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Hepatic and Biliary Cancer

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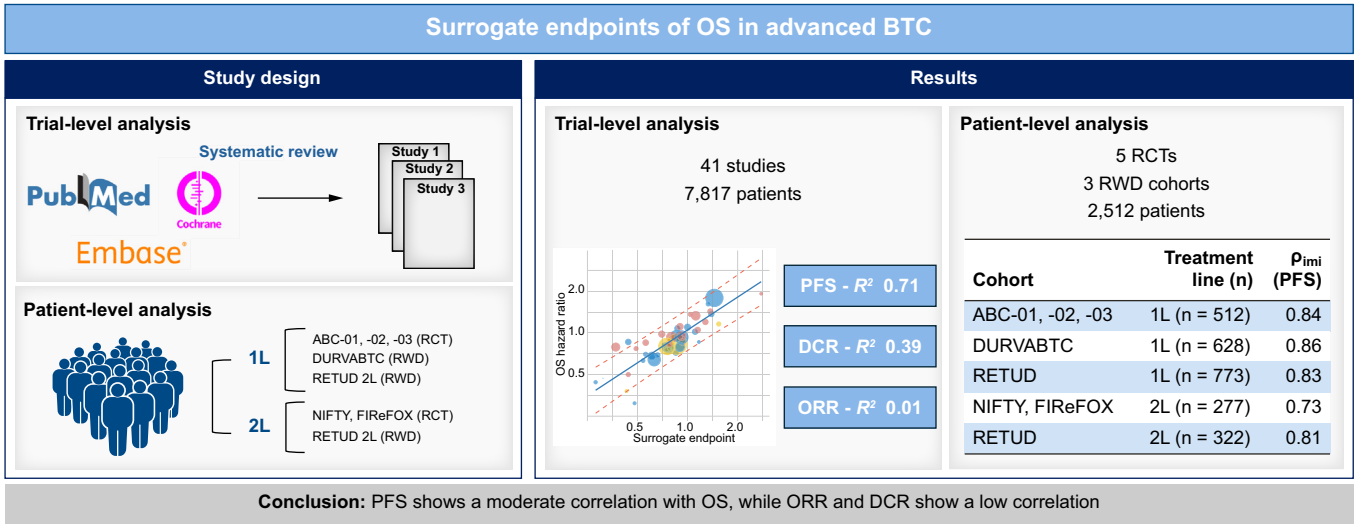
Graphical abstract



Highlights

- PFS showed a moderate correlation with OS at the trial- and patient-level.
- A PFS hazard ratio of 0.61 in a hypothetical trial of 200 patients would likely lead to an OS benefit.
- Disease control rate and response rate showed a low correlation at the trial-level.
- Patients who responded to first- or second-line chemotherapy did not show significantly improved OS.

Impact and implications

The use of validated surrogate endpoints in biliary tract cancer trials may decrease costs and improve study feasibility, particularly with agents that only target small subsets of patients or in trials that incorporate a crossover design. A formal statistical validation of surrogacy requires patient-level and trial-level data. This is the first comprehensive analysis to incorporate novel agents (including immunotherapies and targeted agents), include patient-level data and rigorously and homogeneously extract appropriate measures of treatment effect for endpoint correlation. These results show a moderate correlation for progression-free survival both at the trial- and patient-level and a low correlation for disease control rate and response rate. This information will aid clinicians in appropriately interpreting contemporary clinical trials and guide clinical researchers and trial sponsors involved in clinical trial design. Furthermore, it has important implications for the regulatory approval process and may aid agencies in appropriately evaluating novel drugs.

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Association of candidate surrogate endpoints with overall survival in advanced biliary tract cancer

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Background & Aims: Surrogate endpoints are increasingly used in biliary tract cancer (BTC) trials. While this may expedite drug approval and decrease costs, surrogate endpoints may not always correlate with an overall survival (OS) advantage. We aimed to explore the association of progression-free survival (PFS), objective response rate (ORR) and disease control rate (DCR) with OS at the trial- and patient-level.

Methods: For the trial-level analysis, we performed a systematic review of Pubmed/MEDLINE, Embase, Cochrane, clinicaltrials.gov and conference proceedings for phase II-III trials in advanced BTC. We used a weighted linear regression to measure the correlation of OS with PFS, ORR and DCR. For the patient-level analysis, we analyzed patients included in five randomized trials and three real-world datasets. The protocol is registered with PROSPERO, CRD42023398279.

Results: For the trial-level analysis, we included 41 studies, involving 88 treatment arms and 7,817 patients. The coefficient of determination (R^2) of the model was 0.71 (95% CI 0.56-0.86) for PFS, 0.01 (0-0.08) for ORR and 0.39 (0.14-0.64) for DCR. Predefined subgroup analysis showed consistent results. For the patient-level analysis, we included a total of 2,506 patients, 783 in randomized trials (first-line 512, second-line 271) and 1,723 in routine clinical care (first-line chemotherapy 773, first-line chemotherapy-durvalumab 628, second-line chemotherapy 322). Across the distinct datasets, the correlation coefficient ranged from 0.73 to 0.86 for PFS. A responder analysis found no association between response and survival.

Conclusion: PFS shows a moderate correlation with OS both at the trial- and patient-level, while ORR and DCR show a low correlation. Whilst PFS is currently the best candidate surrogate marker for OS, our results highlight the need for novel endpoints in this field.

Introduction

Biliary tract cancers (BTCs) are a heterogeneous group of aggressive neoplasms arising in the biliary tree.[1] Around 60% of tumors are diagnosed at advanced stages and more than 70% of tumors treated with local curative treatments will eventually relapse,[2] resulting in a dismal median survival of about 1 year despite optimal systemic treatment.[3,4]

In this setting, overall survival (OS) is the most robust, reliable and clinically meaningful endpoint for the design of randomized-controlled trials (RCTs).[5] The relatively low follow-up necessary to reach sufficient events, coupled with the scarcity of effective treatment options beyond first-line therapy, make OS an ideal endpoint and less prone to biases arising from post-progression treatment imbalances and biological differences in molecular subgroups.[6,7] However, some circumstances may hinder the interpretation of OS, such as crossover designs or conditional accelerated approval programs, where the experimental drug is made available to clinicians during the execution of the validation trial, leading to uncontrolled post-progression crossover.

Surrogate endpoints are intended to substitute for final patient-relevant outcomes that directly measure how patients feel, function or survive in clinical trials.[8] The use of surrogates is cost-effective and may overcome some of the challenges associated with OS. The use of these endpoints in oncology trials has increased dramatically in recent years, best reflected by the fact that 78% of drug approvals by the US FDA between 2005 and 2023 were based on surrogate endpoints.[9] However, only 32% of approved indications based on

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surrogate endpoints eventually demonstrated an improvement in OS,[10] highlighting the need for appropriate validation of these endpoints.

Previous studies have explored the association of progression-free survival (PFS) and objective response rate (ORR) with OS in BTC, although the results have been conflicting, the statistical methodology has been suboptimal, and only trial-level information has been included.[11–14] Despite the lack of robust data supporting the use of surrogate endpoints in BTC, 25% of randomized phase II-III trials used ORR as a primary endpoint and 44% used PFS.[15] In addition, the FDA has granted accelerated approval for pemigatinib and futibatinib based on ORR and duration of response for *FGFR2*-rearranged tumors and regular approval to ivosidenib based on PFS for *IDH1*-mutant tumors.[16]

To address these issues and explore the feasibility of using surrogate endpoints in advanced BTC, we performed a comprehensive analysis evaluating the association of PFS, ORR and disease control rate (DCR) at a trial-level through a meta-analysis of RCTs and at a patient-level through an analysis of five cohorts comprising both patients treated within the context of a RCT and in the real-world setting.

Patients and methods

Theoretical framework

One of the most used methodologies for evaluating potential surrogate endpoints is the two-stage meta-analytic framework, which requires individual patient-level data from all trials included in the systematic review to calculate the individual- and trial-level correlation.[17] In this framework, a validated endpoint will meet two conditions: demonstrate a correlation of treatment effects on both endpoints (Condition 1) and a strong correlation between the surrogate and definitive endpoint (Condition 2). One of the major limitations of this approach is that identified trials whose individual data cannot be retrieved are excluded from the trial-level analysis, which leads to a selection bias.[18,19] To address this potential limitation and because we did not have access to individual-level data from all identified trials in the systematic review, we applied an adaptation of this framework that intended to demonstrate both conditions.

For Condition 1 (trial-level), we performed a systematic review and correlation analyses of all trials based on aggregate-level data, as detailed below. For Condition 2 (patient-level), we analyzed two cohorts of patients included in RCTs evaluating first-line (ABC-01,[20] ABC-02[21] and ABC-03[22]) and second-line chemotherapy (NIFTY[23] and FIRe-FOX[24]). Given the complementary information provided by real-world data (RWD),[25] especially in the context of PFS, which is sensitive to the timing of assessments and response evaluation,[26] we also included a cohort of patients treated in the real-world setting with first-line chemotherapy, another cohort treated with cisplatin-gemcitabine and durvalumab and a final cohort of patients treated with second-line chemotherapy.

Protocol and registration

The protocol of the study was registered on the International Prospective Register of Systematic Reviews in February 2023 (PROSPERO registration ID CRD42023398279). Following a protocol amendment in October 2023, incorporating the patient-level data and an improvement in the search strategy, an updated systematic review and a new analysis were performed (see Protocol). We followed the PRISMA reporting guidelines.[27] The study was approved by the Vall d'Hebron Research Ethics Committee (PR(AG) 29/2024).

Search strategy

We searched Medline through Pubmed, Embase, Cochrane Library and ClinicalTrials.gov databases from inception to October 2023 (Table S1). Additionally, we searched references of the selected studies and abstract proceedings from the American Society of Clinical Oncology (ASCO), European Society of Medical Oncology (ESMO), ASCO Gastrointestinal Cancers Symposium (ASCO-GI), ESMO World Congress on Gastrointestinal Cancer and ESMO Asia.

The title and abstract of non-English studies were translated into English for the first screening step. The full text of those studies considered eligible for further evaluation was then translated. Of note, we identified no non-English study that required full-text evaluation.

All abstracts were reviewed and independently evaluated by two investigators through the Rayyan interface. Any disagreements were resolved by consensus with a third reviewer.

Eligibility criteria

Eligible studies were comparative phase II-III RCTs assessing systemic agents in the treatment of advanced BTC and included OS, PFS and/or ORR/DCR as an endpoint (Table S2). Studies that assessed locoregional or maintenance therapies, involved tumors other than BTC (except for periampullary carcinomas), were non-randomized, non-comparative or included patients in the (neo)adjuvant settings were excluded. The most recent and updated version of the trial was included in the final analysis.

Data extraction and quality assessment

We extracted the following data from the available reports: trial and baseline patient characteristics, number of patients included, endpoints, intervention details, median follow-up, response assessment criteria, OS hazard ratio (HR), PFS HR, ORR and DCR.

We generated funnel plots to assess publication bias (taking the 95% CIs to account for the heterogeneity estimated by the model) and used Egger's regression test to assess funnel plot asymmetry. Additionally, a *p* curve analysis was used to assess any further publication bias.

To assess the methodological quality of the included studies, we used two distinct tools: the Cochrane Handbook for Systematic Reviews of Interventions Risk of Bias tool (RoB version 2.0)[28] and the Delphi list.[29] Reports with a low or moderate risk of bias according to Cochrane's RoB or a score ≥5 points in the Delphi list were considered high quality.

A description of patients and datasets used for the individual-level correlation can be found in the supplementary materials and methods.

Statistical analyses

Condition 1 (Trial-level): All extracted endpoints were collected as defined by the trial. For trials that did not report HR, we estimated these with the methods described by Tierney *et al.* The odds ratio (OR) estimates for ORR and DCR were obtained from logistic regression models, including patients with measurable disease and considering non-evaluable patients as non-responders. The HR and OR were log-transformed and the associations estimated using a linear regression model weighed by trial size. The variation of the weighted treatment effects explained by the model was measured with the coefficient of determination (R^2).

The surrogate threshold effect (STE) represents the minimum treatment effect of the intermediate endpoint needed to predict a non-zero effect on OS and is calculated based on the prediction interval. The 95% prediction intervals were constructed for the regression line of the treatment effect on OS *vs*. the surrogate with a weight (*i.e*. trial size) of 200. The STE was defined as the intersection of the upper 95% prediction interval with the horizontal y-axis = 0, representing a hazard ratio of 1.[30,31]

We analyzed predefined subgroups according to the presence of crossover, trial size, type of treatment, disease setting/line of treatment and quality of the trials. We further performed two non-preplanned sensitivity analyses based on disease location and stage by assigning each trial a weight proportional to the number of included patients for each category. Additionally, we performed a leave-one-out cross-validation, whereby each trial was left out once, and the model was refitted with the remaining trials. The resulting model was then applied to the left-out trial to predict the effect of treatment on the reference endpoints. The R^2 of the cross-validated model was calculated as the correlation between the individual predictions made by the model and the actual treatment effects.[32]

Condition 2 (Patient-level): The correlation between OS and PFS was measured by using the normal score rank correlation, calculated by the iterative multiple imputation approach.[33] Although this approach is semiparametric and does not require any assumptions about the marginal distributions, it uses a Gaussian dependency structure. Therefore, we also calculated the rank correlation between OS and PFS using a non-parametric estimator of Spearman's correlation, based on a non-parametric bivariate survival surface estimator.[34] The 95% CIs were calculated by bootstrap resampling 1,000 times.

To evaluate the association between response and OS, we performed a responder analysis.[35–37] Responders were defined as patients who achieved a partial or complete response and non-responders as those with stable disease, progressive disease or whose response status was unknown or non-evaluable. To adjust for immortal-time bias, a landmark analysis was performed[38] at 3-month and 6-month landmark times for first-line trials and 2-month and 4-month times for second-line trials. Only the datasets of patients included in randomized trials were used for this analysis, as no longitudinal response assessment was available for the RWD cohorts.

We scored the strength following the criteria used by Prasad *et al.*:[39] low correlation ($r \leq 0.7$), moderate strength correlation ($r > 0.7$ to $r < 0.85$), and high correlation ($r \geq 0.85$).

All statistical analyses were completed using R version 4.1.2 (R Foundation).

Results

Condition 1: Trial-level association

Of the 8,576 records identified, a total of 41 randomized phase II and phase III clinical trials were eligible, including 44 treatment comparisons, 88 treatment arms and 7,817 patients (Fig. 1; Tables 1, 2 and S3). Most studies were phase II trials (70.7%), included first-line combinations (65.9%), tested chemotherapy (53.7%) or targeted/tyrosine kinase inhibitor (36.6%) agents, and were multicenter (80.5%), while only 2 (4.9%) allowed for crossover. The median follow-up was 10.85 months (IQR 10.1-15.7 months), although 17 (41.5%) trials did not report this information. Twenty trials (48.8%) used PFS as a primary endpoint and 16 (39%) used OS. Eleven (26.8%) were double blind and the remaining 30 trials were open-label.

We found no evidence of publication bias by applying the two distinct detection methods for OS, PFS and ORR (Fig. S1). A funnel plot asymmetry was detected for DCR, although the *p*-curve analysis showed that evidential value was present. The overall risk of bias was low or moderate, and only two studies were found to be at high risk of bias (Fig. S2 and S3). When applying the Delphi assessment criteria,[29] 35 studies were found to be of high quality, and six had a score below 5 points (Fig. S4).

The correlation between PFS and OS showed an R^2 of 0.71 (95% CI 0.56-0.86) and the STE was 0.61 (Fig. 2A), meaning that a HR of 0.61 in a hypothetical trial of 200 patients would likely lead to a non-zero effect on OS. Importantly, the correlations with ORR and DCR were low or non-existent, with R^2 values of 0.01 (95% CI 0-0.08) and 0.39 (95% CI 0.14-0.64), respectively (Fig. 2B,C). Prespecified subgroup analyses based on the line of treatment, presence of crossover, study phase, type of systemic treatment, sample size and trial quality confirmed these findings (Figs 2D, 3, S5 and S6). Non-preplanned sensitivity analyses showed consistent results for distinct disease locations and stages (Fig. S7–S9). The correlation of ORR and DCR with OS remained low across all subgroups. We further calculated the STE for all surrogate endpoints based on different hypothetical sample sizes (Table S4).

Finally, we performed a leave-one-out cross-validation procedure to confirm the correlation observed between OS and PFS. The R^2 ranged from 0.61 to 0.78. All trial HR estimates for OS fell within the predicted intervals except for three (Fig. S10). Two of these were highly influential trials in the cross-validation: the ClarIDHy trial,[40] whose exclusion from the model led to an R^2 of 0.78, and the NuTide:121,[41] whose exclusion led to an R^2 of 0.61. The R^2 remained consistent after individually excluding the remaining trials, with R^2 values that ranged from 0.7 to 0.73 (Fig. S10B).

