigatinib in patients with pretreated cholangiocarcinoma, *FGFR2* gene rearrangements/fusions were found in 98% of patients with IHC and 1% with EHC (1% unknown),[41] and in the ivosidenib study in pretreated patients with cholangiocarcinoma and *IDH1* mutations, 89.5% of patients had IHC and 4% had an extrahepatic/perihilar primary (6.5% unknown primary).[42] These alterations have not been reported in patients with GBC, and they may contribute to better OS, as seen in patients with IHC (*post hoc* analysis of 3 first-line advanced clinical trials in BTC).[43] It has also been reported that ampullary carcinomas (n = 14) can be divided into a good prognosis intestinal-like subgroup and a poor prognosis biliary-like subgroup, with a 5-year OS of 70% *vs.* 28% (p = 0.09) (validated in an independent 80 patient ampullary dataset).[44] Accurate histological identification appears to be important prior to inclusion of patients whose tumours originate in this anatomic location in trials for aBTC, due to potential differences in outcome.

Based on the currently available data, inclusion of all BTC subtypes in prospective aBTC clinical trials is justified, including those with histologically identified biliary-like ampullary tumours,[44,45] but with stratification potentially of GBC *vs.* other primary sites. This stratification should be given particular consideration in molecularly unselected trials, as to date, the biomarker-driven trials predominantly involve recruitment of patients with *FGFR2* fusion/rearrangements or *IDH1* mutations, which are not found in GBC.[36] However, adjusted guidance will likely be required as the application of precision medicine to the aBTC therapeutic pathway evolves.

In IHC, the prevalence of *FGFR2* fusion/rearrangements has been reported as 10–16%[46] and *IDH1* mutations as 18% in US centres.[47] Given that the current study included only 16% of patients with confirmed IHC, recruitment to subgroup studies including populations of patients harbouring these mutations in the first-line aBTC clinical trial setting will be challenging (*e.g.* NCT03656536 [FIGHT-302] and NCT03773302 [PROOF] investigating cisplatin/gemcitabine ± FGFR2 inhibitors in patients with advanced/metastatic or inoperable cholangiocarcinoma with *FGFR2* gene fusions/translocations), but achievable, with sustained international collaborative efforts. This also highlights the need for on-going studies in unselected aBTC populations in the

first-line setting (*e.g.* NCT03875235 [TOPAZ-1], NCT04003636 [Keynote-966] and NCT04163900 [NuTide 121]; evaluating NUC-1031 plus cisplatin *vs.* cisplatin/gemcitabine in patients with aBTC).

This study also suggests that alternative combination therapies to cisplatin/gemcitabine may result in similar OS estimates,[48,49] and may potentially be considered in patients who may have a contraindication to receiving cisplatin, such as renal disease or diabetic-induced neuropathy, for example. It should be noted though that many of these studies were non-randomised and so validation of these combination regimens in randomised studies is imperative. However, one might argue that the focus of future efforts should principally be on building on the established efficacy benefit of the cisplatin/gemcitabine combination, through chemotherapy combinations,[50] and/or targeted/novel therapies ± immunotherapy.

Landmark survival analysis allows for accurate prognosis estimates of survival amongst patients with aBTC and may help in adequate powering of second-line clinical studies as, by definition, patients will have survived long enough to be recruited to such studies. This study also provides important information for patients who have already survived for some time. For example, in a patient with aBTC who has already survived for 3 years following trial randomisation, the landmark survival is 61% (the survival probability, excluding those patients who have died at this point), and is greater than the estimated 1 year survival rate for a newly diagnosed patient with aBTC, which was 41% in this collaborative study. The factors favouring survival at 1-year landmark time included receiving combination therapy *vs.* monotherapy, as expected,[6] and an IHC or CCA-NS primary tumour location, which may be associated with genomic signatures and a different tumour biology.[43,46] Metastatic stage *vs.* locally advanced was associated with shorter survival, while ECOG-PS (with the majority of patients having a known ECOG-PS of 0 or 1) and gender had no apparent effect on survival, analogous to a combination systemic therapy study in the first-line setting in patients with metastatic colorectal cancer, where gender also had no impact on efficacy.[51] Interestingly, in the ABC-02 study, those patients with locally advanced disease had a greater numerical reduction in risk of death (53%) on combination cisplatin/gemcitabine than those with metastatic disease (26%).[6]

Limitations of this analysis include the non-availability of certain data in some studies, heterogeneity of trials and treatments given in the included series, in first- and potentially subsequent lines of therapy. Data was not available for subsequent lines of therapy in the included studies, except for ABC-02[6] and ABC-03[35]; given that these trials enrolled patients with advanced disease, the use of locoregional treatment would be anticipated to be minimal unless within clinical trials[52] (of data available, 1% of those enrolled in ABC-02 and -03 received locoregional therapy, perhaps reflecting the inaccessibility of these technologies within the years of trial recruitment, and therefore their impact on outcomes in the overall cohort is probably negligible) and curative intent resection would not have been anticipated.