Condition 2: Patient-level association

We analyzed five datasets involving 2,506 patients diagnosed with advanced BTC who received systemic treatments: a pooled population of 512 patients included in the ABC-01,[20] -02[21] and -03[22] trials, a RWD dataset of 628 patients treated with first-line cisplatin-gemcitabine and durvalumab, a RWD dataset of 773 patients treated with first-line chemotherapy, a pooled population of 271 patients included in the NIFTY[23] and

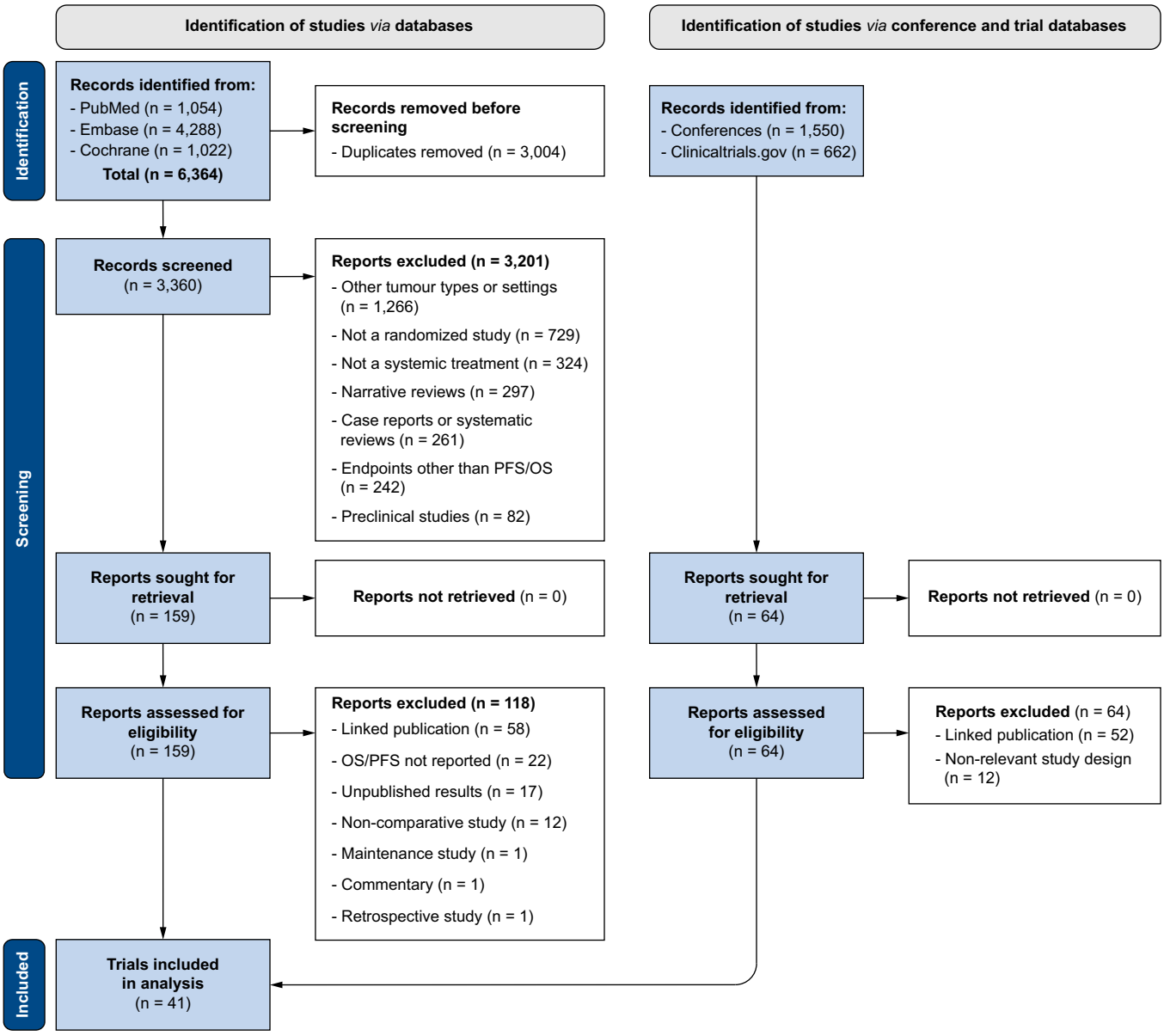

Fig. 1. PRISMA flowchart reporting the results of the systematic review.

FIReFOX[24] trials and a RWD dataset of 322 patients treated with standard second-line chemotherapy (Table S5–S8).

We estimated the correlation between PFS and OS at the patient-level using two distinct methods. We applied the multiple imputation approach[33] and found a rank correlation ranging between 0.73 and 0.86 across all five datasets (Table 3). Only the pooled population of NIFTY[23] and FIReFOX[24] trials showed a slightly lower correlation of 0.73, while all other datasets showed a rank correlation above 0.8. We also calculated the correlation using a more conservative, non-parametric estimator of Spearman's correlation.[34] This approach rendered similar results, although the correlation estimated by this method tended to be lower in all datasets, with a rank correlation that ranged between 0.68 and 0.82 (Table S9). We found consistent results across distinct disease locations and stages (Table S10 and S11).

Finally, to estimate the association between ORR and OS, we performed a responder analysis.[35–37] We only included datasets of patients treated in RCTs, as longitudinal response data was not available in the RWD. In the first-line setting, 370 patients had measurable disease and were included in this analysis. The ORR was 23% and the DCR was 77.8%. Responders did not experience better survival, either at the 3-month or 6-month landmark times (Fig. 4). In the second-line setting, 256 patients were included in the analysis. The ORR was 9.4% and the DCR was 64.1%. Similar to the first-line setting, responders did not experience better survival (Fig. S11). However, given the low response rate in the second-

Table 1. Characteristics of the trials, treatment comparisons and patients included in the studies.

	Patients (n = 7,817)	Trials (n = 41)	Comparisons (n = 44)[1]
Age, median (IQR)	63 (60.5–64)	-	-
Missing	151 (1.9%)		
Sex, n (%)		-	-
Males	3,952 (50.6%)		
Females	3,818 (48.8%)		
Missing	47 (0.6%)		
Tumor location, n (%)			
Intrahepatic	3,445 (44.1%)	37 (90.2%)	38 (86.4%)
Extrahepatic	1,410 (18%)	36 (87.8%)	37 (84.1%)
Gallbladder	2,272 (29.1%)	40 (97.6%)	43 (97.7%)
Ampullary	192 (2.5%)	17 (41.5%)	18 (40.9%)
Other	36 (0.5%)	-	-
Missing	462 (5.9%)	-	-
Disease stage, n (%)			
Locally advanced	1,457 (18.6%)	38[2] (95%)	41[2] (95.3%)
Metastatic	5,810 (74.3%)	41 (100%)	44 (100%)
Missing	550 (7%)	-	-
ECOG status, n (%)			
0	3,194 (40.9%)	40 (97.6%)	42 (95.5%)
1	3,569 (45.7%)	40 (97.6%)	42 (95.5%)
2-3	311 (4%)	14 (34.1%)	16 (36.4%)
Missing	743 (9.5%)	-	-
Number of centers, n (%)			
Multicenter	7,088 (90.7%)	33 (80.5%)	34 (77.3%)
Single-center	634 (8.1%)	6 (14.6%)	8 (18.2%)
Missing	95 (1.2%)	2 (4.9%)	2 (4.5%)
Treatment line, n (%)			
First line	6,164 (78.9%)	27 (65.9%)	29 (65.9%)
Beyond first line	1,653 (21.1%)	14 (34.1%)	15 (34.1%)
Systemic agents, n (%)			
Chemotherapy	5,295 (67.7%)	22[3] (53.7%)	23 (52.3%)
Immunotherapy	1,153 (14.7%)	5 (12.2%)	5 (11.4%)
Targeted therapy	1,066 (13.6%)	15[3] (36.6%)	16 (36.4%)
Placebo/BSC	303 (3.9%)	-	-
Clinical trial phase, n (%)			
Phase II	2,814 (36%)	29 (70.7%)	31 (70.5%)
Phase III	5,003 (64%)	12 (29.3%)	13 (29.5%)
Crossover, n (%)	53 (0.7%)	2 (4.9%)	2 (4.5%)
Follow-up (months), median (IQR)	-	10.85 (10.1–15.7)	-
Missing		17 (41.5%)	

BSC, best supportive care; ECOG, Eastern Cooperative Oncology Group.
[1]Three trials[54–56] contained three arms, leading to two comparisons.
[2]One trial[57] did not specify whether locally advanced patients were included.
[3]One trial[55] had two experimental arms, one including chemotherapy and another targeted therapy.

line setting, the number of responders at each landmark time is low and precludes any definitive conclusions.

Discussion

Inappropriate validation of intermediate endpoints may lead to the approval of potentially ineffective or even harmful treatments.[10] Previous studies have evaluated the association of PFS and response with OS at the trial-level in the context of first-[12,14] and second-line treatment of BTC.[11,13] Our analysis can be distinguished from these studies in several important ways: First, it is the only one, to our knowledge, that has included trial- and patient-level data. Second, it includes contemporary trials testing distinct systemic agents, including immunotherapies and targeted agents. Third, we rigorously extracted and calculated the HR for time-to-event endpoints and OR for binomial endpoints to ensure homogeneous analyses of these variables and appropriate measures of treatment effect. Finally, we also included RWD to complement the RCT information.

This comprehensive analysis suggests that the correlation for PFS is moderate both at the trial- and patient-level but is low for ORR and DCR in advanced BTC. Whether the strength of the correlation is sufficient to justify the use of PFS as a surrogate endpoint is arguable and controversial. For instance, PFS would meet the surrogacy criteria established by the BSES[42,43] and ReSEEM[17] guidelines, while the IQWiG[44] guidelines would consider the evidence "Unclear". Regulatory agencies have not established criteria for defining surrogate endpoints. We believe that PFS could be used as a primary endpoint in advanced BTC in circumstances when OS may be confounded, such as crossover designs or accelerated approval programs that may lead to uncontrolled post-progression crossover in the confirmatory trial. In these circumstances, a careful evaluation of OS should continue to be mandatory to ensure no detrimental effect is observed.[5,45] The magnitude of the benefit in PFS should also be considered. Our analysis of the STE shows that a magnitude of 0.61 (0.67 after excluding crossover trials) in PFS would likely lead to an OS

Table 2. Characteristics and design of the trials included in the systematic review.

Trial[1]	Treatments	Phase	N	Blinding	Primary Endpoint	Response evaluation	Timing of scans
ABC-02	CG Gemcitabine	III	410	Open-label	OS	RECIST 1.0	Q12w
ABC-03	CG+cediranib CG+placebo	II	124	Double blind	PFS	RECIST 1.1	Q12w
BilT-01	Nivo-ipi CG-nivo	II	68	Open-label	PFS 6 months	RECIST 1.1/irRECIST	Q8w
BREGO	mGEMOX+regorafenib mGEMOX	II	66	Open-label	NA	RECIST 1.0	NA
BT22	CG Gemcitabine	II	83	Open-label	OS 1 year	NA	Q8w
Chen 2015	GEMOX+cetuximab GEMOX	II	122	Open-label	ORR	RECIST 1.1	Q8w
ClarIDHy	Ivosidenib Placebo	III	187	Double blind	PFS	RECIST 1.1	Q6w
FIReFOX	mFOLFIRI mFOLFOX	II	118	Open-label	OS 6 months	RECIST 1.1	Q6w
Gambit	Irinotecan+Cisplatin CG	II	47	Open-label	ORR	RECIST 1.1	NA
GB-SELECT	CAPIRI Irinotecan	II	98	Open-label	OS 6 months	RECIST 1.1	Q8w
GEMSO-AIO	Gemcitabine+sorafenib Gemcitabine	II	97	Double blind	PFS	RECIST 1.0	Q8w
Ikeda 2023	Nanvuranlat Placebo	II	104	Double blind	PFS	RECIST 1.1	NA
IMbrave151	CG+atezolizumab+bevacizumab CG+atezolizumab+placebo	II	162	Double blind	PFS	RECIST 1.1	Q9w
JCOG0805	SG S1	II	101	Open-label	OS 1 year	RECIST 1.0	Q6w
JCOG1113	SG CG	III	354	Open-label	OS	RECIST 1.1	Q6w
Kang 2012	SG CG	II	96	Open-label	PFS 6 months	RECIST 1.0	Q6w
Kataria 2022	Capecitabine BSC	II/III	69	Open-label	OS	RECIST 1.1	NA
Kataria 2022	Erlotinib BSC	II/III	69	Open-label	OS	RECIST 1.1	NA
KEYNOTE-966	CG+pembrolizumab CG-placebo	III	1,069	Double blind	OS	RECIST 1.1	Q6w
KHBO1401-MITSUBA	CG CGS	III	246	Open-label	OS	RECIST 1.1	Q12w
Kim 2019	CAPOX GEMOX	III	222	Open-label	PFS	RECIST 1.1	Q6w
Lee 2012	GEMOX+erlotinib GEMOX	III	268	Open-label	PFS	RECIST 1.0	Q6w
Markussen 2020	GEMOX-capecitabine CG	II	96	Open-label	PFS	RECIST 1.1	Q12w
NALIRICC	5FU-nalIRI 5FU	II	100	Open-label	PFS	RECIST 1.1	Q6w
NIFTY	5FU-nalIRI 5FU	II	174	Open-label	PFS	RECIST 1.1	Q6w

(*continued on next page*)

Table 2. (*continued*)

Trial[1]	Treatments	Phase	N	Blinding	Primary Endpoint	Response evaluation	Timing of scans
Nutide:121	Cisplatin+NUC1031 CG	III	773	Open-label	OS, ORR	RECIST 1.1	Q9w
Pape 2020	CAP7.1 BSC	II	27	Open-label	DCR	RECIST 1.1	Q8w
PICCA	CG+panitumumab CG	II	90	Open-label	PFS 6 months	RECIST 1.0	Q6w
REACHIN	Regorafenib Placebo	II	66	Double blind	PFS	RECIST 1.1	Q6w
Schinzari 2017	FOLFOX4 De Gramont	II	48	Open-label	OS	RECIST 1.1	Q8w
Sharma 2010	mGEMOX BSC	II	53	Open-label	OS, ORR, toxicity	RECIST 1.0	Q6w
Sharma 2010	FUFA BSC	II	55	Open-label	OS, ORR, toxicity	RECIST 1.0	Q6w
Sharma 2019	mGEMOX CG	III	243	Open-label	OS	RECIST 1.1	NA
Shirahama 2017	PPV+CPA PPV	II	49	Open-label	Immune response	RECIST 1.0	Q8w
SWOG 1815	CG+Nab/paclitaxel CG	III	441	Open-label	OS	RECIST 1.1	Q9w
SWOG S1310	Trametinib 5FU/capecitabine	II	44	Open-label	OS	RECIST 1.1	Q6w
TOPAZ-1	CG+durvalumab CG	III	685	Double blind	OS	RECIST 1.1	Q6w
TreeTopp	Varlitinib+capecitabine Placebo+capecitabine	II	127	Double blind	ORR, PFS	RECIST 1.1	Q6w
Ueno 2021	Reminostat+S1 Placebo+S1	II	101	Double blind	PFS	RECIST 1.1	Q6w
Valle 2021	Ramucirumab Placebo	II	207	Double blind	PFS	RECIST 1.1	Q6w
Valle 2021	Merestinib Placebo	II	203	Double blind	PFS	RECIST 1.1	Q6w
Vecti-BIL	GEMOX+panitumumab GEMOX	II	89	Open-label	PFS	RECIST 1.1	Q8w
Yang 2022	Cisplatin+Nab/paclitaxel CG	II	67	Open-label	PFS	NA	NA
Zheng 2018	XELIRI Irinotecan	II	60	Open-label	PFS	RECIST 1.1	Q6w

BSC, best supportive care; CG, cisplatin + gemcitabine; DCR, disease control rate; NA, not available; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.
[1]A complete list of the studies referenced in the table is found in the Supplementary Materials.

Surrogate endpoints of OS in BTC

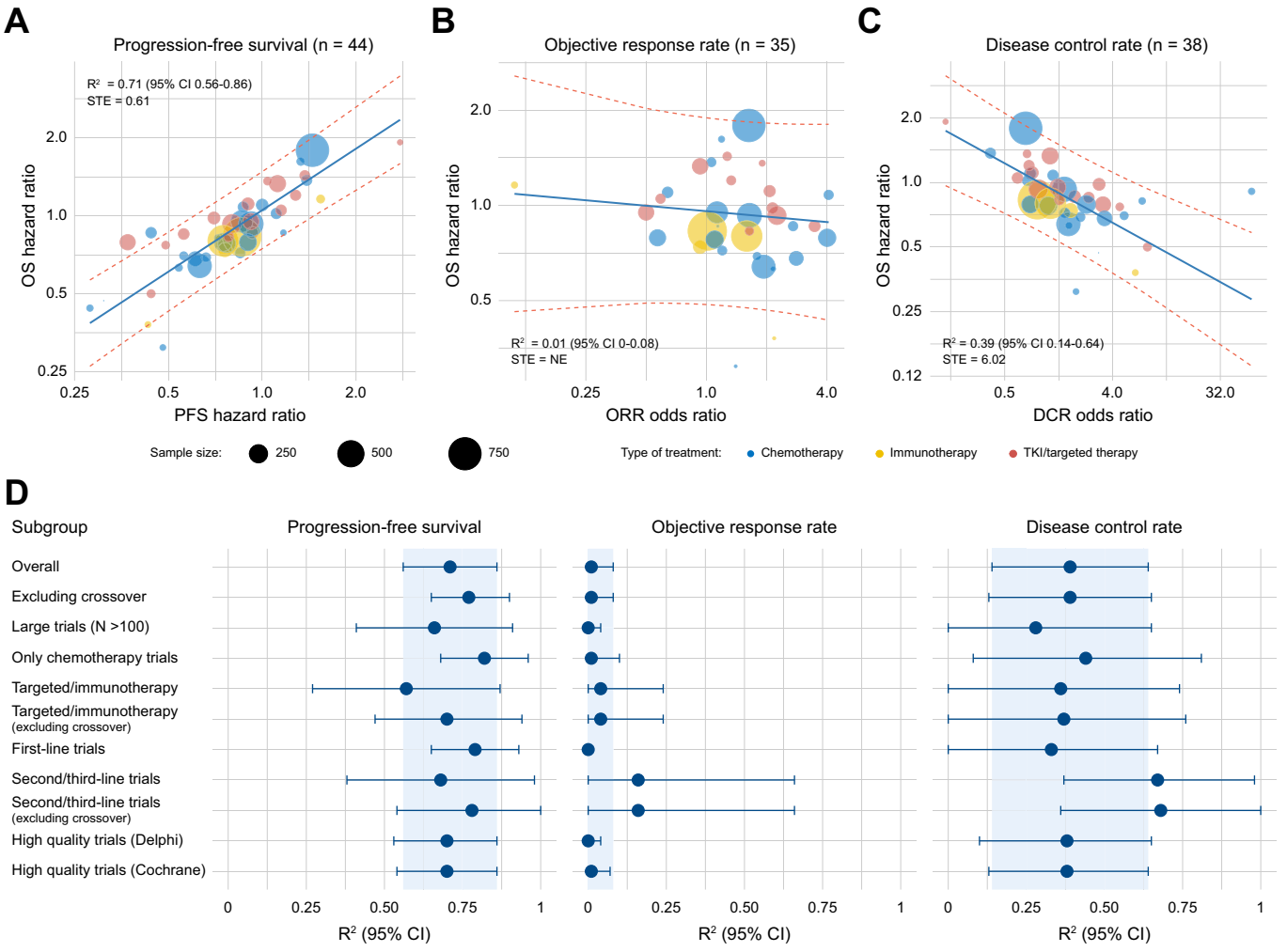

Fig. 2. Trial-level correlation of PFS, ORR and DCR with OS (Condition 1). Bubble plot assessing the correlation of (A) PFS, (B) ORR and (C) DCR with OS. Every bubble represents a trial, the color represents the treatment type and the size is proportional to the number of patients included in the trial. The hazard ratios and odds ratios are presented in the logarithmic scale. The red lines show the 95% prediction interval for a weight (*i.e.* sample size) of 200. (D) Subgroup analysis assessing the coefficient of determination across different subgroups according to the indicated criteria (left column). The shaded blue rectangles indicate the reference R^2 and its 95% CI of the global correlation. The correlation was estimated by using a linear regression model weighed by trial size. The variation of the weighted treatment effects explained by the model was measured with the coefficient of determination (R^2). DCR, disease control rate; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; STE, surrogate threshold effect.

benefit in a 200-patient randomized trial, which may be informative for interpreting and designing future studies. In addition, the use of a STE may provide a more reasonable standard for evaluating the magnitude of a treatment benefit in BTC when using PFS as a surrogate endpoint, such as the ones proposed by the ESMO Magnitude of Clinical Benefit Scale guidelines.[46] However, our data also highlight the importance of further refining and developing novel endpoints. In the case of PFS, for example, the use of time to treatment failure, which incorporates treatment discontinuation due to toxicity as an event to avoid informative censoring[26,47–49] or considering the pattern of progression may help to better capture OS.[50]

The results of our study do not support the use of either ORR or DCR as surrogate endpoints in this setting. Several factors may account for this finding. First, BTCs are frequently infiltrative and irregular, making it challenging to radiologically monitor the disease.[51] Second, patients who do not achieve a response might not be uniformly disadvantaged, especially when receiving non-cytotoxic agents, as these may confer improved survival by restraining tumor progression without inducing radiological responses.[3,40] Third, BTCs are densely fibrotic tumors in which treatment-induced tumor death may not necessarily lead to tumor shrinkage. Other parameters, such as metabolic changes, may be more accurate in discriminating response.[52] Finally, the low ORR observed with most systemic therapies in BTC may decrease the prognostic discrimination of response and lead to this poor correlation.

Several limitations should be considered when interpreting this study. First, the systematic review included a heterogeneous group of trials involving different study lines, treatment regimens and patient populations. Nonetheless, this high heterogeneity is necessary to support the assertion of the validity of a surrogate for application in a new trial.[53] Additionally, we conducted several predefined subgroup and sensitivity analyses which showed consistent levels of correlation. Second,

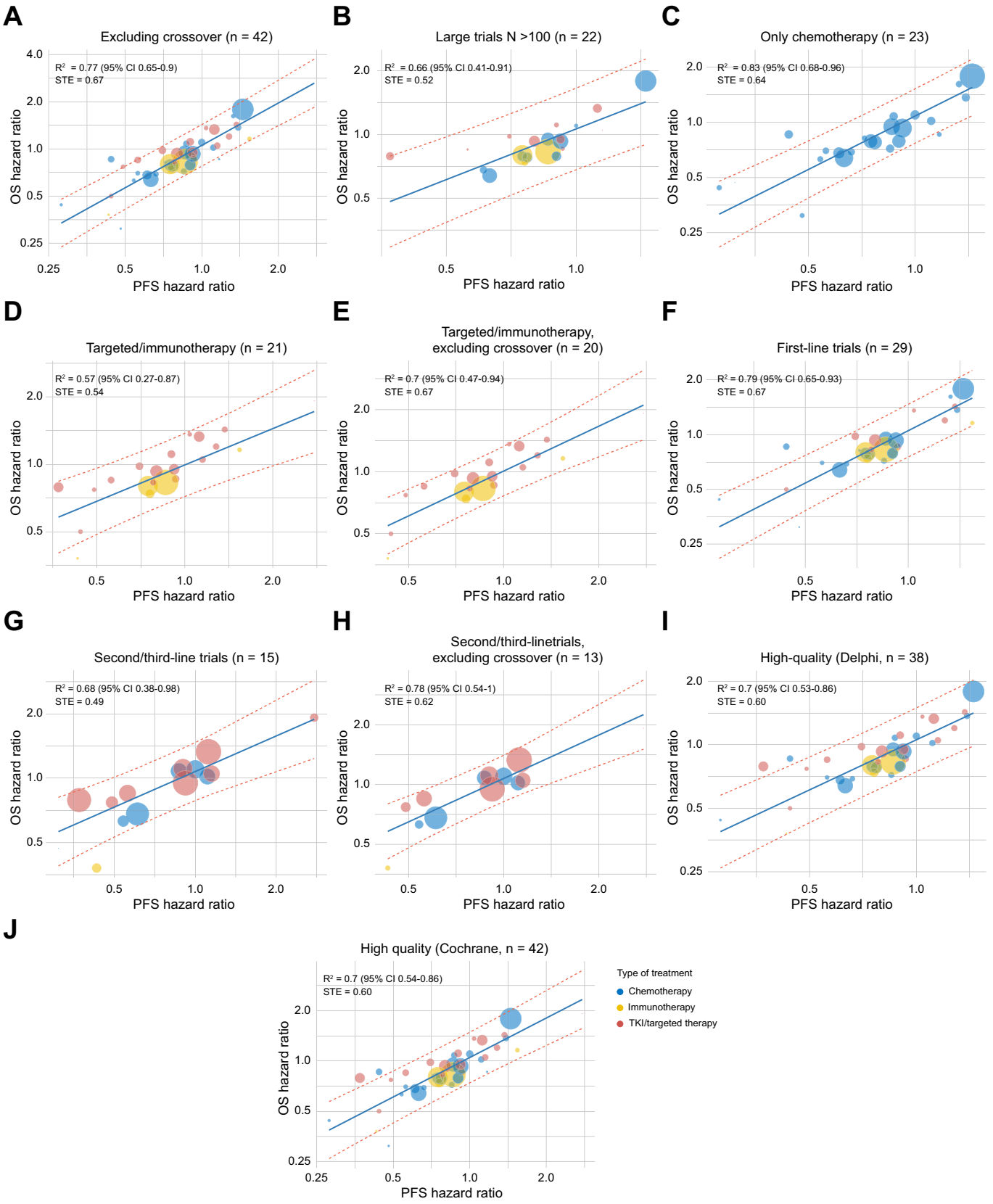

Fig. 3. Bubble plots showing the trial-level correlation for PFS and OS across different subgroups. Every bubble represents a trial, the color represents the treatment type and the size is proportional to the number of patients included in the trial. The hazard ratios are presented in the logarithmic scale. The red lines show the 95% prediction interval for a weight (*i.e.* sample size) of 200. The correlation was estimated by using a linear regression model weighed by trial size. The variation of the weighted treatment effects explained by the model was measured with the coefficient of determination (R^2). OS, overall survival; PFS, progression-free survival; STE, surrogate threshold effect.

Table 3. Patient-level correlation of PFS with OS across the different datasets using the iterative imputation method.

Cohort	Setting	Treatment line	N (events)	Follow-up (95% CI)	Median OS (95% CI)	Median PFS (95% CI)	ρ_{imi} (95% CI)
ABC-01, -02, -03	RCT	First line	512 (497)	51 (41.1-NA)	10.2 (9-11.5)	6.5 (6-7.4)	0.84 (0.81-0.86)
DURVABTC	RWD	First line	628 (190)	8.4 (7.8-9.4)	14.9 (13.4-17.8)	8.2 (7.5-8.9)	0.86 (0.81-0.9)
RETUD	RWD	First line	773 (623)	32 (25.3-37.3)	9.7 (8.7-10.4)	5 (4.5-5.4)	0.83 (0.8-0.85)
NIFTY, FIReFOX	RCT	Second line	277 (236)	33 (27-37.2)	6.3 (5.5-7.4)	2.6 (2.4-2.9)	0.73 (0.67-0.79)
RETUD	RWD	Second line	322 (279)	24.8 (22.3-NA)	5.2 (4.8-6)	2.8 (2.5-3)	0.81 (0.78-0.83)

The correlation coefficient ρ_{imi} was measured by using a normal score rank correlation calculated by the iterative multiple imputation approach.
Follow-up, OS, and PFS measured in months.
NA, not available; OS, overall survival; PFS, progression-free survival; RCT, randomized-controlled trial; RWD, real-world data.

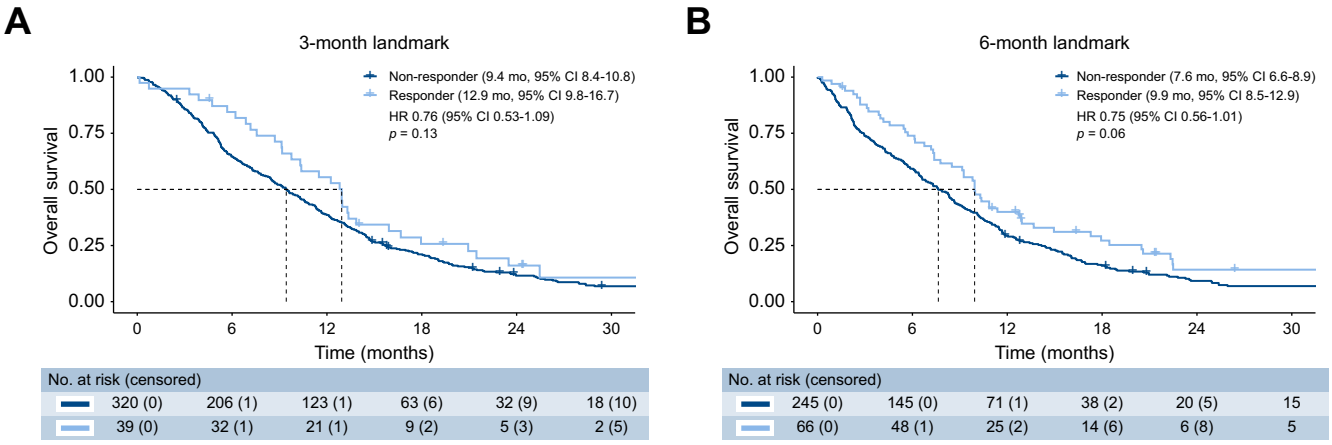

Fig. 4. Impact of response on survival in patients treated with first-line chemotherapy. Kaplan-Meier estimates of overall survival between responders and non-responders (Condition 2) who were alive and had achieved response at (A) 3-month and (B) 6-month landmark times. The HRs were estimated by applying a Cox regression model and the *p* values obtained from the Cox regression model. HR, hazard ratios.

the trial-level correlation was performed with aggregate data rather than patient-level data. We intentionally modelled the trial-level and individual-level correlation separately to ensure a broad inclusion of trials in the first condition and decrease the risk of selection bias. Third, most of the trials explored chemotherapy or tyrosine kinase inhibitors. The meta-analysis will have to be updated when further randomized studies exploring immunotherapy combinations and targeted therapies (especially FGFR inhibitors) become available. Importantly, the association of ORR/DCR and PFS with OS will have to be confirmed in individual-level data for patients treated with these therapies. Fourth, trials did not uniformly time the radiological assessments nor use a uniform definition for response evaluation. Although this may influence PFS and ORR/DCR, it is reflective of the current scenario of RCTs and highlights the need to establish a uniform set of criteria for defining and evaluating PFS in future trials.

In conclusion, our results caution against the routine use of surrogate endpoints in randomized trials testing systemic agents in advanced BTC and highlight the need for further developments to better capture OS. However, until better surrogate endpoints are developed and validated, PFS should be prioritized over ORR and DCR. Furthermore, validation in RCTs including targeted therapies and immunotherapies will be necessary to confidently extrapolate these results to trials assessing these therapies.

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Abbreviations

ASCO, American Society of Clinical Oncology; BTC, biliary tract cancer; DCR, disease control rate; ESMO, European Society of Medical Oncology; HR, hazard ratio; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RCT, randomized-controlled trial; RWD, real-world data; STE, surrogate threshold effect.

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Conflict of interest

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

Authors' contributions

FC: acquisition of data; data analysis and interpretation; manuscript writing, study concept and design. ***CFF***: acquisition of data; interpretation of data; critical revision of the manuscript. ***JB***: acquisition of data; interpretation of data; critical revision of the manuscript. ***JWK***: acquisition of data; interpretation of data; critical revision of the manuscript. ***MR***: acquisition of data; interpretation of data; critical revision of the manuscript. ***ALC***: acquisition of data; interpretation of data; critical revision of the manuscript. ***AL***: acquisition of data; interpretation of data; critical revision of the manuscript. ***MK***: acquisition of data; interpretation of data; critical revision of the manuscript. ***FS***: acquisition of data; interpretation of data; critical revision of the manuscript. ***AC***: acquisition of data; interpretation of data; critical revision of the manuscript. ***AL***: acquisition of data; interpretation of data; critical revision of the manuscript. ***JH***: acquisition of data; interpretation of data; critical revision of the manuscript. ***LR***: acquisition of data; interpretation of data; critical revision of the manuscript. ***JA***: acquisition of data; interpretation of data; critical revision of the manuscript. ***DLV***: acquisition of data; interpretation of data; critical revision of the manuscript. ***MBF***: acquisition of data; critical revision of the manuscript. ***SV***: acquisition of data; data analysis and interpretation; critical revision of the manuscript. ***KMK***: acquisition of data; critical revision of the manuscript. ***TVT***: data analysis and interpretation; critical revision of the manuscript. ***AM***: acquisition of data; interpretation of data; critical revision of the manuscript. ***ACG***: acquisition of data; interpretation of data; critical revision of the manuscript. ***CY***: acquisition of data; interpretation of data; critical revision of the manuscript. ***JWV***: acquisition of data; interpretation of data; critical revision of the manuscript. ***TM*** acquisition of data; data analysis and interpretation; manuscript writing, study concept and design.