However, to date, no prospective phase III trial has reported a survival advantage over that reported in ABC-02,[6] and so the conclusions reached seem applicable to standard clinical practice and answer important questions utilising a large prospectively collected dataset in a poor prognosis disease. All data were from centres of excellence in treating patients with this diagnosis and so accurate primary site diagnosis is expected, but not guaranteed. Another limitation associated with LS analysis is that when comparing groups such as monotherapy *vs.* combination therapy in evaluable patients at 1 year, baseline characteristics, for example, may be different between these groups. However, the landmark times chosen correspond to clinically meaningful periods of time in patients with aBTC. In addition, as many of the analysed trials were non-randomised phase II studies, outcomes on therapy (monotherapy *vs.* combination) may be affected by selection bias, with those included in combination studies potentially being clinically fitter.

Conclusions

Patients with GBC have worse OS than those with other anatomic BTC primary sites and preclinical studies are needed to advance knowledge of the molecular pathogenesis of BTCs. This will aid in the identification of biomarkers and novel treatment options for GBC and other BTC subtypes.[53] Landmark survival estimates provide extremely valuable and encouraging information for patients who surpass their expected median PFS and OS projected at diagnosis, or at therapeutic initiation, and critically, the time extension may afford them the opportunity to participate in future practice-changing trials.

Abbreviations

aBTC, advanced biliary tract cancer; BTC, biliary tract cancer; CCA-NS, cholangiocarcinoma-not specified; EHC, extrahepatic cholangiocarcinoma; HR, hazard ratio; IHC, intrahepatic cholangiocarcinoma; LS, landmark survival; NR, not reported; OS, overall survival; PFS, progression-free survival.

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current study. They did fund the data collection for ABC-02 and analysis was performed by Andre Lopes, who is funded by CRUK. They did not have a role in the interpretation of the data or in writing the manuscript.

Conflict of interest

MMN has received honoraria from Ipsen, NuCana and Mylan, research funding from Ipsen, NuCana and Servier (previously SHIRE) and travel assistance from Ipsen, Bayer and Novartis. AL has no conflicts of interest to declare. HW has received honoraria from Lilly, Merck, Roche, and Celgene, speaker fees from Merck and Celgene, research funding from Sirtex and Pfizer, and travel assistance from Merck, Sirtex, Lilly, and Celgene. DM has honoraria and non-financial support from Amgen, Bayer, Ipsen, Merck Serono, Merck Sharp and Dohme, Roche, Sanofi, Servier; honoraria from Incyte, Shire, HalioDx and Agios. DG receives indirect research funding from Amgen, Celgene, and Pfizer and has stock ownership in Sirtex. JS has received consultancy fees from Merck and Amgen. TO receives honoraria from Chugai Pharmaceutical Co., Ltd, Pfizer Japan, Inc., Novartis Pharma K.K., Taiho Pharmaceutical Co., Ltd, Merck Serono Co., Ltd, Eli Lilly Japan K.K., Dainippon Sumitomo Pharma Co., Ltd, Eisai Co., Ltd, Bayer, Ltd, FUJI FILM Co., Ltd, and Yakult Honsha Co., Ltd. He also has a consulting or advisory role with Eli Lilly Japan K.K., Yakult Honsha Co., Ltd, Amgen, Dainippon Sumitomo Pharma Co., Ltd, Taiho Pharmaceutical Co., Ltd, OncoTherapy Science, Inc., Nobelpharma Co., Ltd, Ono Pharmaceutical Co., Ltd, Nippon Boehringer Ingelheim Co., Ltd, Nano Carrier Co., Ltd, Chugai Pharmaceutical Co., Ltd, Novartis Pharma K.K., and Zeria Pharmaceutical Co., Ltd. He receives indirect research funding from Chugai Pharmaceutical Co., Ltd, Eli Lilly Japan K.K., Eisai Co., Ltd, Novartis Pharma K.K., Shizuoka Industry, Takeda Bio Development Center Ltd, Yakult Honsha Co., Ltd, OncoTherapy Science, Inc., Otsuka Pharmaceutical Co., Ltd, Taiho Pharmaceutical Co., Ltd, Sceti Medical Labo K.K., Nippon Boehringer IngelheimCo., Ltd, Kowa Company, Ltd,KyowaHakko Kirin Co., Ltd, Merck Serono Co., Ltd, Ono Pharmaceutical Co., Ltd, Bayer, Ltd, Pfizer Japan, Inc., AstraZeneca K.K., and Dainippon Sumitomo Pharma Co., Ltd. JK receives research funding from Astra Zeneca. DW has received educational grant support from Roche, and honoraria from Bristol-Myers Squibb, Servier Suisse, Merck Sharp & Dohme, Bayer, EMD Serono, Lilly, Sanofi, Celgene, Astra Zeneca, AbbVie, Sanofi-Aventis Deutchland, SHIRE and Pfizer outside this submitted work. TA has served in a consulting/advisory role and or received honoraria from, Amgen, Bristol-Myers Squibb, Chugai, Clovis, Halliodx, MSD Oncology, Pierre Fabre, Roche/Ventana, Sanofi, Servier and has received travel, accommodation, and expenses from Roche/Ventana, MSD Oncology, and Bristol-Myers Squibb. DC receives indirect research funding from AstraZeneca, Amgen, Celgene, Merck, Serono, Sanofi, Merrimack, and Medimmune, Bayer, 4SC, Clovis, Eli Lilly and Janssen. MM receives research funding from Bayer and Lilly. LJ has received travel and accommodation funding from Amgen, Roche, and Sanofi. DK has not declared any conflicts of interest. TBS research funding (to institution): Boston Biomedical, Bayer, Amgen, Merck, Celgene, Lilly, Ipsen, Clovis, Seattle Genetics, Array Biopharma, Genentech, Abgenomics, Incyte, BMS. Consulting (to institution): Ipsen, Array Biopharma, Bayer, Genentech, Incyte and Merck. IDMC/DSMB (to self): Astra Zeneca, Exelixis, Lilly, PanCan and 1Globe. Scientific Advisory Board: Imugene, Immuneering and Sun Biopharmahas. JB has received honoraria from Merck Serono, Roche, Sanofi, and Bayer. JWV received honoraria in advisory capacity from Astra Zeneca, Agios, Taiho, Merck, Celgene, QED, PCI Biotech, Incyte, Pieris Pharmaceuticals, Genoscience Pharma, Mundipharma EDO and research funding from Lilly.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