Data availability statement

All trial-level data are presented in the Article or Supplementary Materials. Study protocol is available on PROSPERO, registration number CRD42023398279. Participant-level information cannot be shared due to confidentiality agreements. Requests for raw, individual-level data should be directed to the study Sponsors. All the codes used in the analysis can be provided to qualified researchers upon reasonable request to the corresponding author.

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Supplementary data

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References

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[1] Valle JW, Kelley RK, Nervi B, et al. Biliary tract cancer. Lancet 2021;397:428–444. https://doi.org/10.1016/S0140-6736(21)00153-7.

[2] Izquierdo-Sanchez L, Lamarca A, La Casta A, et al. Cholangiocarcinoma landscape in Europe: diagnostic, prognostic and therapeutic insights from the ENSCCA Registry. J Hepatol 2022;76:1109–1121. https://doi.org/10.1016/j.jhep.2021.12.010.

[3] Oh D-Y, Ruth He A, Qin S, et al. Durvalumab plus gemcitabine and cisplatin in advanced biliary tract cancer. NEJM Evid 2022;1. https://doi.org/10.1056/EVIDoa2200015.
[4] Kelley RK, Ueno M, Yoo C, et al. Pembrolizumab in combination with gemcitabine and cisplatin compared with gemcitabine and cisplatin alone for patients with advanced biliary tract cancer (KEYNOTE-966): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2023;401:1853–1865. https://doi.org/10.1016/S0140-6736(23)00727-4.
[5] Merino M, Kasamon Y, Theoret M, et al. Irreconcilable differences: the divorce between response rates, progression-free survival, and overall survival. J Clin Oncol 2023;41:2706–2712. https://doi.org/10.1200/JCO.23.00225.
[6] Saad ED, Buyse M. Statistical controversies in clinical research: end points other than overall survival are vital for regulatory approval of anticancer agents. Ann Oncol 2016;27:373–378. https://doi.org/10.1093/annonc/mdv562.
[7] Korn EL, Freidlin B, Abrams JS. Overall survival as the outcome for randomized clinical trials with effective subsequent therapies. J Clin Oncol 2011;29:2439–2442. https://doi.org/10.1200/JCO.2011.34.6056.
[8] Ciani O, Davis S, Tappenden P, et al. Validation of surrogate endpoints in advanced solid tumors: systematic review of statistical methods, results, and implications for policy makers. Int J Technol Assess Health Care 2014;30:312–324. https://doi.org/10.1017/S0266462314000300.
[9] Elbaz J, Haslam A, Prasad V. An empirical analysis of overall survival in drug approvals by the US FDA (2006–2023). Cancer Med 2024;13. https://doi.org/10.1002/cam4.7190.
[10] Naci H, Zhang Y, Woloshin S, et al. Overall survival benefits of cancer drugs initially approved by the US Food and Drug Administration on the basis of immature survival data: a retrospective analysis. Lancet Oncol 2024;25:760–769. https://doi.org/10.1016/S1470-2045(24)00152-9.
[11] Neuzillet C, Malka D, Lièvre A, et al. Correlation between efficacy endpoints in patients with advanced biliary tract cancer treated by systemic second-line therapies: analysis of aggregated data from a systematic literature review. Clin Res Hepatol Gastroenterol 2022;46:102010. https://doi.org/10.1016/j.clinre.2022.102010.
[12] Moriwaki T, Yamamoto Y, Gosho M, et al. Correlations of survival with progression-free survival, response rate, and disease control rate in advanced biliary tract cancer: a meta-analysis of randomised trials of first-line chemotherapy. Br J Cancer 2016;114:881–888. https://doi.org/10.1038/bjc.2016.83.
[13] Lamarca A, Hubner RA, David Ryder W, et al. Second-line chemotherapy in advanced biliary cancer: a systematic review. Ann Oncol 2014;25:2328–2338. https://doi.org/10.1093/annonc/mdu162.
[14] Eckel F, Schmid RM. Chemotherapy in advanced biliary tract carcinoma: a pooled analysis of clinical trials. Br J Cancer 2007;96:896–902. https://doi.org/10.1038/sj.bjc.6603648.
[15] Belin L, Tan A, De Rycke Y, et al. Progression-free survival as a surrogate for overall survival in oncology trials: a methodological systematic review. Br J Cancer 2020;122:1707–1714. https://doi.org/10.1038/s41416-020-0805-y.
[16] Lamarca A, Macarulla T. Facts and hopes in the systemic therapy of biliary tract carcinomas. Clin Cancer Res 2024. https://doi.org/10.1158/1078-0432.CCR-22-2438.
[17] Xie W, Halabi S, Tierney JF, et al. A systematic review and recommendation for reporting of surrogate endpoint evaluation using meta-analyses. JNCI Cancer Spectr 2019;3. https://doi.org/10.1093/jncics/pkz002.
[18] Gharzai LA, Jiang R, Wallington D, et al. Intermediate clinical endpoints for surrogacy in localised prostate cancer: an aggregate meta-analysis. Lancet Oncol 2021;22:402–410. https://doi.org/10.1016/S1470-2045(20)30730-0.
[19] Kemp R, Prasad V. Surrogate endpoints in oncology: when are they acceptable for regulatory and clinical decisions, and are they currently overused? BMC Med 2017;15:134. https://doi.org/10.1186/s12916-017-0902-9.
[20] Valle JW, Wasan H, Johnson P, et al. Gemcitabine alone or in combination with cisplatin in patients with advanced or metastatic cholangiocarcinomas or other biliary tract tumours: a multicentre randomised phase II study – the UK ABC-01 Study. Br J Cancer 2009;101:621–627. https://doi.org/10.1038/sj.bjc.6605211.
[21] Valle J, Wasan H, Palmer DH, et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Engl J Med 2010;362:1273–1281. https://doi.org/10.1056/NEJMoa0908721.
[22] Valle JW, Wasan H, Lopes A, et al. Cediranib or placebo in combination with cisplatin and gemcitabine chemotherapy for patients with advanced biliary tract cancer (ABC-03): a randomised phase 2 trial. Lancet Oncol 2015;16:967–978. https://doi.org/10.1016/S1470-2045(15)00139-4.
[23] Yoo C, Kim K, Jeong JH, et al. Liposomal irinotecan plus fluorouracil and leucovorin versus fluorouracil and leucovorin for metastatic biliary tract cancer after progression on gemcitabine plus cisplatin (NIFTY): a multicentre, open-label, randomised, phase 2b study. Lancet Oncol 2021;22:1560–1572. https://doi.org/10.1016/S1470-2045(21)00486-1.
[24] **Choi IS**, **Kim KH**, Lee JH, et al. A randomised phase II study of oxaliplatin/5-FU (mFOLFOX) versus irinotecan/5-FU (mFOLFIRI) chemotherapy in locally advanced or metastatic biliary tract cancer refractory to first-line gemcitabine/cisplatin chemotherapy. Eur J Cancer 2021;154:288–295. https://doi.org/10.1016/j.ejca.2021.06.019.
[25] Ramsey SD, Onar-Thomas A, Wheeler SB. Real-world database studies in oncology: a call for standards. J Clin Oncol 2024;42:977–980. https://doi.org/10.1200/JCO.23.02399.
[26] Booth CM, Eisenhauer EA, Gyawali B, et al. Progression-free survival should not Be used as a primary end point for registration of anticancer drugs. J Clin Oncol 2023. https://doi.org/10.1200/JCO.23.01423.
[27] Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021:n71. https://doi.org/10.1136/bmj.n71.
[28] Higgins JPT, Thomas J, Chandler J, et al. Cochrane Handbook for systematic reviews of interventions version 6.4. Cochrane; 2023 (updated August 2023).
[29] Verhagen AP, de Vet HCW, de Bie RA, et al. The Delphi List: a criteria list for quality assessment of randomized clinical trials for conducting systematic reviews developed by Delphi consensus. J Clin Epidemiol 1998;51:1235–1241. https://doi.org/10.1016/S0895-4356(98)00131-0.
[30] Johnson KR, Ringland C, Stokes BJ, et al. Response rate or time to progression as predictors of survival in trials of metastatic colorectal cancer or non-small-cell lung cancer: a meta-analysis. Lancet Oncol 2006;7:741–746. https://doi.org/10.1016/S1470-2045(06)70800-2.
[31] Burzykowski T, Buyse M. Surrogate threshold effect: an alternative measure for meta-analytic surrogate endpoint validation. Pharm Stat 2006;5:173–186. https://doi.org/10.1002/pst.207.
[32] Conforti F, Pala L, Sala I, et al. Evaluation of pathological complete response as surrogate endpoint in neoadjuvant randomised clinical trials of early stage breast cancer: systematic review and meta-analysis. BMJ 2021:e066381. https://doi.org/10.1136/bmj-2021-066381.
[33] Schemper M, Kaider A, Wakounig S, et al. Estimating the correlation of bivariate failure times under censoring. Stat Med 2013;32:4781–4790. https://doi.org/10.1002/sim.5874.
[34] Eden SK, Li C, Shepherd BE. Nonparametric estimation of Spearman's rank correlation with bivariate survival data. Biometrics 2022;78:421–434. https://doi.org/10.1111/biom.13453.
[35] Norsworthy KJ, Gao X, Ko C-W, et al. Response rate, event-free survival, and overall survival in newly diagnosed acute myeloid leukemia: US food and drug administration trial-level and patient-level analyses. J Clin Oncol 2022;40:847–854. https://doi.org/10.1200/JCO.21.01548.
[36] Blumenthal GM, Karuri SW, Zhang H, et al. Overall response rate, progression-free survival, and overall survival with targeted and standard therapies in advanced non–small-cell lung cancer: US food and drug administration trial-level and patient-level analyses. J Clin Oncol 2015;33:1008–1014. https://doi.org/10.1200/JCO.2014.59.0489.
[37] Simon R, Makuch RW. A non-parametric graphical representation of the relationship between survival and the occurrence of an event: application to responder versus non-responder bias. Stat Med 1984;3:35–44. https://doi.org/10.1002/sim.4780030106.
[38] Anderson JR, Cain KC, Gelber RD. Analysis of survival by tumor response. J Clin Oncol 1983;1:710–719. https://doi.org/10.1200/JCO.1983.1.11.710.
[39] Prasad V, Kim C, Burotto M, et al. The strength of association between surrogate end points and survival in oncology. JAMA Intern Med 2015;175:1389. https://doi.org/10.1001/jamainternmed.2015.2829.
[40] Abou-Alfa GK, Macarulla T, Javle MM, et al. Ivosidenib in IDH1-mutant, chemotherapy-refractory cholangiocarcinoma (ClarIDHy): a multicentre, randomised, double-blind, placebo-controlled, phase 3 study. Lancet Oncol 2020;21:796–807. https://doi.org/10.1016/S1470-2045(20)30157-1.
[41] Knox J, Bazin I, Oh D, et al. O-2 Phase III study of NUC-1031 + cisplatin vs gemcitabine + cisplatin for first-line treatment of patients with advanced biliary tract cancer (NuTide:121). Ann Oncol 2023;34:S180–S181. https://doi.org/10.1016/j.annonc.2023.04.017.
[42] Lassere MN, Johnson KR, Schiff M, et al. Is blood pressure reduction a valid surrogate endpoint for stroke prevention? an analysis incorporating a systematic review of randomised controlled trials, a by-trial weighted errors-in-

variables regression, the surrogate threshold effect (STE) and the biomarker-surrogacy (BioSurrogate) evaluation schema (BSES). BMC Med Res Methodol 2012;12:27. https://doi.org/10.1186/1471-2288-12-27.

[43] Lassere MN. The Biomarker-Surrogacy Evaluation Schema: a review of the biomarker-surrogate literature and a proposal for a criterion-based, quantitative, multidimensional hierarchical levels of evidence schema for evaluating the status of biomarkers as surrogate endpoints. Stat Methods Med Res 2008;17:303–340. https://doi.org/10.1177/0962280207082719.

[44] Institute for Quality and Efficiency in Health Care (IQWiG). Validity of surrogate endpoints in oncology: executive summary of rapid report A10-05, Version 1.1. Inst Qual Efficiency Health Care Executive Summ 2011.

[45] Garnick MB. Preserving the sanctity of overall survival for drugs approved on the basis of progression-free survival: tivozanib as a case study. J Clin Oncol 2013;31:3746–3748. https://doi.org/10.1200/JCO.2013.51.4869.

[46] Cherny NI, Dafni U, Bogaerts J, et al. ESMO-magnitude of clinical benefit Scale version 1.1. Ann Oncol 2017;28:2340–2366. https://doi.org/10.1093/annonc/mdx310.

[47] Tannock IF, Pond GR, Booth CM. Biased evaluation in cancer drug trials—how use of progression-free survival as the primary end point can mislead. JAMA Oncol 2022;8:679. https://doi.org/10.1001/jamaoncol.2021.8206.

[48] Fojo T, Simon RM. Inappropriate censoring in Kaplan-Meier analyses. Lancet Oncol 2021;22:1358–1360. https://doi.org/10.1016/S1470-2045(21)00473-3.

[49] Gilboa S, Pras Y, Mataraso A, et al. Informative censoring of surrogate endpoint data in phase 3 oncology trials. Eur J Cancer 2021;153:190–202. https://doi.org/10.1016/j.ejca.2021.04.044.

[50] Walia A, Tuia J, Prasad V. Progression-free survival, disease-free survival and other composite end points in oncology: improved reporting is needed. Nat Rev Clin Oncol 2023;20:885–895. https://doi.org/10.1038/s41571-023-00823-5.

[51] Harry VN, Semple SI, Parkin DE, et al. Use of new imaging techniques to predict tumour response to therapy. Lancet Oncol 2010;11:92–102. https://doi.org/10.1016/S1470-2045(09)70190-1.

[52] Sahani DV, Hayano K, Galluzzo A, et al. Measuring treatment response to systemic therapy and predicting outcome in biliary tract cancer: comparing tumor size, volume, density, and metabolism. AJR Am J Roentgenol 2015;204:776–781. https://doi.org/10.2214/AJR.14.13223.

[53] Inker LA, Collier W, Greene T, et al. A meta-analysis of GFR slope as a surrogate endpoint for kidney failure. Nat Med 2023;29:1867–1876. https://doi.org/10.1038/s41591-023-02418-0.

[54] Valle JW, Vogel A, Denlinger CS, et al. Addition of ramucirumab or merestinib to standard first-line chemotherapy for locally advanced or metastatic biliary tract cancer: a randomised, double-blind, multicentre, phase 2 study. Lancet Oncol 2021;22:1468–1482. https://doi.org/10.1016/S1470-2045(21)00409-5.

[55] Kataria B, Sharma A, Pramanik R, et al. PD-9 Three-arm phase II/III randomized controlled trial in patients with unresectable/metastatic gall bladder cancer with poor performance status: Erlotinib or capecitabine v/s best supportive care. Ann Oncol 2022;33:S242. https://doi.org/10.1016/j.annonc.2022.04.087.

[56] Sharma A, Dwary AD, Mohanti BK, et al. Best supportive care compared with chemotherapy for unresectable gall bladder cancer: a randomized controlled study. J Clin Oncol 2010;28:4581–4586. https://doi.org/10.1200/JCO.2010.29.3605.

[57] Assenat E, Blanc JF, Bouattour M, et al. 48P (BREGO) Regorafenib combined with modified m-GEMOX in patients with advanced biliary tract cancer (BTC): a phase II randomized trial. Ann Oncol 2021;32:S376–S377. https://doi.org/10.1016/j.annonc.2021.08.327.