MMN came up with the concept and design of this study. AL performed statistical analysis. All authors contributed data and have read and interpreted data and edited and approved the final version of this manuscript.

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Declarations

Ethics approval and consent to participate. All patients gave written informed consent to participate in individual trials. All trials were approved by appropriate research ethics committees and regulatory authorities and conducted in accordance with the Declaration of Helsinki.

Availability of data and materials

The International Biliary Tract Cancer Collaborators provided approval for the use of these data and data are stored within the Cancer Research UK (CRUK) & University College London (UCL) Cancer Trials Centre (CTC). The data that support the findings of this study are available from Cancer Research UK & UCL Cancer Trials Centre, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Cancer Research UK & UCL Cancer Trials Centre.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2020.05.014.

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Landmark survival analysis and impact of anatomic site of origin in prospective clinical trials of biliary tract cancer

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Table S1……2

Table S1. Details of prospective trials included in analysis.

Relevant publication	***N*[a]**	**Phase of trial**	**Systemic Therapy**
Andre et al 2008[39]	67	II, Non-randomised	Gemcitabine/Oxaliplatin
Bekaii-Saab et al 2011[40]	28	II, Non-randomised	Selumetinib
Bridgewater et al 2016 (ABC-04)[41]	13	Ib, Non-randomised	Cisplatin/Gemcitabine/Selumetinib
Ferraro et al 2016 (TACTIC)[42]	48	II, Non-randomised	Cisplatin/Gemcitabine/Panitumumab
Goldstein et al 2011[43]	50	II, Non-randomised	Cisplatin/Gemcitabine
Jensen et al 2012[44]	46	II, Non-randomised	Gemcitabine/Oxaliplatin/Panitumumab/ Capecitabine
Koeberle et al 2008[45]	44	II, Non-randomised	Gemcitabine/Capecitabine
Lassen et al 2011[46]	41	II, Non-randomised	Gemcitabine/Oxaliplatin/Capecitabine
Malka et al 2014 (BINGO)[47]	150	II, Randomised	Gemcitabine/Oxaliplatin ± Cetuximab
Moehler et al 2014 (AIO)[48]	102	II, Randomised	Gemcitabine ± Sorafenib
Okusaka et al 2010 (BT22)[49]	83	II, Randomised	Gemcitabine ± Cisplatin
Peck et al 2012[50]	9	II, Non-randomised	Lapatinib
Rao et al 2005[51]	54	III, Randomised	5-Fluorouracil/Etoposide/Leucovorin versus Epirubicin/Cisplatin/5-Fluorouracil

Riechelmann et al 2007[33]	75	II, Non-randomised	Gemcitabine/Capecitabine
Valle et al 2010 (ABC-02)[6]	410	III, Randomised	Gemcitabine ± Cisplatin
Valle et al 2015 (ABC-03)[20]	124	II, Randomised	Cisplatin/Gemcitabine ± Cediranib
Vogel et al 2018 (PICCA)[52]	90	II, Randomised	Cisplatin/Gemcitabine ± Panitumumab
Wagner et al 2009[53]	72	II, Non-randomised	Gemcitabine/Oxaliplatin/5-Fluorouracil

N: Number of patients included in trials, [a]Due to non-availability of some data, all patients were not included in overall analysis.

JOURNAL
OF HEPATOLOGY

Journal of Hepatology

CTAT methods

Tables for a "Complete, Transparent, Accurate and Timely account" (CTAT) are now mandatory for all revised submissions. The aim is to enhance the reproducibility of methods.

- Only include the parts relevant to your study
- Refer to the CTAT in the main text as 'Supplementary CTAT Table'
- Do not add subheadings
- Add as many rows as needed to include all information
- Only include one item per row

If the CTAT form is not relevant to your study, please outline the reasons why:

In relation to 1.1: no antibodies involved. In relation to 1.2: no cell lines involved. In relation to 1.3: no organisms involved. In relation to 1.4: there were no sequence based reagents involved. In relation to 1.5: there were no biological samples involved. In relation to 1.6: there is no deposited data. Wording has been included in manuscript under "Availability of data and materials" section, as follows: "The data that support the findings of this study are available from Cancer Research UK & UCL Cancer Trials Centre, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Cancer Research UK & UCL Cancer Trials Centre. In relation to 1.7: details are included below of software used. In relation to 1.8: there were no drugs/proteins/vectors used. In relation to 1.9: I have included my details: Mairéad McNamara. In relation to 2.0: this is not a report of a randomised controlled trial.

1.1 Antibodies

Name	Citation	Supplier	Cat no.	Clone no.

1.2 Cell lines

Name	Citation	Supplier	Cat no.	Passage no.	Authentication test method

1.3 Organisms

Name	Citation	Supplier	Strain	Sex	Age	Overall n number

1.4 Sequence based reagents

Name	Sequence	Supplier

1.5 Biological samples

Description	Source	Identifier

1.6 Deposited data

Name of repository	Identifier	Link

1.7 Software

Software name	Manufacturer	Version
Stata statistical software package	Stata Corporation, College Station, Texas	version 15.1

1.8 Other (e.g. drugs, proteins, vectors etc.)

1.9 Please provide the details of the corresponding methods author for the manuscript:

Mairéad McNamara: Mairead.McNamara@christie.nhs.uk

2.0 Please confirm for randomised controlled trials all versions of the clinical protocol are included in the submission. These will be published online as supplementary information.

Not applicable.

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ICMJE Form for Disclosure of Potential Conflicts of Interest

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Non-Financial Support: Examples include drugs/equipment supplied by the entity, travel paid by the entity, writing assistance, administrative support, etc.
Other: Anything not covered under the previous three boxes
Pending: The patent has been filed but not issued
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Royalties: Funds are coming in to you or your institution due to your patent

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Section 1. Identifying Information

1. Given Name (First Name): Mairead
2. Surname (Last Name): McNamara
3. Date: 07-April-2020

4. Are you the corresponding author? ☑ Yes ☐ No

5. Manuscript Title
Landmark survival analysis and impact of anatomic site of biliary tract tumour origin in prospective advanced clinical trials

6. Manuscript Identifying Number (if you know it)
JHEPAT-D-20-00313

Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☐ Yes ☑ No

Section 3. Relevant financial activities outside the submitted work.

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the "Add +" box. You should report relationships that were **present during the 36 months prior to publication.**

Are there any relevant conflicts of interest? ☑ Yes ☐ No

If yes, please fill out the appropriate information below.

Name of Entity	Grant?	Personal Fees?	Non-Financial Support?	Other?	Comments
Ipsen	☑	☐	☐	☐	
NuCana	☑	☐	☐	☐	
Mylan	☐	☐	☐	☑	
Servier	☑	☐	☐	☐	
Bayer	☐	☐	☐	☑	
Novartis	☐	☐	☐	☑	

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Dr. McNamara reports grants from Ipsen, grants from NuCana, other from Mylan, grants from Servier, other from Bayer, other from Novartis, outside the submitted work.

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Section 1. Identifying Information

1. Given Name (First Name): Andre
2. Surname (Last Name): Lopes
3. Date: 07-April-2020

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Mairead McNamara

5. Manuscript Title: Landmark survival analysis and impact of anatomic site of biliary tract tumour origin in prospective advanced clinical trials

6. Manuscript Identifying Number (if you know it): JHEPAT-D-20-00313

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

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Dr. Lopes has nothing to disclose.

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Section 1. Identifying Information

1. Given Name (First Name): Harpreet
2. Surname (Last Name): Wasan
3. Date: 07-April-2020

4. Are you the corresponding author? ☐ Yes ☑ No
Corresponding Author's Name: Mairead McNamara

5. Manuscript Title
Landmark survival analysis and impact of anatomic site of biliary tract tumour origin in prospective advanced clinical trials

6. Manuscript Identifying Number (if you know it)
JHEPAT-D-20-00313

Section 2. The Work Under Consideration for Publication

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Are there any relevant conflicts of interest? ☑ Yes ☐ No

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Name of Entity	Grant?	Personal Fees?	Non-Financial Support?	Other?	Comments
Lilly	☐	☐	☐	☑	Honoraria
Merck	☐	☐	☐	☑	Honoraria
Roche	☐	☐	☐	☑	Honoraria
Celgene	☐	☐	☐	☑	Honoraria
Sirtex	☑	☐	☐	☐	
Pfizer	☑	☐	☐	☐	
Sirtex	☐	☐	☐	☑	Travel

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): David
2. Surname (Last Name): Malka
3. Date: 07-April-2020

4. Are you the corresponding author? ☐ Yes ☑ No
Corresponding Author's Name: Mairead McNamara

5. Manuscript Title: Landmark survival analysis and impact of anatomic site of biliary tract tumour origin in prospective advanced clinical trials

6. Manuscript Identifying Number (if you know it): JHEPAT-D-20-00313

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Ipsen	☐	☐	☐	☑	Honoraria
Merck Serono	☐	☐	☐	☑	Honoraria
Merck Sharp and Dohme	☐	☐	☐	☑	Honoraria
Roche	☐	☐	☐	☑	Honoraria
Sanofi	☐	☐	☐	☑	Honoraria
Servier	☐	☐	☐	☑	Honoraria

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Shire	☐	☐	☐	☑	Honoraria
HalioDx	☐	☐	☐	☑	Honoraria
Agios	☐	☐	☐	☑	Honoraria

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4. Intellectual Property.