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Association of candidate surrogate endpoints with overall survival in advanced biliary tract cancer

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Supplementary materials and methods

Patients and datasets

The following cohorts were included in the study:

First-line RCT cohort: We included a pooled population of patients enrolled in the first-line trials ABC-01[1], ABC-02[2] and ABC-03[3]. The ABC-01 study was a phase II study that enrolled 86 patients who were randomized to cisplatin-gemcitabine or gemcitabine. Response evaluation was performed locally every 12 weeks following the RECIST 1.0 criteria[4]. The ABC-02 was a phase III trial that enrolled 410 patients who were randomized to cisplatin-gemcitabine or gemcitabine. Response evaluation was performed locally every 12 weeks following the RECIST 1.0 criteria. The ABC-03 study was a randomized phase II trial that tested the combination of cisplatin-gemcitabine-cediranib or cisplatin-gemcitabine-placebo in 124 patients. Response evaluation was performed locally every 12 weeks following the RECIST 1.1 criteria[5]. Patients with periampullary carcinoma were excluded. Overall, the pooled population included 512 patients (81, 307 and 124 patients from the ABC-01, -02, and -03 studies, respectively; although the ABC-02 clinical trial reported a total of 388 patients (excluding periampullary carcinomas), 81 had been patients previously recruited into the ABC-01).

Second line RCT cohort: We included a pooled population of patients included in the second-line NIFTY[6,7] and FIReFOX[8] trials. NIFTY was a randomized phase II trial that enrolled 174 patients who received 5FU/LV or the combination of 5FU/LV with nal-irinotecan. Response evaluation was performed centrally every 6 weeks following the RECIST 1.1 criteria. FIReFOX was a phase

II trial that randomized 118 patients to either modified FOLFOX or modified FOLFIRI. Response evaluation was performed locally every 6 weeks following the RECIST 1.1 criteria. After excluding patients with periampullary carcinoma, a total of 271 patients were included.

DURVABTC RWD cohort: In this cohort, we included patients diagnosed with advanced BTC and treated with a combination of cisplatin-gemcitabine and durvalumab at 39 sites in 11 countries[9]. Patient data were retrospectively collected and included sociodemographic, clinical features, tumor characteristics, treatment outcomes and survival data. Response evaluation followed local practice guidelines.

RETUD cohorts: We included all patients diagnosed with advanced BTC included in the RETUD registry who received first-line and/or second-line systemic chemotherapy[10]. The RETUD registry is a Spanish epidemiological cohort study that involves 33 sites and has included consecutive cases of histologically confirmed BTC since January 2017. Data are managed through a secured web-based data platform available to researchers, that includes filters and a query-generating system to guarantee reliability and control of missing and inconsistent data. Patient data include sociodemographic, clinical features, tumour characteristics, treatment outcomes and survival data. Response evaluation follows local practice guidelines.

Definition of endpoints

For the real-world datasets, we defined OS as the time from treatment initiation to death from any cause and PFS as the time from treatment initiation to progression or death from any cause, whichever occurred first. Patients who did not experience a PFS or OS event were censored at the date of last follow-up.

For the patients included in RCTs, OS was defined as the time from randomization to death from any cause and PFS as the time from randomization to progression or death from any cause, whichever occurred first. Patients who did not experience a PFS or OS event were censored at the date of last follow-up. Response was assessed following the guidelines originally used in the trial.

Supplementary tables

Table S1: Search strategy for the systematic review performed on PubMed.

Database: PubMed			
Search	**Date**	**Search terms**	**Number of results**
#1	17/10/2023	"Antineoplastic Combined Chemotherapy Protocols"[MeSH Terms]	160620
#2	17/10/2023	"chemother*"[Title/Abstract]	507165
#3	17/10/2023	"systemic therap*"[Title/Abstract]	22708
#4	17/10/2023	"systemic treatmen*"[Title/Abstract]	15211
#5	17/10/2023	"targeted therap*"[Title/Abstract]	74645
#6	17/10/2023	Drug Combinations[MeSH Terms]	100753
#7	17/10/2023	Drug Administration Schedule[MeSH Terms]	105693
#8	17/10/2023	**#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7**	834067
#9	17/10/2023	Cholangiocarcinoma[MeSH Terms]	12457
#10	17/10/2023	Cholangiocarcinoma[Title/Abstract]	17935
#11	17/10/2023	Biliary Tract Neoplasms[MeSH Terms]	33773
#12	17/10/2023	"gallbladder cancer"[Title/Abstract]	4680
#13	17/10/2023	"bile duct neoplasms"[Title/Abstract]	350
#14	17/10/2023	"biliary tract carcinoma"[Title/Abstract]	352
#15	17/10/2023	"biliary tract cancer*"[Title/Abstract]	2615
#16	17/10/2023	"biliary cancer"[Title/Abstract]	699
#17	17/10/2023	"biliary duct carcinoma"[Title/Abstract]	28
#18	17/10/2023	**#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17**	43852
#19	17/10/2023	Double-Blind Method[MeSH Terms]	176240
#20	17/10/2023	"clinical trial"[Text Word]	800820
#21	17/10/2023	"randomized"[Text Word]	1037166
#22	17/10/2023	"randomized controlled trial"[Text Word]	646296
#23	17/10/2023	"randomised"[Text Word]	133649
#24	17/10/2023	"randomised controlled trial"[Text Word]	32188
#25	17/10/2023	"phase 2 clinical trial"[Text Word]	874
#26	17/10/2023	"phase 2 trial"[Text Word]	2997
#27	17/10/2023	"phase 2 study"[Text Word]	3121
#28	17/10/2023	"phase 2 clinical study"[Text Word]	88
#29	17/10/2023	"phase ii clinical trial"[Text Word]	3037
#30	17/10/2023	"phase ii trial"[Text Word]	12094
#31	17/10/2023	"phase ii clinical study"[Text Word]	385
#32	17/10/2023	"phase ii study"[Text Word]	15067
#33	17/10/2023	"phase 2"[Text Word]	25708
#34	17/10/2023	"phase ii"[Text Word]	88693
#35	17/10/2023	"phase 2a clinical trial"[Text Word]	47
#36	17/10/2023	"phase 2a trial"[Text Word]	133

#37	17/10/2023	"phase 2a study"[Text Word]	188
#38	17/10/2023	"phase 2a clinical study"[Text Word]	9
#39	17/10/2023	"phase iia clinical trial"[Text Word]	90
#40	17/10/2023	"phase iia trial"[Text Word]	170
#41	17/10/2023	"phase iia clinical study"[Text Word]	20
#42	17/10/2023	"phase iia study"[Text Word]	202
#43	17/10/2023	"phase 2a"[Text Word]	741
#44	17/10/2023	"phase iia"[Text Word]	883
#45	17/10/2023	"phase 2b clinical trial"[Text Word]	40
#46	17/10/2023	"phase 2b trial"[Text Word]	199
#47	17/10/2023	"phase 2b study"[Text Word]	229
#48	17/10/2023	"phase 2b clinical study"[Text Word]	6
#49	17/10/2023	"phase iib clinical trial"[Text Word]	117
#50	17/10/2023	"phase iib trial"[Text Word]	257
#51	17/10/2023	"phase iib clinical study"[Text Word]	10
#52	17/10/2023	"phase iib study"[Text Word]	231
#53	17/10/2023	"phase 2b"[Text Word]	1043
#54	17/10/2023	"phase iib"[Text Word]	1305
#55	17/10/2023	"phase 1/2"[Text Word]	1681
#56	17/10/2023	"phase i/ii"[Text Word]	8371
#57	17/10/2023	"phase 1/2 clinical study"[Text Word]	27
#58	17/10/2023	"phase i/ii clinical study"[Text Word]	100
#59	17/10/2023	"phase 1/2 clinical trial"[Text Word]	144
#60	17/10/2023	"phase i/ii clinical trial"[Text Word]	756
#61	17/10/2023	"phase 2/3 clinical study"[Text Word]	5
#62	17/10/2023	"phase ii/iii clinical study"[Text Word]	7
#63	17/10/2023	"phase 2/3 clinical trial"[Text Word]	43
#64	17/10/2023	"phase ii/iii clinical trial"[Text Word]	84
#65	17/10/2023	"phase iii randomized trial"[Text Word]	545
#66	17/10/2023	"phase ii randomized trial"[Text Word]	237
#67	17/10/2023	"randomized phase ii trial"[Text Word]	1238
#68	17/10/2023	"randomized phase iii trial"[Text Word]))	1411
#69	17/10/2023	**#19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68**	1583403
#70	17/10/2023	**#8 AND #16 AND #69**	1054

Table S2: Eligibility criteria following the PICOS framework

PICOS	Eligibility criteria
Population	Adult patients treated with systemic chemotherapy for locally advanced or metastatic biliary tract cancer (including intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma and gallbladder carcinoma). RCTs including other tumour types will be excluded.
intervention/comparator	Systemic therapies, including chemotherapy, targeted therapies or immunotherapies. Both monotherapy and combinations will be included. Combinations with local or locoregional therapies will be excluded.
Outcomes	OS, PFS, ORR and/or DCR. Trials not reporting OS or not reporting either PFS or ORR will be excluded.
Study Design	Randomized phase II or phase III trials will be included. Sample size will not be considered an eligibility criterion.
Language	No language limit will be applied.

DCR, disease control rate; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RCTs, randomized controlled trials.

Table S3: Characteristics and design of the trials included in the systematic review.

Trial	Treatments	Phase	N	N[a] of centres	Recruitment period	Stratification factors	Blinding	Primary Endpoint	Secondary endpoint	Response evaluation	Timing of scans
ABC-02[2]	CG Gemcitabine	III	410	37	February 2002 - October 2008	Primary tumour site Extent of disease Performance status Previous therapy Recruiting centre	Open-label	OS	PFS, ORR, AEs	RECIST 1.0	Q12w
ABC-03[3]	CG+cediranib CG+placebo	II	124	14	April 2011 - September 2012	Primary tumour site Extent of disease Performance status Previous therapy Recruiting centre	Double blind	PFS	OS, ORR, AEs, QoL	RECIST 1.1	Q12w
BilT-01[11]	Nivo-ipi CG-nivo	II	68	6	September 2017 - June 2019	None	Open-label	PFS 6 months	ORR, PFS, OS, AEs	RECIST 1.1/irRECIST	Q8w
BREGO[12]	mGEMOX+regorafenib mGEMOX	II	66	NA	NA	Primary tumour site Recruiting centre	Open-label	NA	NA	RECIST 1.0	NA
BT22[13]	CG Gemcitabine	II	83	9	September 2006 - October 2008	Primary tumour site Presence of primary tumour	Open-label	OS 1 year	PFS, ORR, safety	NA	Q8w
Chen 2015[14]	GEMOX+cetuximab GEMOX	II	122	12	December 2010 - May 2012	KRAS status Performance status Primary tumour site	Open-label	ORR	DCR, PFS, OS safety	RECIST 1.1	Q8w
ClarIDHy[15]	Ivosidenib Placebo	III	187	49	February 2017 - March 2019	Number of previous lines	Double blind	PFS	OS, ORR, PFS investigator, safety, tolerability, QoL	RECIST 1.1	Q6w
FIReFOX[16]	mFOLFIRI mFOLFOX	II	118	NA	August 2015 - Novembre 2019	Primary tumour site Performance status	Open-label	OS 6 months	ORR, DCR, PFS, safety	RECIST 1.1	Q6w
Gambit[17]	Irinotecan+Cisplatin CG	II	47	NA	January 2013 - April 2018	NA	Open-label	ORR	PFS, OS, DCR, safety	RECIST 1.1	NA

GB-SELECT[18]	CAPIRI Irinotecan	II	98	2	August 2018 - January 2020	None	Open-label	OS 6 months	PFS, ORR, DCR, QoL	RECIST 1.1	Q8w
GEMSO-AIO[19]	Gemcitabine+sorafenib Gemcitabine	II	97	11	NA	None	Double blind	PFS	Safety, OS, ORR, SD duration, PFS 1 year, QoL	RECIST 1.0	Q8w
Ikeda 2023[20]	Nanvuranlat Placebo	II	104	14	NA	Primary tumour site Prior resection	Double blind	PFS	OS, DCR	RECIST 1.1	NA
IMbrave151[21]	CG+atezolizumab+bevacizumab CG+atezolizumab+placebo	II	162	NA	NA	Primary tumour site Extent of disease Geographic region	Double blind	PFS	ORR, DoR, DCR, OS, safety, PRO/QoL	RECIST 1.1	Q9w
JCOG0805[22]	SG S1	II	101	19	February 2009 - April 2010	Primary tumour site Extent of disease Recruiting centre	Open-label	OS 1 year	PFS, ORR, AEs, SAEs	RECIST 1.0	Q6w
JCOG1113[23]	SG CG	III	354	33	May 2013 - March 2016	Primary tumour site Prior resection Recruiting centre	Open-label	OS	PFS, ORR, AEs, SAEs	RECIST 1.1	Q6w
Kang 2012[24]	SG CG	II	96	1	March 2008 - March 2009	Primary tumour site Extent of disease	Open-label	PFS 6 months	OS, ORR, toxicity	RECIST 1.0	Q6w
Kataria 2022[25]	Capecitabine BSC	II/III	69	1	December 2017 - January 2021	None	Open-label	OS	PFS, ORR, QoL	RECIST 1.1	NA
Kataria 2022[25]	Erlotinib BSC	II/III	69	1	December 2017 - January 2021	None	Open-label	OS	PFS, ORR, QoL	RECIST 1.1	NA
KEYNOTE-966[26]	CG+pembrolizumab CG-placebo	III	1069	175	October 2019 - June 2021	Primary tumour site Extent of disease Geographic region	Double blind	OS	PFS, ORR, DoR, safety	RECIST 1.1	Q6w
KHBO1401-MITSUBA[27]	CG CGS	III	246	39	July 2014 - February 2016	Primary tumour site Performance status Prior resection	Open-label	OS	PFS, ORR, safety	RECIST 1.1	Q12w
Kim 2019[28]	CAPOX GEMOX	III	222	10	December 2011 - June 2016	Recruiting centre	Open-label	PFS	OS, ORR, safety	RECIST 1.1	Q6w
Lee 2012[29]	GEMOX+erlotinib GEMOX	III	268	11	February 2009 - August 2010	Recruiting centre Presence of measurable disease	Open-label	PFS	OS, ORR, QoL, safety	RECIST 1.0	Q6w

Markussen 2020[30]	GEMOX-capecitabine CG	II	96	2	July 2014 - Novembre 2017	Performance status	Open-label	PFS	OS, ORR, toxicity	RECIST 1.1	Q12w
NALIRICC[31]	5FU-nalIRI 5FU	II	100	17	NA	Primary tumour site	Open-label	PFS	OS, ORR, AEs, QoL	RECIST 1.1	Q6w
NIFTY[32]	5FU-nalIRI 5FU	II	174	5	September 2018 - February 2020	Primary tumour site Prior resection Recruiting centre	Open-label	PFS	OS, ORR, safety, QoL	RECIST 1.1	Q6w
Nutide:121[33]	Cisplatin+ NUC1031 CG	III	773	125	December 2019 - March 2022	Primary tumour site Extent of disease Measurable disease Geographic region	Open-label	OS, ORR	PFS, Safety	RECIST 1.1	Q9w
Pape 2020[34]	CAP7.1 BSC	II	27	NA	NA	None	Open-label	DCR	PFS, TTF, OS, safety	RECIST 1.1	Q8w
PICCA[35]	CG+ panitumumab CG	II	90	17	July 2011 - December 2015	Primary tumour site Leucocyte count Alkaline phosphatase	Open-label	PFS 6 months	ORR, OS, toxicity	RECIST 1.0	Q6w
REACHIN[36]	Regorafenib Placebo	II	66	12	May 2014 - February 2018	None	Double blind	PFS	OS, ORR, DCR, safety	RECIST 1.1	Q6w
Schinzari 2017[37]	FOLFOX4 De Gramont	II	48	NA	January 2008 - June 2010	None	Open-label	OS	PFS, ORR	RECIST 1.1	Q8w
Sharma 2010[38]	mGEMOX BSC	II	53	1	June 2006 - October 2008	None	Open-label	OS, ORR, toxicity	PFS	RECIST 1.0	Q6w
Sharma 2010[38]	FUFA BSC	II	55	1	June 2006 - October 2008	None	Open-label	OS, ORR, toxicity	PFS	RECIST 1.0	Q6w
Sharma 2019[39]	mGEMOX CG	III	243	1	February 2011 - July 2015	None	Open-label	OS	PFS, ORR	RECIST 1.1	NA
Shirahama 2017[40]	PPV+CPA PPV	II	49	1	November 2011 - December 2014	Extent of disease Performance status	Open-label	Immune response	OS, PFS, safety	RECIST 1.0	Q8w
SWOG 1815[41]	CG+Nab/paclitaxel CG	III	441	NA	February 2019 - February 2021	Primary tumour site Extent of disease Performance status	Open-label	OS	ORR, PFS, DCR, safety	RECIST 1.1	Q9w
SWOG S1310[42]	Trametinib 5FU/capecitabine	II	44	NA	February 2014 - March 2015	Primary tumour site Chemotherapy regimen	Open-label	OS	PFS, ORR	RECIST 1.1	Q6w

TOPAZ-1[43]	CG+durvalumab CG	III	685	105	April 2019 - December 2020	Primary tumour site Disease status	Double blind	OS	PFS, ORR, DoR, DCR	RECIST 1.1	Q6w
TreeTopp[44]	Varlitinib+ capecitabine Placebo+ capecitabine	II	127	56	May 2018 - December 2019	Primary tumour site Geographic region	Double blind	ORR, PFS	OS, AEs	RECIST 1.1	Q6w
Ueno 2021[45]	Reminostat+S1 Placebo+S1	II	101	21	March 2018 - February 2019	Primary tumour site Prior resection Performance status Recruiting centre	Double blind	PFS	OS, ORR, DCR, safety	RECIST 1.1	Q6w
Valle 2021[46]	Ramucirumab Placebo	II	207	81	May 2016 - August 2017	Primary tumour site Extent of disease Geographic region	Double blind	PFS	OS, ORR, DCR, QoL, safety	RECIST 1.1	Q6w
Valle 2021[46]	Merestinib Placebo	II	203	81	May 2016 - August 2017	Primary tumour site Extent of disease Geographic region	Double blind	PFS	OS, ORR, DCR, QoL, safety	RECIST 1.1	Q6w
Vecti-BIL[47]	GEMOX+ panitumumab GEMOX	II	89	12	June 2010 - September 2013	Primary tumour site Performance status	Open-label	PFS	OS, ORR, safety	RECIST 1.1	Q8w
Yang 2022[48]	Cisplatin+ Nab/paclitaxel CG	II	67	NA	NA	NA	Open-label	PFS	OS, ORR, safety	NA	NA
Zheng 2018[49]	XELIRI Irinotecan	II	60	1	September 2015 - September 2017	None	Open-label	PFS	OS	RECIST 1.1	Q6w

AEs, adverse events; BSC, best supportive care; CG, cisplatin + gemcitabine; DCR, disease control rate; DoR, duration of response; NA, not available; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; QoL, quality of life; SAE, serious adverse events; SD, stable disease; TTF, time to treatment failure.