This section asks about patents and copyrights, whether pending, issued, licensed and/or receiving royalties.

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Non-Financial Support: Examples include drugs/equipment supplied by the entity, travel paid by the entity, writing assistance, administrative support, etc.
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Royalties: Funds are coming in to you or your institution due to your patent

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): David
2. Surname (Last Name): Goldstein
3. Date: 07-April-2020

4. Are you the corresponding author? ☐ Yes ☑ No
Corresponding Author's Name: Mairead McNamara

5. Manuscript Title
Landmark survival analysis and impact of anatomic site of biliary tract tumour origin in prospective advanced clinical trials

6. Manuscript Identifying Number (if you know it)
JHEPAT-D-20-00313

Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☐ Yes ☑ No

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Are there any relevant conflicts of interest? ☑ Yes ☐ No

If yes, please fill out the appropriate information below.

Name of Entity	Grant?	Personal Fees?	Non-Financial Support?	Other?	Comments
Amgen	☑	☐	☐	☐	Research funding
Celgene	☑	☐	☐	☐	Research funding
Pfizer	☑	☐	☐	☐	Research funding
Sirtex	☐	☐	☐	☑	Stock ownership

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Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

Section 5. Relationships not covered above

Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

☐ Yes, the following relationships/conditions/circumstances are present (explain below):

☑ No other relationships/conditions/circumstances that present a potential conflict of interest

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Section 6. Disclosure Statement

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Dr. Goldstein reports grants from Amgen, grants from Celgene, grants from Pfizer, other from Sirtex, outside the submitted work; .

Evaluation and Feedback

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Jenny
2. Surname (Last Name): Shannon
3. Date: 07-April-2020

4. Are you the corresponding author? ☐ Yes ☑ No
Corresponding Author's Name: Mairead McNamara

5. Manuscript Title: Landmark survival analysis and impact of anatomic site of biliary tract tumour origin in prospective advanced clinical trials

6. Manuscript Identifying Number (if you know it): JHEPAT-D-20-00313

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Are there any relevant conflicts of interest? ☑ Yes ☐ No

If yes, please fill out the appropriate information below.

Name of Entity	Grant?	Personal Fees?	Non-Financial Support?	Other?	Comments
Merck	☐	☐	☐	☑	Consultancy fees
Amgen	☐	☐	☐	☑	Consultancy fees

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Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

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Dr. Shannon reports other from Merck, other from Amgen, outside the submitted work; .

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Section 1. Identifying Information

1. Given Name (First Name): Takuji
2. Surname (Last Name): Okusaka
3. Date: 07-April-2020

4. Are you the corresponding author? ☐ Yes ☑ No
Corresponding Author's Name: Mairead McNamara

5. Manuscript Title: Landmark survival analysis and impact of anatomic site of biliary tract tumour origin in prospective advanced clinical trials

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Section 2. The Work Under Consideration for Publication

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

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Are there any relevant conflicts of interest? ☑ Yes ☐ No

If yes, please fill out the appropriate information below.

Name of Entity	Grant?	Personal Fees?	Non-Financial Support?	Other?	Comments
Chugai Pharmaceutical	☐	☐	☐	☑	Honoraria
Pfizer	☐	☐	☐	☑	Honoraria
Novartis	☐	☐	☐	☑	Honoraria
Taiho	☐	☐	☐	☑	Honoraria
Merck Serono	☐	☐	☐	☑	Honoraria
Eli Lilly	☐	☐	☐	☑	Honoraria
Dainippon Sumitomo	☐	☐	☐	☑	Honoraria
Eisai	☐	☐	☐	☑	Honoraria