Table S4: Estimated STE for PFS, DCR and ORR in different hypothetical trials with varying sample sizes.

Hypothetical trial size	PFS STE (HR)	DCR STE (OR)	ORR STE (OR)
***N* = 50**	0.39	37.78	NE
***N* = 100**	0.51	12.85	NE
***N* = 150**	0.57	7.99	NE
***N* = 200**	0.61	6.02	NE
***N* = 400**	0.69	3.55	NE
***N* = 600**	0.73	2.82	NE
***N* = 800**	0.75	2.46	NE
***N* = 1000**	0.77	2.25	NE
***N* = 1200**	0.78	2.1	NE

The STE was defined as the intersection of the upper 95% prediction interval with the horizontal y-axis=0 of the linear regression model, representing a hazard ratio of 1.
DCR, disease control rate; HR, hazard ratio; OR, odds ratio; ORR, objective response rate; PFS, progression free survival; STE, surrogate threshold effect.

Table S5: Baseline characteristics of patients included in the ABC-01, ABC-02 and ABC-03 trials.

	Cohort (N=512)
Age (median, IQR)	64 (58-70)
Sex (N, %)	
Male	238 (46.5%)
Female	274 (53.5%)
Location (N, %)	
Intrahepatic	123 (24%)
Hiliar	53 (10.4%)
Distal	141 (27.5%)
Gallbladder	122 (23.8%)
Cholangiocarcinoma NOS	20 (3.9%)
Missing	53 (10.4%)
Stage (N, %)	
Locally advanced	121 (23.6%)
Metastatic	391 (76.4%)
CA19.9 (UI/mL, median IQR)	105 (24.4-776.5)
Grade of differentiation	
Well	42 (8.2%)
Moderate	158 (30.9%)
Poor	93 (18.2%)
Not specified	219 (42.8%)
Histology	
Adenocarcinoma	464 (90.6%)
Adenosquamous	4 (0.8%)
Carcinoma NOS	32 (6.3%)
Other	12 (2.3%)
ECOG-PS (N, %)	
0	177 (34.6%)
1	283 (55.3%)
2	51 (10%)
Missing	1 (0.2%)
Prior surgery (N, %)	191 (37.3%)
Missing	40 (7.8%)
Prior biliary stenting (N, %)	227 (44.3%)
Missing	43 (8.3%)
Treatment received (N, %)	
Cisplatin-gemcitabine	195 (38.1%)
Cisplatin-gemcitabine-placebo	62 (12.1%)
Cisplatin-gemcitabine-cediranib	62 (12.1%)
Gemcitabine	193 (37.7%)

ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range.

Table S6: Baseline characteristics of patients included in the NIFTY and FIReFOX trials (FAS population).

	Cohort (N=271)
Age, median (range)	64 (26-84)
Sex (N, %)	
Male	164 (60.5%)
Female	107 (39.5%)
Tumour location (N, %)	
Intrahepatic	116 (42.8%)
Extrahepatic	72 (26.6%)
Gallbladder	83 (30.6%)
Disease setting (N, %)	
Initially metastatic	232 (85.6%)
Recurrence after curative surgery	39 (14.4%)
ECOG performance Status (N, %)	
0	43 (15.9%)
1	228 (84.1%)
First-line CG duration (N, %)	
< 3 months	68 (25.1%)
≥ 3 months	203 (74.9%)
First-line CG duration (N, %)	
< 6 months	170 (62.7%)
≥ 6 months	101 (37.3%)
Baseline serum CA 19-9 (N, %)	
< 172 IU/mL	127 (46.9%)
≥ 172 IU/mL	144 (53.1%)
Baseline serum CA 19-9 (N, %)	
< 400 IU/mL	152 (56.1%)
≥ 400 IU/mL	119 (43.9%)
Post study treatment	
Yes	108 (39.9%)
No	163 (60.1%)

CG, cisplatin-gemcitabine; ECOG, Eastern Cooperative Oncology Group; FAS, full analysis set.

Table S7: Baseline characteristics of patients included in the first-line RWD of cisplatin-gemcitabine combined with durvalumab cohort.

	Cohort (N=628)
Age (median, IQR)	68 (59-74)
Sex (N, %)	
Male	334 (53.2%)
Female	294 (46.8%)
Location (N, %)	
Intrahepatic	335 (53.3%)
Hiliar	105 (16.7%)
Distal	58 (9.2%)
Gallbladder	130 (20.7%)
Stage (N, %)	
Locally advanced	144 (22.9%)
Metastatic	483 (76.9%)
MIssing	1 (0.2%)
CA19.9 (UI/mL, median IQR)	105 (24.4-776.5)
Etiology (N, %)	
HBV	38 (6.1%)
HCV	21 (3.3%)
Non-viral	371 (59.1%)
Unknown	198 (31.5%)
ECOG-PS (N, %)	
0	304 (48.4%)
1	303 (48.2%)
2	18 (2.9%)
3-4	3 (4.8%)
Prior surgery (N, %)	172 (27.4%)
Prior adjuvant treatment (N, %)	106 (61.6%)

CG-Durva, cisplatin-gemcitabine-durvalumab; ECOG, Eastern Cooperative Oncology Group; HBV, Hepatitis B virus; HCV, Hepatitis C virus; IQR, interquartile range; RWD, real-world data.

Table S8: Baseline characteristics of patients included in the first-line and second-line RETUD RWD chemotherapy cohorts.

	First-line cohort (N=773)	Second-line cohort (N=322)
Age (median, IQR)	68 (60-74)	65 (56-72)
Sex (N, %)		
Male	418 (54.1%)	166 (51.6%)
Female	355 (45.9%)	156 (48.4%)
Location (N, %)		
Intrahepatic	460 (59.5%)	200 (62.1%)
Hiliar	97 (12.5%)	35 (10.9%)
Distal	115 (14.9%)	44 (13.7%)
Gallbladder	101 (13.1%)	43 (13.4%)
Stage at diagnosis (N, %)		
Resectable	145 (18.8%)	59 (18.3%)
Locally advanced	169 (21.9%)	60 (18.6%)
Metastatic	459 (59.4%)	203 (63%)
Metastatic location (N, %)		
Liver	388 (50.2%)	173 (53.7%)
Lung	154 (19.9%)	65 (20.2%)
Bone	69 (8.9%)	36 (11.2%)
ECOG-PS (N, %)		
0	150 (19.4%)	86 (26.7%)
1	315 (40.8%)	147 (45.7%)
2	97 (12.5%)	15 (4.7%)
3-4	7 (0.9%)	2 (0.6%)
Missing	204 (26.4%)	72 (22.4%)
Prior surgery (N, %)	204 (26.4%)	90 (28%)
Chemotherapy regimen (N, %)	Cisplatin-Gemcitabine: 504 (65.2%) GEMOX: 60 (7.8%) Gemcitabine: 118 (15.3%) Other: 91 (11.8%)	FOLFOX: 90 (28%) CAPOX: 46 (14.3%) Capecitabine: 60 (18.6%) Irinotecan-based: 39 (12.1%) Other: 87 (27%)

ChT, chemotherapy; ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; RWD, real-world data.

Table S9: Patient-level correlation of PFS with OS across the different datasets using Spearman's non-parametric correlation estimate for bivariate survival data.

Cohort	Setting	Treatment line	N (events)	Follow-up (mo, 95% CI)	Median OS (mo, 95% CI)	Median PFS (mo, 95% CI)	ρ_s (95% CI)
Pooled ABC-01, -02, -03	RCT	First line	512 (497)	51 (41.1-NA)	10.2 (9-11.5)	6.5 (6-7.4)	0.82 (0.78-0.86)
CG-Durva	RWD	First line	628 (190)	8.4 (7.8-9.4)	14.9 (13.4-17.8)	8.2 (7.5-8.9)	0.69 (0.6-0.76)
RETUD	RWD	First line	773 (623)	32 (25.3-37.3)	9.7 (8.7-10.4)	5 (4.5-5.4)	0.79 (0.75-0.83)
NIFTY, FIReFOX	RCT	Second line	277 (236)	33 (27-37.2)	6.3 (5.5-7.4)	2.6 (2.4-2.9)	0.7 (0.63-0.78)
RETUD	RWD	Second line	322 (279)	24.8 (22.3-NA)	5.2 (4.8-6)	2.8 (2.5-3)	0.77 (0.71-0.83)

The ρ_s between OS and PFS was calculated by using a nonparametric estimator of Spearman's correlation, based on a nonparametric bivariate survival surface estimator.
CI, confidence interval; mo, months; NA, not available; RCT, randomized controlled trial; RWD, real-world data.

Table S10: Patient-level correlation of PFS with OS stratified according to tumour location

INTRAHEPATIC CHOLANGIOCARCINOMA								
Cohort	**Setting**	**Treatment line**	**N (events)**	**Follow-up (mo, 95% CI)**	**Median OS (mo, 95% CI)**	**Median PFS (mo, 95% CI)**	**ρ_{imi} (95% CI)**	**ρ_s (95% CI)**
ABC-01, -02, -03	RCT	First line	123 (110)	58.3 (33.4-NA)	12.4 (9.9-15.1)	7.9 (5.9-8.5)	0.82 (0.75-0.87)	0.79 (0.7-0.89)
DURVABTC	RWD	First line	335 (117)	8.5 (7.8-10.6)	14.8 (11.3-16.3)	7.8 (7.1-8.9)	0.87 (0.82-0.9)	0.76 (0.65-0.85)
RETUD	RWD	First line	460 (389)	32.7 (26.5-NA)	9.1 (8.1-10.2)	4.8 (3.9-5.3)	0.83 (0.79-0.86)	0.79 (0.74-0.84)
NIFTY, FIReFOX	RCT	Second line	116 (104)	33 (26.3-NA)	5.6 (4.8-6.7)	2 (1.5-2.7)	0.76 (0.67-0.83)	0.72 (0.63-0.82)
RETUD	RWD	Second line	200 (177)	25.5 (22.3-NA)	5.5 (4.9-6.7)	2.8 (2.5-3.1)	0.82 (0.79-0.85)	0.79 (0.72-0.86)
EXTRAHEPATIC CHOLANGIOCARCINOMA								
Cohort	**Setting**	**Treatment line**	**N (events)**	**Follow-up (mo, 95% CI)**	**Median OS (mo, 95% CI)**	**Median PFS (mo, 95% CI)**	**ρ_{imi} (95% CI)**	**ρ_s (95% CI)**
ABC-01, -02, -03	RCT	First line	194 (178)	51 (27.4-NA)	10.7 (8.8-12.6)	6.9 (6.3-8.3)	0.87 (0.82-0.9)	0.84 (0.78-0.91)
DURVABTC	RWD	First line	163 (37)	9.4 (7.9-10.7)	NA (13.6-NA)	9.4 (8.6-10)	0.86 (0.66-0.95)	0.66 (0.54-0.79)
RETUD	RWD	First line	212 (162)	35 (20.3-51.2)	10.6 (8.6-11.7)	5.3 (4.2-6.3)	0.84 (0.79-0.87)	0.79 (0.72-0.87)
NIFTY, FIReFOX	RCT	Second line	72 (61)	25.8 (24.8-NA)	7 (4.8-8.4)	2.9 (2.5-4.1)	0.69 (0.54-0.8)	0.7 (0.53-0.87)
RETUD	RWD	Second line	79 (66)	22.5 (14.6-NA)	4.7 (4.4-7)	2.6 (2.1-3.3)	0.76 (0.7-0.8)	0.73 (0.61-0.87)
GALLBLADDER CARCINOMA								
Cohort	**Setting**	**Treatment line**	**N (events)**	**Follow-up (mo, 95% CI)**	**Median OS (mo, 95% CI)**	**Median PFS (mo, 95% CI)**	**ρ_{imi} (95% CI)**	**ρ_s (95% CI)**
ABC-01, -02, -03	RCT	First line	122 (120)	42 (42-NA)	8.5 (7.3-11.4)	5.7 (5-7.3)	0.81 (0.74-0.87)	0.82 (0.73-0.9)
DURVABTC	RWD	First line	130 (36)	7 (6.2-8.8)	15 (10.2-NA)	7.3 (6.5-8.5)	0.8 (0.58-0.91)	0.6 (0.42-0.8)
RETUD	RWD	First line	101 (72)	15.8 (12.9-NA)	9.9 (8.7-13.2)	5.3 (4.3-7)	0.83 (0.75-0.89)	0.81 (0.71-0.93)
NIFTY, FIReFOX	RCT	Second line	83 (69)	34.2 (27-NA)	7.3 (6.8-10.3)	3.1 (2.6-4.4)	0.71 (0.55-0.81)	0.66 (0.53-0.8)
RETUD	RWD	Second line	43 (36)	NA (8-NA)	4.3 (3.3-6.8)	2.7 (2.5-3.8)	0.88 (0.85-0.91)	0.83 (0.7-0.97)

The correlation coefficient ρ_{imi} was measured by using a normal score rank correlation calculated by the iterative multiple imputation approach.The ρ_s was calculated by using a nonparametric estimator of Spearman's correlation, based on a nonparametric bivariate survival surface estimator.
CI, confidence interval; mo, months; NA, not available; OS, overall survival; PFS, progression-free survival; RCT, randomized controlled trial; RWD, real-world data.

Table S11: Patient-level correlation of PFS with OS stratified according to disease stage.