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Bayer	☐	☐	☐	☑	Honoraria
Fuji film	☐	☐	☐	☑	Honoraria
Yakult Honsha	☐	☐	☐	☑	Honoraria
Eli Lilly	☐	☐	☐	☑	Consultancy
Yakult Honsha	☐	☐	☐	☑	Consultancy
Amgen	☐	☐	☐	☑	Consultancy
Dainippon Sumitomo	☐	☐	☐	☑	Consultancy
Taiho	☐	☐	☐	☑	Consultancy
OncoTherapy Science	☐	☐	☐	☑	Consultancy
Nobelpharma	☐	☐	☐	☑	Consultancy
Nippon Boehringer Ingelheim	☐	☐	☐	☑	Consultancy
Nano Carrier Co	☐	☐	☐	☑	Consultancy
Chugai Pharma	☐	☐	☐	☑	Consultancy
Novartis	☐	☐	☐	☑	Consultancy
Zeria Pharma	☐	☐	☐	☑	Consultancy
Chugai Pharma	☑	☐	☐	☐	Research funding
Eli Lilly	☑	☐	☐	☐	Research funding
Eisai	☑	☐	☐	☐	Research funding
Novartis	☑	☐	☐	☐	Research funding
Shizuoka Industry	☑	☐	☐	☐	Research funding
Takeda	☑	☐	☐	☐	Research funding
Yakult Honsha	☑	☐	☐	☐	Research funding
OncoTherapy Science	☑	☐	☐	☐	Research funding
Otsuka Pharma	☑	☐	☐	☐	Research funding
Taiho	☑	☐	☐	☐	Research funding
Sceti Medical	☑	☐	☐	☐	Research funding
Nippon Boehringer Ingelheim	☑	☐	☐	☐	Research funding
Kowa company	☑	☐	☐	☐	Research funding
Kyowa Hakko Kirin Co	☑	☐	☐	☐	Research funding
Merck Serono	☑	☐	☐	☐	Research funding

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Ono Pharma	☑	☐	☐	☐	Research funding
Bayer	☑	☐	☐	☐	Research funding
Pfizer	☑	☐	☐	☐	Research funding
Astra Zeneca	☑	☐	☐	☐	Research funding
Dainippon Sumitomo Pharma	☑	☐	☐	☐	Research funding

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

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Dr. Okusaka reports other from Chugai Pharmaceutical, other from Pfizer, other from Novartis, other from Taiho, other from Merck Serono, other from Eli Lilly, other from Dainippon Sumitomo, from null, other from Eisai, other from Bayer, other from Fuji film, other from Yakult Honsha, other from Eli Lilly, other from Yakult Honsha, other from Amgen, other from Dainippon Sumitomo, other from Taiho, other from OncoTherapy Science, other from Nobelpharma, other from Nippon Boehringer Ingelheim, other from Nano Carrier Co, other from Chugai Pharma, other from Novartis, other from Zeria Pharma, grants from Chugai Pharma, grants from Eli Lilly, grants from Eisai, grants from Novartis, grants from Shizuoka Industry, grants from Takeda, grants from Yakult Honsha, grants from OncoTherapy Science, grants from Otsuka Pharma, . grants from Taiho, grants from Sceti Medical, grants from Nippon Boehringer Ingelheim, grants from Kowa company, grants from Kyowa Hakko Kirin Co, grants from Merck Serono, grants from Ono Pharma, grants from Bayer, grants from Pfizer, grants from Astra Zeneca, grants from Dainippon Sumitomo Pharma, outside the submitted work; .

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Jennifer J
2. Surname (Last Name): Knox
3. Date: 07-April-2020

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Mairead McNamara

5. Manuscript Title: Landmark survival analysis and impact of anatomic site of biliary tract tumour origin in prospective advanced clinical trials

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If yes, please fill out the appropriate information below.

Name of Entity	Grant?	Personal Fees?	Non-Financial Support?	Other?	Comments
Astra Zeneca	☑	☐	☐	☐	Research funding

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

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Royalties: Funds are coming in to you or your institution due to your patent

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Anna Dorothea
2. Surname (Last Name): Wagner
3. Date: 07-April-2020

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Mairead McNamara

5. Manuscript Title: Landmark survival analysis and impact of anatomic site of biliary tract tumour origin in prospective advanced clinical trials

6. Manuscript Identifying Number (if you know it): JHEPAT-D-20-00313

Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☐ Yes ☑ No

Section 3. Relevant financial activities outside the submitted work.

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Are there any relevant conflicts of interest? ☑ Yes ☐ No

If yes, please fill out the appropriate information below.

Name of Entity	Grant?	Personal Fees?	Non-Financial Support?	Other?	Comments
Roche	☑	☐	☐	☐	Educational Grant
Bristol-Myers Squibb	☐	☐	☐	☑	Honoraria
Servier Suisse	☐	☐	☐	☑	Honoraria
Merck Sharp & Dohme	☐	☐	☐	☑	Honoraria
Bayer	☐	☐	☐	☑	Honoraria
EMD Serono	☐	☐	☐	☑	Honoraria
Lilly	☐	☐	☐	☑	Honoraria
Celgene	☐	☐	☐	☑	Honoraria

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Name of Entity	Grant?	Personal Fees?	Non-Financial Support?	Other?	Comments
Astra Zeneca	☐	☐	☐	☑	Honoraria
AbbVie	☐	☐	☐	☑	Honoraria
Sanofi-Aventis	☐	☐	☐	☑	Honoraria
Shire	☐	☐	☐	☑	Honoraria
Pfizer	☐	☐	☐	☑	Honoraria

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

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Dr. Wagner reports grants from Roche, other from Bristol-Myers Squibb, other from Servier Suisse, other from Merck Sharp & Dohme, other from Bayer, other from EMD Serono, other from Lilly, other from Celgene, other from Astra Zeneca, other from AbbVie, other from Sanofi-Aventis, other from Shire, other from Pfizer, outside the submitted work; .