LOCALLY ADVANCED								
Cohort	**Setting**	**Treatment line**	**N (events)**	**Follow-up (mo, 95% CI)**	**Median OS (mo, 95% CI)**	**Median PFS (mo, 95% CI)**	**ρ_{imi} (95% CI)**	**ρ_s (95% CI)**
ABC-01, -02, -03	RCT	First line	121 (108)	58.3 (41.5-NA)	13.3 (10.3-15.6)	6.9 (5.9-9)	0.87 (0.82-0.91)	0.85 (0.78-0.93)
DURVABTC	RWD	First line	144 (25)	9.3 (8-10.7)	23.3 (18.4-NA)	9.5 (8.5-12.2)	0.73 (0.42-0.8)	0.47 (0.21-0.77)
RETUD	RWD	First line	166 (114)	19.5 (17-31.1)	10.2 (8.7-12.1)	6.4 (5-7.3)	0.83 (0.77-0.88)	0.79 (0.7-0.89)
NIFTY, FIReFOX	RCT	Second line	39 (34)	34.2 (34.2-NA)	7.6 (4.7-13.4)	3 (2.4-4.7)	0.82 (0.67-0.91)	0.77 (0.62-0.96)
RETUD	RWD	Second line	51 (41)	24.8 (24.8-NA)	4.6 (3.5-7.9)	2.8 (2.3-4.4)	0.88 (0.85-0.9)	0.85 (0.73-0.99)
METASTATIC								
Cohort	**Setting**	**Treatment line**	**N (events)**	**Follow-up (mo, 95% CI)**	**Median OS (mo, 95% CI)**	**Median PFS (mo, 95% CI)**	**ρ_{imi} (95% CI)**	**ρ_s (95% CI)**
ABC-01, -02, -03	RCT	First line	391 (370)	42 (33.4-NA)	9.6 (8.6-10.7)	6.4 (5.5-7.3)	0.82 (0.79-0.85)	0.81 (0.77-0.86)
DURVABTC	RWD	First line	483 (165)	8 (7.6-9.5)	13.3 (11.3-15.6)	7.5 (6.9-8.5)	0.86 (0.79-0.91)	0.74 (0.66-0.81)
RETUD	RWD	First line	607 (509)	35 (26.9-46.1)	9.6 (8.6-10.3)	4.7 (4.1-5.3)	0.83 (0.8-0.85)	0.79 (0.75-0.83)
NIFTY, FIReFOX	RCT	Second line	232 (200)	28.9 (26.3-NA)	6.2 (5.4-7.2)	2.6 (2.2-2.8)	0.71 (0.64-0.77)	0.69 (0.61-0.77)
RETUD	RWD	Second line	271 (238)	23.7 (22.3-NA)	5.3 (4.9-6.2)	2.8 (2.5-3)	0.8 (0.77-0.82)	0.75 (0.69-0.82)

The correlation coefficient ρ_{imi} was measured by using a normal score rank correlation calculated by the iterative multiple imputation approach.The ρ_s was calculated by using a nonparametric estimator of Spearman's correlation, based on a nonparametric bivariate survival surface estimator.
CI, confidence interval; mo, months; NA, not available; OS, overall survival; PFS, progression-free survival; RCT, randomized controlled trial; RWD, real-world data.

Supplementary references

Author names in bold designate shared co-first authorship

[1] Valle JW, Wasan H, Johnson P, et al. Gemcitabine alone or in combination with cisplatin in patients with advanced or metastatic cholangiocarcinomas or other biliary tract tumours: a multicentre randomised phase II study – The UK ABC-01 Study. Br J Cancer 2009;101:621–7. https://doi.org/10.1038/sj.bjc.6605211.

[2] Valle J, Wasan H, Palmer DH, et al. Cisplatin plus Gemcitabine versus Gemcitabine for Biliary Tract Cancer. N Engl J Med 2010;362:1273–81. https://doi.org/10.1056/NEJMoa0908721.

[3] Valle JW, Wasan H, Lopes A, et al. Cediranib or placebo in combination with cisplatin and gemcitabine chemotherapy for patients with advanced biliary tract cancer (ABC-03): a randomised phase 2 trial. Lancet Oncol 2015;16:967–78. https://doi.org/10.1016/S1470-2045(15)00139-4.

[4] Therasse P, Arbuck SG, Eisenhauer EA, et al. New Guidelines to Evaluate the Response to Treatment in Solid Tumors. JNCI: J Natl Cancer Inst 2000;92:205–16. https://doi.org/10.1093/jnci/92.3.205.

[5] Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228–47. https://doi.org/10.1016/j.ejca.2008.10.026.

[6] Yoo C, Kim K, Jeong JH, et al. Liposomal irinotecan plus fluorouracil and leucovorin versus fluorouracil and leucovorin for metastatic biliary tract cancer after progression on gemcitabine plus cisplatin (NIFTY): a multicentre, open-label, randomised, phase 2b study. Lancet Oncol 2021;22:1560–72. https://doi.org/10.1016/S1470-2045(21)00486-1.

[7] Hyung J, Kim I, Kim K, et al. Treatment With Liposomal Irinotecan Plus Fluorouracil and Leucovorin for Patients With Previously Treated Metastatic Biliary Tract Cancer. JAMA Oncol 2023;9:692. https://doi.org/10.1001/jamaoncol.2023.0016.

[8] **Choi IS, Kim KH**, Lee JH, et al. A randomised phase II study of oxaliplatin/5-FU (mFOLFOX) versus irinotecan/5-FU (mFOLFIRI) chemotherapy in locally advanced or metastatic biliary tract cancer refractory to first-line gemcitabine/cisplatin chemotherapy. Eur J Cancer 2021;154:288–95. https://doi.org/10.1016/j.ejca.2021.06.019.

[9] **Rimini M, Fornaro L,** Rizzato MD, et al. Durvalumab plus gemcitabine and cisplatin in advanced biliary tract cancer: A large real-life worldwide population. Eur J Cancer 2024;208:114199. https://doi.org/10.1016/j.ejca.2024.114199.

[10] Macarulla T, Barrero M, Adeva J, et al. Epidemiological biliary tract cancer characterization: A patient cohort from the Spanish RETUD registry. J Clin Oncol 2022;40:480–480. https://doi.org/10.1200/JCO.2022.40.4_suppl.480.

[11] Sahai V, Griffith KA, Beg MS, et al. A randomized phase 2 trial of nivolumab, gemcitabine, and cisplatin or nivolumab and ipilimumab in previously untreated advanced biliary cancer: BilT-01. Cancer 2022;128:3523–30. https://doi.org/10.1002/cncr.34394.

[12] Assenat E, Blanc JF, Bouattour M, et al. 48P (BREGO) Regorafenib combined with modified m-GEMOX in patients with advanced biliary tract

cancer (BTC): A phase II randomized trial. Ann Oncol 2021;32:S376–7. https://doi.org/10.1016/j.annonc.2021.08.327.
[13] Okusaka T, Nakachi K, Fukutomi A, et al. Gemcitabine alone or in combination with cisplatin in patients with biliary tract cancer: a comparative multicentre study in Japan. Br J Cancer 2010;103:469–74. https://doi.org/10.1038/sj.bjc.6605779.
[14] **Chen JS, Hsu C, Chiang NJ, Tsai CS**, et al. A KRAS mutation status-stratified randomized phase II trial of gemcitabine and oxaliplatin alone or in combination with cetuximab in advanced biliary tract cancer. Ann Oncol 2015;26:943–9. https://doi.org/10.1093/annonc/mdv035.
[15] Zhu AX, Macarulla T, Javle MM, et al. Final Overall Survival Efficacy Results of Ivosidenib for Patients With Advanced Cholangiocarcinoma With *IDH1* Mutation. JAMA Oncol 2021;7:1669. https://doi.org/10.1001/jamaoncol.2021.3836.
[16] **Choi IS, Kim KH**, Lee JH, et al. A randomised phase II study of oxaliplatin/5-FU (mFOLFOX) versus irinotecan/5-FU (mFOLFIRI) chemotherapy in locally advanced or metastatic biliary tract cancer refractory to first-line gemcitabine/cisplatin chemotherapy. Eur J Cancer 2021;154:288–95. https://doi.org/10.1016/j.ejca.2021.06.019.
[17] dos Santos LV, Pinto GSF, Ferraz MWS, et al. Cisplatin plus irinotecan versus cisplatin plus gemcitabine in the treatment of advanced or metastatic gallbladder or biliary tract cancer: Results of a randomized phase II trial (NCT01859728)– the Gambit trial. J Clin Oncol 2020;38:529–529. https://doi.org/10.1200/JCO.2020.38.4_suppl.529.
[18] Ramaswamy A, Ostwal V, Sharma A, et al. Efficacy of Capecitabine Plus Irinotecan vs Irinotecan Monotherapy as Second-line Treatment in Patients With Advanced Gallbladder Cancer. JAMA Oncol 2021;7:436. https://doi.org/10.1001/jamaoncol.2020.6166.
[19] Moehler M, Maderer A, Schimanski C, et al. Gemcitabine plus sorafenib versus gemcitabine alone in advanced biliary tract cancer: A double-blind placebo-controlled multicentre phase II AIO study with biomarker and serum programme. Eur J Cancer 2014;50:3125–35. https://doi.org/10.1016/j.ejca.2014.09.013.
[20] Ikeda M, Ueno M, Furukawa M, et al. Subgroup analysis of double-blind, placebo-controlled Ph. 2 study of nanvuranlat in treatment of pre-treated, advanced, refractory biliary tract cancer (BTC): Patients with high LAT1 expression and response to nanvuranlat. J Clin Oncol 2023;41:4011–4011. https://doi.org/10.1200/JCO.2023.41.16_suppl.4011.
[21] El-Khoueiry AB, Ren Z, Chon H, et al. IMbrave151: A phase 2, randomized, double-blind, placebo-controlled study of atezolizumab with or without bevacizumab in combination with cisplatin plus gemcitabine in patients with untreated, advanced biliary tract cancer. J Clin Oncol 2023;41:491–491. https://doi.org/10.1200/JCO.2023.41.4_suppl.491.
[22] Morizane C, Okusaka T, Mizusawa J, et al. Randomized phase II study of gemcitabine plus S-1 versus S-1 in advanced biliary tract cancer: A Japan Clinical Oncology Group trial (JCOG 0805). Cancer Sci 2013;104:1211–6. https://doi.org/10.1111/cas.12218.
[23] Morizane C, Okusaka T, Mizusawa J, et al. Combination gemcitabine plus S-1 versus gemcitabine plus cisplatin for advanced/recurrent biliary tract

cancer: the FUGA-BT (JCOG1113) randomized phase III clinical trial. Ann Oncol 2019;30:1950–8. https://doi.org/10.1093/annonc/mdz402.
[24] Kang MJ, Lee J-L, Kim TW, et al. Randomized phase II trial of S-1 and cisplatin versus gemcitabine and cisplatin in patients with advanced biliary tract adenocarcinoma. Acta Oncol (Madr) 2012;51:860–6. https://doi.org/10.3109/0284186X.2012.682628.
[25] Kataria B, Sharma A, Pramanik R, et al. PD-9 Three-arm phase II/III randomized controlled trial in patients with unresectable/metastatic gall bladder cancer with poor performance status: Erlotinib or capecitabine v/s best supportive care. Ann Oncol 2022;33:S242. https://doi.org/10.1016/j.annonc.2022.04.087.
[26] Kelley RK, Ueno M, Yoo C, et al. Pembrolizumab in combination with gemcitabine and cisplatin compared with gemcitabine and cisplatin alone for patients with advanced biliary tract cancer (KEYNOTE-966): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2023;401:1853–65. https://doi.org/10.1016/S0140-6736(23)00727-4.
[27] Ioka T, Kanai M, Kobayashi S, et al. Randomized phase <scp>III</scp> study of gemcitabine, cisplatin plus S-1 versus gemcitabine, cisplatin for advanced biliary tract cancer (KHBO1401- MITSUBA). J Hepatobiliary Pancreat Sci 2023;30:102–10. https://doi.org/10.1002/jhbp.1219.
[28] **Kim ST, Kang JH,** Lee J, et al. Capecitabine plus oxaliplatin versus gemcitabine plus oxaliplatin as first-line therapy for advanced biliary tract cancers: a multicenter, open-label, randomized, phase III, noninferiority trial. Ann Oncol 2019;30:788–95. https://doi.org/10.1093/annonc/mdz058.
[29] Lee J, Park SH, Chang H-M, et al. Gemcitabine and oxaliplatin with or without erlotinib in advanced biliary-tract cancer: a multicentre, open-label, randomised, phase 3 study. Lancet Oncol 2012;13:181–8. https://doi.org/10.1016/S1470-2045(11)70301-1.
[30] Markussen A, Jensen LH, Diness LV, Larsen FO. Treatment of Patients with Advanced Biliary Tract Cancer with Either Oxaliplatin, Gemcitabine, and Capecitabine or Cisplatin and Gemcitabine—A Randomized Phase II Trial. Cancers (Basel) 2020;12:1975. https://doi.org/10.3390/cancers12071975.
[31] Vogel A, Wenzel P, Folprecht G, et al. 53MO Nal-IRI and 5-FU/LV compared to 5-FU/LV in patients with cholangio- and gallbladder carcinoma previously treated with gemcitabine-based therapies (NALIRICC – AIO-HEP-0116). Ann Oncol 2022;33:S563–4. https://doi.org/10.1016/j.annonc.2022.07.081.
[32] Yoo C, Kim K, Jeong JH, et al. Liposomal irinotecan plus fluorouracil and leucovorin versus fluorouracil and leucovorin for metastatic biliary tract cancer after progression on gemcitabine plus cisplatin (NIFTY): a multicentre, open-label, randomised, phase 2b study. Lancet Oncol 2021;22:1560–72. https://doi.org/10.1016/S1470-2045(21)00486-1.
[33] Knox J, Bazin I, Oh D, et al. O-2 Phase III study of NUC-1031 + cisplatin vs gemcitabine + cisplatin for first-line treatment of patients with advanced biliary tract cancer (NuTide:121). Ann Oncol 2023;34:S180–1. https://doi.org/10.1016/j.annonc.2023.04.017.
[34] Pape U-F, Kasper S, Meiler J, et al. Efficacy and Safety of CAP7.1 as Second-Line Treatment for Advanced Biliary Tract Cancers: Data from a Randomised Phase II Study. Cancers (Basel) 2020;12:3149. https://doi.org/10.3390/cancers12113149.

[35] Vogel A, Kasper S, Bitzer M, et al. PICCA study: panitumumab in combination with cisplatin/gemcitabine chemotherapy in KRAS wild-type patients with biliary cancer—a randomised biomarker-driven clinical phase II AIO study. Eur J Cancer 2018;92:11–9. https://doi.org/10.1016/j.ejca.2017.12.028.
[36] Demols A, Borbath I, Van den Eynde M, et al. Regorafenib after failure of gemcitabine and platinum-based chemotherapy for locally advanced/metastatic biliary tumors: REACHIN, a randomized, double-blind, phase II trial. Ann Oncol 2020;31:1169–77. https://doi.org/10.1016/j.annonc.2020.05.018.
[37] Schinzari G, Rossi E, Mambella G, et al. First-line Treatment of Advanced Biliary Ducts Carcinoma: A Randomized Phase II Study Evaluating 5-FU/LV Plus Oxaliplatin (Folfox 4) Versus 5-FU/LV (de Gramont Regimen). Anticancer Res 2017;37:5193–7. https://doi.org/10.21873/anticanres.11942.
[38] Sharma A, Dwary AD, Mohanti BK, et al. Best Supportive Care Compared With Chemotherapy for Unresectable Gall Bladder Cancer: A Randomized Controlled Study. J Clin Oncol 2010;28:4581–6. https://doi.org/10.1200/JCO.2010.29.3605.
[39] Sharma A, Kalyan Mohanti B, Pal Chaudhary S, et al. Modified gemcitabine and oxaliplatin or gemcitabine + cisplatin in unresectable gallbladder cancer: Results of a phase III randomised controlled trial. Eur J Cancer 2019;123:162–70. https://doi.org/10.1016/j.ejca.2019.10.004.
[40] Shirahama T, Muroya D, Matsueda S, et al. A randomized phase II trial of personalized peptide vaccine with low dose cyclophosphamide in biliary tract cancer. Cancer Sci 2017;108:838–45. https://doi.org/10.1111/cas.13193.
[41] Shroff RT, Guthrie KA, Scott AJ, et al. SWOG 1815: A phase III randomized trial of gemcitabine, cisplatin, and nab-paclitaxel versus gemcitabine and cisplatin in newly diagnosed, advanced biliary tract cancers. J Clin Oncol 2023;41:LBA490–LBA490. https://doi.org/10.1200/JCO.2023.41.4_suppl.LBA490.
[42] Kim RD, McDonough S, El-Khoueiry AB, et al. Randomised phase II trial (SWOG S1310) of single agent MEK inhibitor trametinib Versus 5-fluorouracil or capecitabine in refractory advanced biliary cancer. Eur J Cancer 2020;130:219–27. https://doi.org/10.1016/j.ejca.2020.01.026.
[43] Oh D-Y, Ruth He A, Qin S, et al. Durvalumab plus Gemcitabine and Cisplatin in Advanced Biliary Tract Cancer. NEJM Evid 2022;1. https://doi.org/10.1056/EVIDoa2200015.
[44] Javle MM, Oh D-Y, Ikeda M, et al. Varlitinib plus capecitabine in second-line advanced biliary tract cancer: a randomized, phase II study (TreeTopp). ESMO Open 2022;7:100314. https://doi.org/10.1016/j.esmoop.2021.100314.
[45] Ueno M, Morizane C, Furukawa M, et al. A randomized, double-blind, phase II study of oral histone deacetylase inhibitor resminostat plus S-1 versus placebo plus S-1 in biliary tract cancers previously treated with gemcitabine plus platinum-based chemotherapy. Cancer Med 2021;10:2088–99. https://doi.org/10.1002/cam4.3813.
[46] Valle JW, Vogel A, Denlinger CS, et al. Addition of ramucirumab or merestinib to standard first-line chemotherapy for locally advanced or

metastatic biliary tract cancer: a randomised, double-blind, multicentre, phase 2 study. Lancet Oncol 2021;22:1468–82. https://doi.org/10.1016/S1470-2045(21)00409-5.