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ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Thierry
2. Surname (Last Name): Andre
3. Date: 07-April-2020

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Mairead McNamara

5. Manuscript Title: Landmark survival analysis and impact of anatomic site of biliary tract tumour origin in prospective advanced clinical trials

6. Manuscript Identifying Number (if you know it): JHEPAT-D-20-00313

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

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If yes, please fill out the appropriate information below.

Name of Entity	Grant?	Personal Fees?	Non-Financial Support?	Other?	Comments
Amgen	☐	☐	☐	☑	Honoraria
Bristol Myers-Squibb	☐	☐	☐	☑	Honoraria
Chugai	☐	☐	☐	☑	Honoraria
Clovis	☐	☐	☐	☑	Honoraria
Halliodx	☐	☐	☐	☑	Honoraria
MSD Oncology	☐	☐	☐	☑	Honoraria
Pierre Fabre	☐	☐	☐	☑	Honoraria
Roche/Ventana	☐	☐	☐	☑	Honoraria

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Sanofi	☐	☐	☐	☑	Honoraria
Servier	☐	☐	☐	☑	Honoraria
Roche/Ventana	☐	☐	☐	☑	Travel
MSD Oncology	☐	☐	☐	☑	Travel
Bristol-Myers Squibb	☐	☐	☐	☑	Travel

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

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Dr. Andre reports other from Amgen, other from Bristol Myers-Squibb, other from Chugai, other from Clovis, other from Halliodx, other from MSD Oncology, other from Pierre Fabre, other from Roche/Ventana, other from Sanofi, other from Servier, other from Roche/Ventana, other from MSD Oncology, other from Bristol-Myers Squibb, outside the submitted work; .

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): David
2. Surname (Last Name): Cunningham
3. Date: 07-April-2020

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Mairead McNamara

5. Manuscript Title: Landmark survival analysis and impact of anatomic site of biliary tract tumour origin in prospective advanced clinical trials

6. Manuscript Identifying Number (if you know it): JHEPAT-D-20-00313

Section 2. The Work Under Consideration for Publication

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

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Astra Zeneca	☑	☐	☐	☐	Research funding
Amgen	☑	☐	☐	☐	Research funding
Celgene	☑	☐	☐	☐	Research funding
Merck	☑	☐	☐	☐	Research funding
Serono	☑	☐	☐	☐	Research funding
Sanofi	☑	☐	☐	☐	Research funding
Merrimack	☑	☐	☐	☐	Research funding
Medimmune	☑	☐	☐	☐	Research funding

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Bayer	☐	☐	☐	☑	Research funding
4SC	☐	☐	☐	☑	Research funding
Clovis	☐	☐	☐	☑	Research funding
Eli Lilly	☐	☐	☐	☑	Research funding
Janssen	☐	☐	☐	☑	Research funding

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Markus
2. Surname (Last Name): Moehler
3. Date: 07-April-2020

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Mairead McNamara

5. Manuscript Title: Landmark survival analysis and impact of anatomic site of biliary tract tumour origin in prospective advanced clinical trials

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Lilly	☑	☐	☐	☐	Research funding

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Lars Henrik
2. Surname (Last Name): Jensen
3. Date: 07-April-2020

4. Are you the corresponding author? ☐ Yes ☑ No
Corresponding Author's Name: Mairead McNamara

5. Manuscript Title
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Are there any relevant conflicts of interest? ☑ Yes ☐ No

If yes, please fill out the appropriate information below.

Name of Entity	Grant?	Personal Fees?	Non-Financial Support?	Other?	Comments
Amgen	☐	☐	☐	☑	Travel
Roche	☐	☐	☐	☑	Travel
Sanofi	☐	☐	☐	☑	Travel

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

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Section 5. Relationships not covered above

Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

☐ Yes, the following relationships/conditions/circumstances are present (explain below):

☑ No other relationships/conditions/circumstances that present a potential conflict of interest

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Section 6. Disclosure Statement

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Dr. Jensen reports other from Amgen, other from Roche, other from Sanofi, outside the submitted work; .

Evaluation and Feedback

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Non-Financial Support: Examples include drugs/equipment supplied by the entity, travel paid by the entity, writing assistance, administrative support, etc.
Other: Anything not covered under the previous three boxes
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Licensed: The patent has been licensed to an entity, whether earning royalties or not
Royalties: Funds are coming in to you or your institution due to your patent

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name)
Dieter

2. Surname (Last Name)
Koeberle

3. Date
07-April-2020

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name
Mairead McNamara

5. Manuscript Title
Landmark survival analysis and impact of anatomic site of biliary tract tumour origin in prospective advanced clinical trials

6. Manuscript Identifying Number (if you know it)
JHEPAT-D-20-00313

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Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☐ Yes ☑ No

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

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Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

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Dr. Koeberle has nothing to disclose.

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Section 1. Identifying Information

1. Given Name (First Name): Tanios
2. Surname (Last Name): Bekaii-Saab
3. Date: 07-April-2020

4. Are you the corresponding author? ☐ Yes ☑ No
Corresponding Author's Name: Mairead McNamara

5. Manuscript Title
Landmark survival analysis and impact of anatomic site of biliary tract tumour origin in prospective advanced clinical trials

6. Manuscript Identifying Number (if you know it)
JHEPAT-D-20-00313

Section 2. The Work Under Consideration for Publication

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

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Are there any relevant conflicts of interest? ☑ Yes ☐ No

If yes, please fill out the appropriate information below.

Name of Entity	Grant?	Personal Fees?	Non-Financial Support?	Other?	Comments
Boston Biomedical	☑	☐	☐	☐	Research funding
Bayer	☑	☐	☐	☐	Research funding
Amgen	☑	☐	☐	☐	Research funding
Merck	☑	☐	☐	☐	Research funding
Celgene	☑	☐	☐	☐	Research funding
Lilly	☑	☐	☐	☐	Research funding
Ipsen	☑	☐	☐	☐	Research funding
Clovis	☑	☐	☐	☐	Research funding

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Name of Entity	Grant?	Personal Fees?	Non-Financial Support?	Other?	Comments
Seattle genetics	☑	☐	☐	☐	Research funding
Array Biopharma	☑	☐	☐	☐	Research funding
Genetech	☑	☐	☐	☐	Research funding
Abgenomics	☑	☐	☐	☐	Research funding
Incyte	☑	☐	☐	☐	Research funding
BMS	☑	☐	☐	☐	Research funding
Ipsen	☐	☐	☐	☑	Consultancy
Array Biopharma	☐	☐	☐	☑	Consultancy
Bayer	☐	☐	☐	☑	Consultancy
Genentech	☐	☐	☐	☑	Consultancy
Incyte	☐	☐	☐	☑	Consultancy
Merck	☐	☐	☐	☑	Consultancy
Astra Zeneca	☐	☐	☐	☑	IDMC
Exelixis	☐	☐	☐	☑	IDMC
Lilly	☐	☐	☐	☑	IDMC
PanCan	☐	☐	☐	☑	IDMC
1Globe	☐	☐	☐	☑	IDMC
Imugene	☐	☐	☐	☑	Advisory Board
Immuneering and Sun Biopharmahas	☐	☐	☐	☑	Advisory Board

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Dr. Bekaii-Saab reports grants from Boston Biomedical, grants from Bayer, grants from Amgen, grants from Merck, grants from Celgene, grants from Lilly, grants from Ipsen, grants from Clovis, grants from Seattle genetics, grants from Array Biopharma, grants from Genetech, grants from Abgenomics, grants from Incyte, grants from BMS, other from Ipsen, other from Array Biopharma, other from Bayer, other from Genentech, other from Incyte, other from Merck, other from Astra Zeneca, other from Exelixis, other from Lilly, other from PanCan, other from 1Globe, other from Imugene, other from Immuneering and Sun Biopharmahas, outside the submitted work; .

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): John
2. Surname (Last Name): Bridgewater
3. Date: 07-April-2020

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Mairead McNamara

5. Manuscript Title: Landmark survival analysis and impact of anatomic site of biliary tract tumour origin in prospective advanced clinical trials

6. Manuscript Identifying Number (if you know it): JHEPAT-D-20-00313

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Merck Serono	☐	☐	☐	☑	Honoraria
Roche	☐	☐	☐	☑	Honoraria
Sanofi	☐	☐	☐	☑	Honoraria
Bayer	☐	☐	☐	☑	Honoraria

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Dr. Bridgewater reports other from Merck Serono, other from Roche, other from Sanofi, other from Bayer, outside the submitted work; .

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Juan W
2. Surname (Last Name): Valle
3. Date: 07-April-2020

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Corresponding Author's Name: Mairead McNamara

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Are there any relevant conflicts of interest? ☑ Yes ☐ No

If yes, please fill out the appropriate information below. If you have more than one entity press the "ADD" button to add a row. Excess rows can be removed by pressing the "X" button.

Name of Institution/Company	Grant?	Personal Fees?	Non-Financial Support?	Other?	Comments
Lilly	☑	☐	☐	☐	Research funding

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Astra Zeneca	☐	☐	☐	☑	Honoraria
Agios	☐	☐	☐	☑	Honoraria
Taiho	☐	☐	☐	☑	Honoraria

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Merck	☐	☐	☐	☑	Honoraria
Celgene	☐	☐	☐	☑	Honoraria
QED	☐	☐	☐	☑	Honoraria
PCI Biotech	☐	☐	☐	☑	Honoraria
Incyte	☐	☐	☐	☑	Honoraria
Pieris Pharma	☐	☐	☐	☑	Honoraria
Genoscience Pharma	☐	☐	☐	☑	Honoraria
Mundipharma EDO	☐	☐	☐	☑	Honoraria

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Dr. Valle reports grants from Lilly, during the conduct of the study; other from Astra Zeneca, other from Agios, other from Taiho, other from Merck, other from Celgene, other from QED, other from PCI Biotech, other from Incyte, other from Pieris Pharma, other from Genoscience Pharma, other from Mundipharma EDO, outside the submitted work; .

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