[47] Leone F, Marino D, Cereda S, et al. Panitumumab in combination with gemcitabine and oxaliplatin does not prolong survival in wild-type *KRAS* advanced biliary tract cancer: A randomized phase 2 trial (Vecti-BIL study). Cancer 2016;122:574–81. https://doi.org/10.1002/cncr.29778.

[48] Yang X, Zhuang L, Dai Y, et al. A prospective, multicenter, phase II trial of albumin-paclitaxel plus cisplatin versus gemcitabine plus cisplatin in first-line treatment of advanced biliary tract tumors. J Clin Oncol 2022;40:4099–4099. https://doi.org/10.1200/JCO.2022.40.16_suppl.4099.

[49] **Zheng Y, Tu X**, Zhao P, et al. A randomised phase II study of second-line XELIRI regimen versus irinotecan monotherapy in advanced biliary tract cancer patients progressed on gemcitabine and cisplatin. Br J Cancer 2018;119:291–5. https://doi.org/10.1038/s41416-018-0138-2.

Supplementary figures

Fig. S1: Assessment of publication bias. (A, C, E, G) Funnel plot including all the studies selected for the analysis for OS (A), PFS (C), DCR (E) and ORR (G). P-values were calculated using Egger's regression test to assess for funnel plot asymmetry. (B, D, F, H) P-curve analysis for OS (B), PFS (D), DCR (F) and ORR (H) showing a significant right-skewedness test with a non-significant flatness test, concluding that evidential value is present.
HR, hazard ratio.

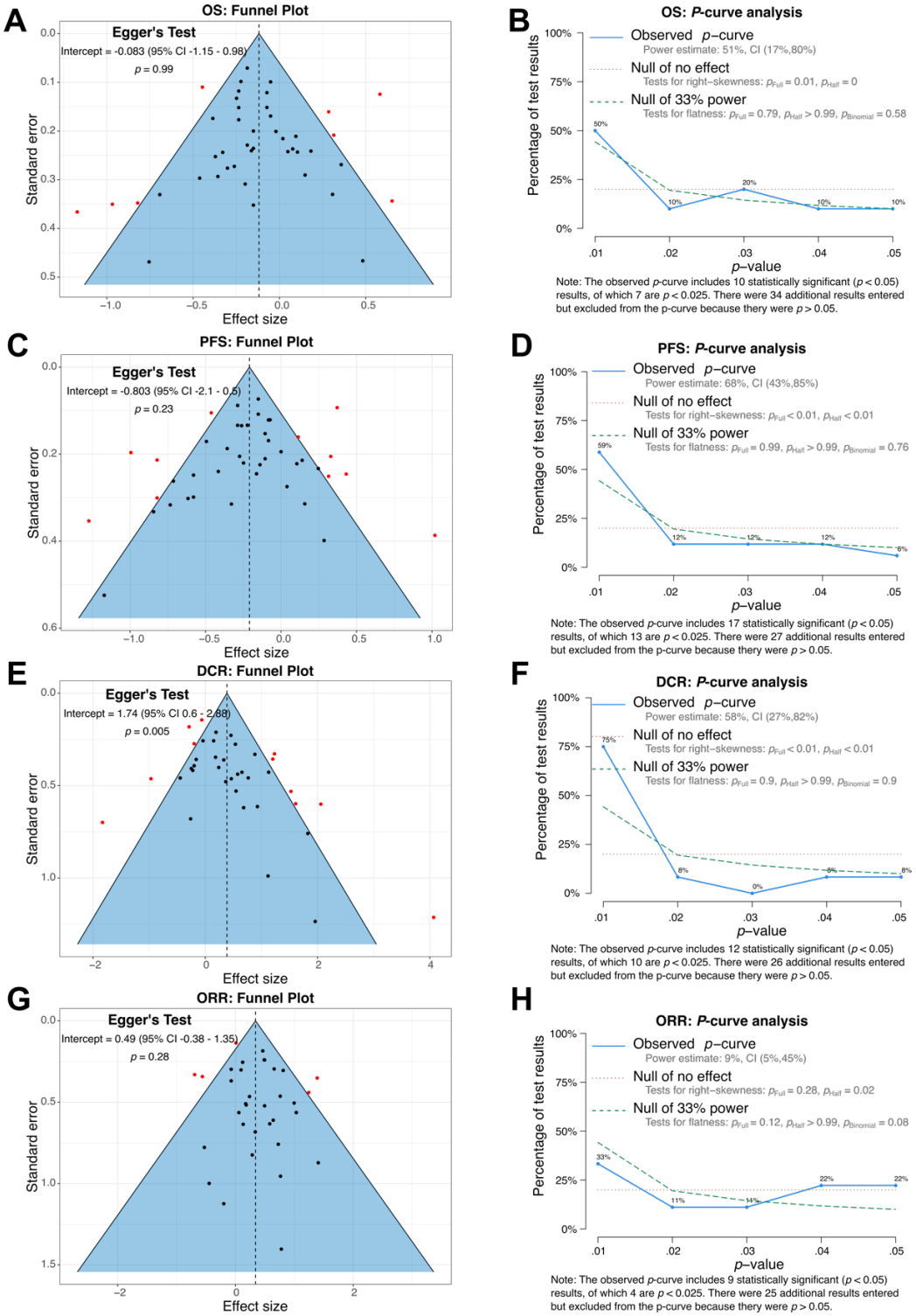


Fig. S2: Cochrane's risk of bias assessment for each trial. Each barplot depicts a domain included in the Cochrane assessment tool. The color represents the risk of bias based on the author's judgement.

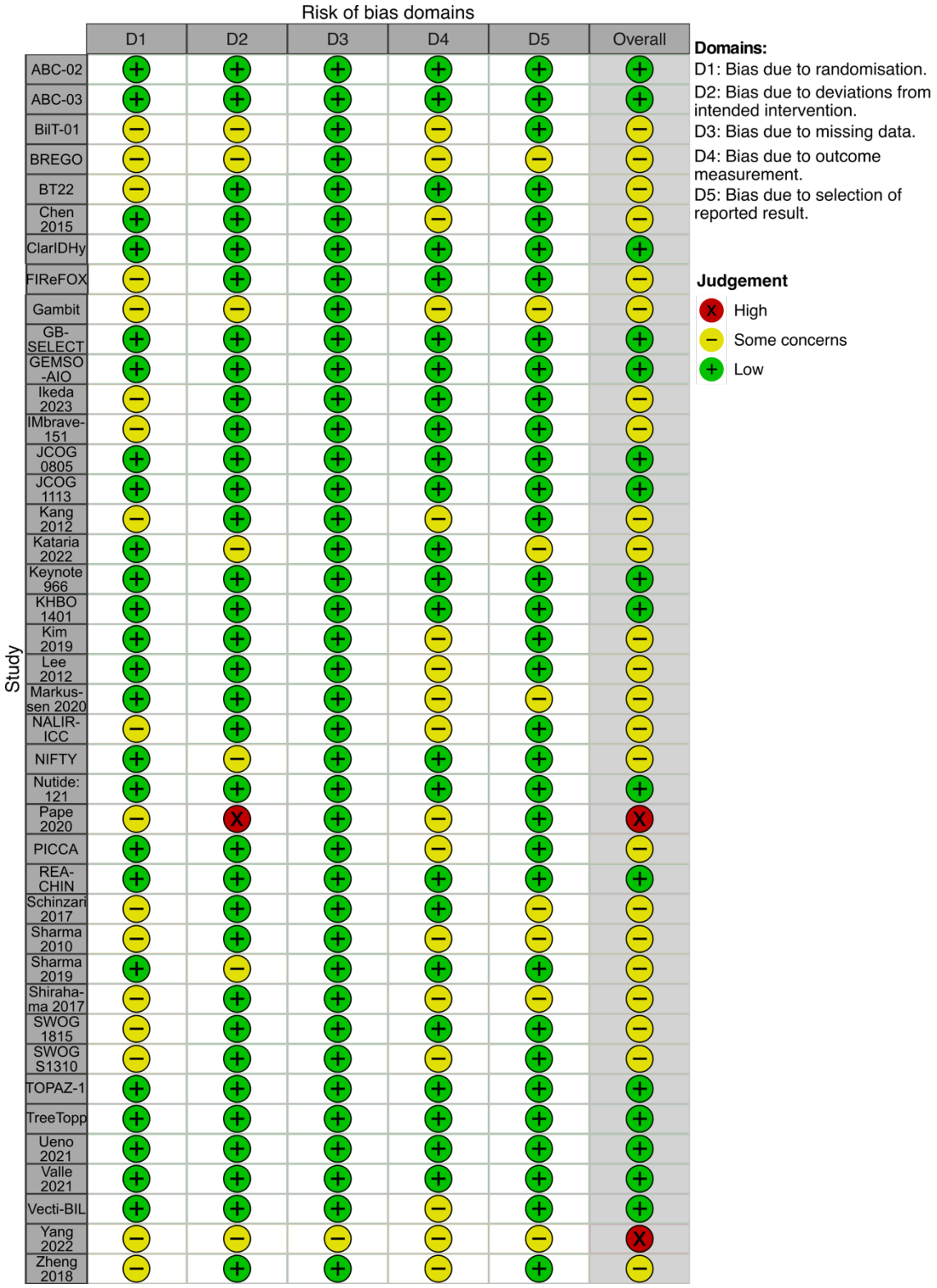


Fig. S3: Cochrane's risk of bias assessment summary. Each barplot depicts a domain included in the Cochrane assessment tool. The color represents the risk of bias based on the author's judgement.

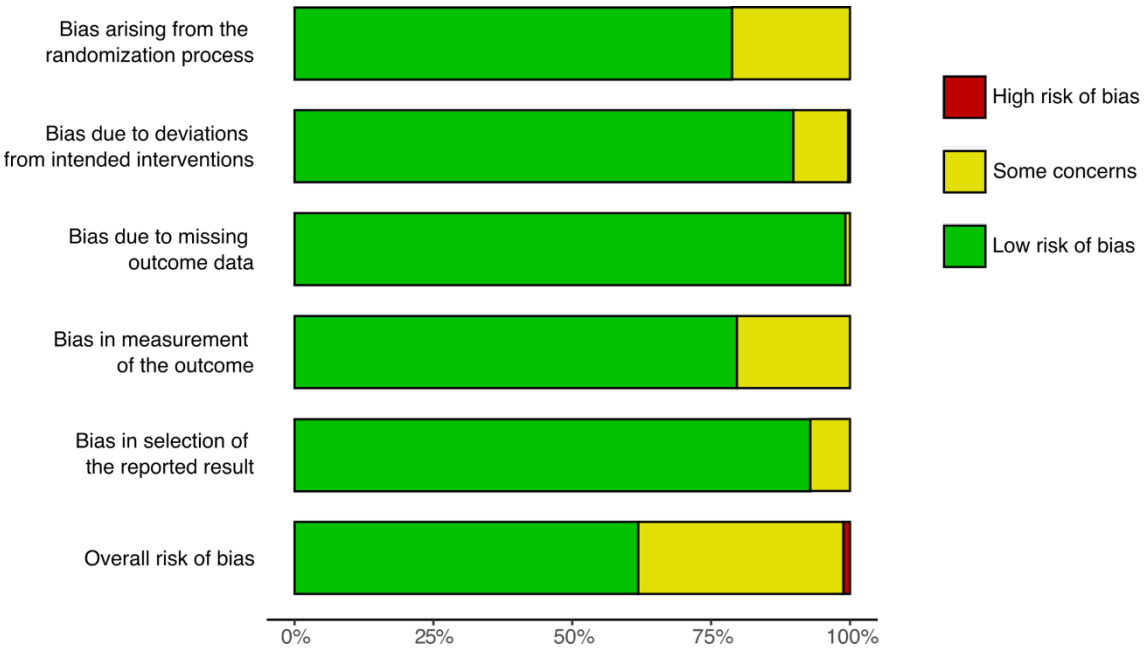


Fig. S4: Delphi quality assessment of each trial. Heatmap assessing nine different Delphi items for each trial. A blue box indicates the trial met the item and a gray box indicates it did not. The bars on the right indicate the Delphi total score.

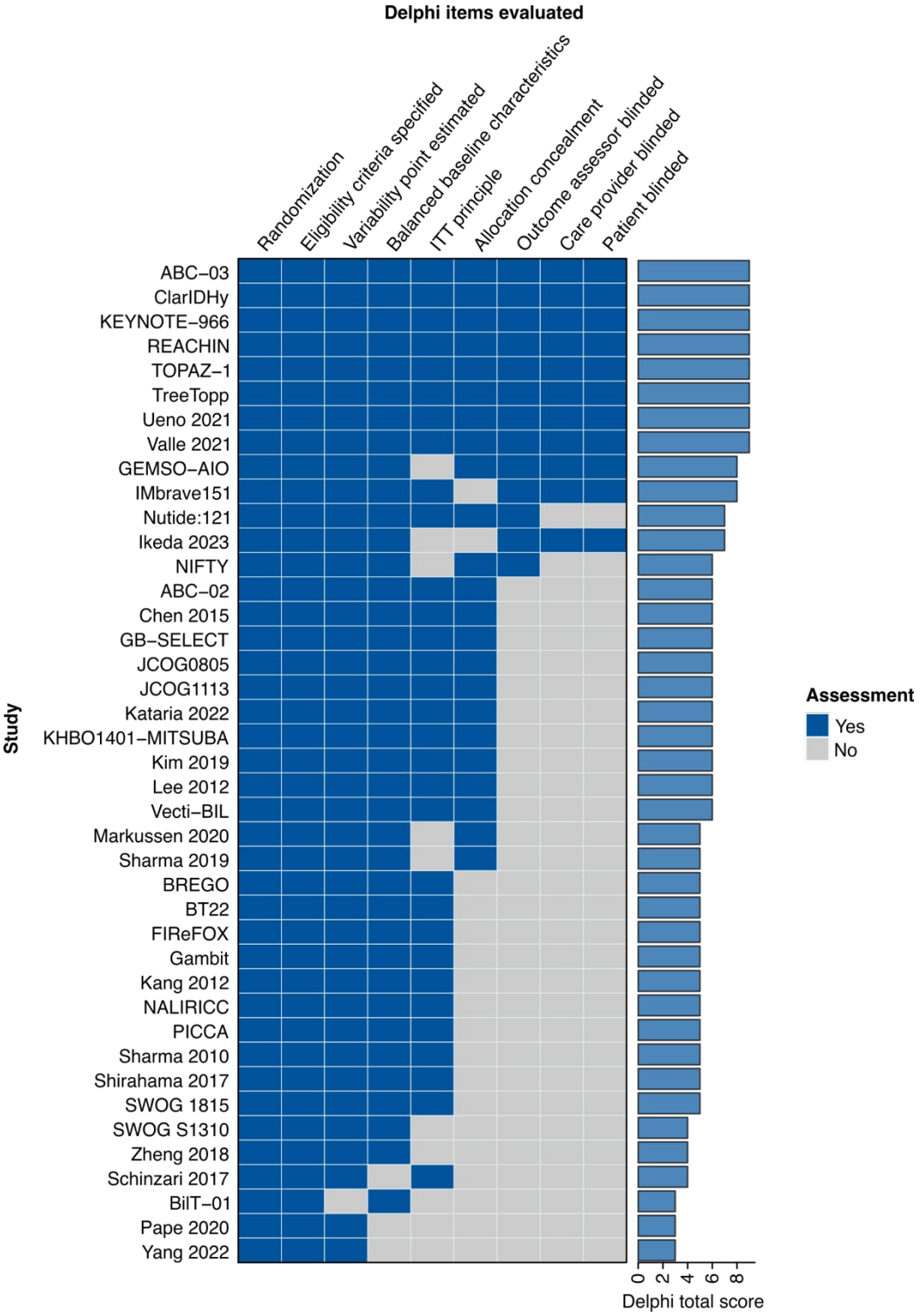


Fig. S5: Bubble plots showing the trial-level correlation for ORR and OS across different subgroups. Every bubble represents a trial, the colour represents the treatment type and the size is proportional to the number of patients included in the trial. The odds ratios are presented in the logarithmic scale. The red lines show the 95% prediction interval for a weight (i.e sample size) of 200. The correlation was estimated by using a linear regression model weighed by trial size. The variation of the weighted treatment effects explained by the model was measured with the coefficient of determination (R^2).
CI, confidence interval; ORR, objective response rate; OS, overall survival; STE, surrogate threshold effect.

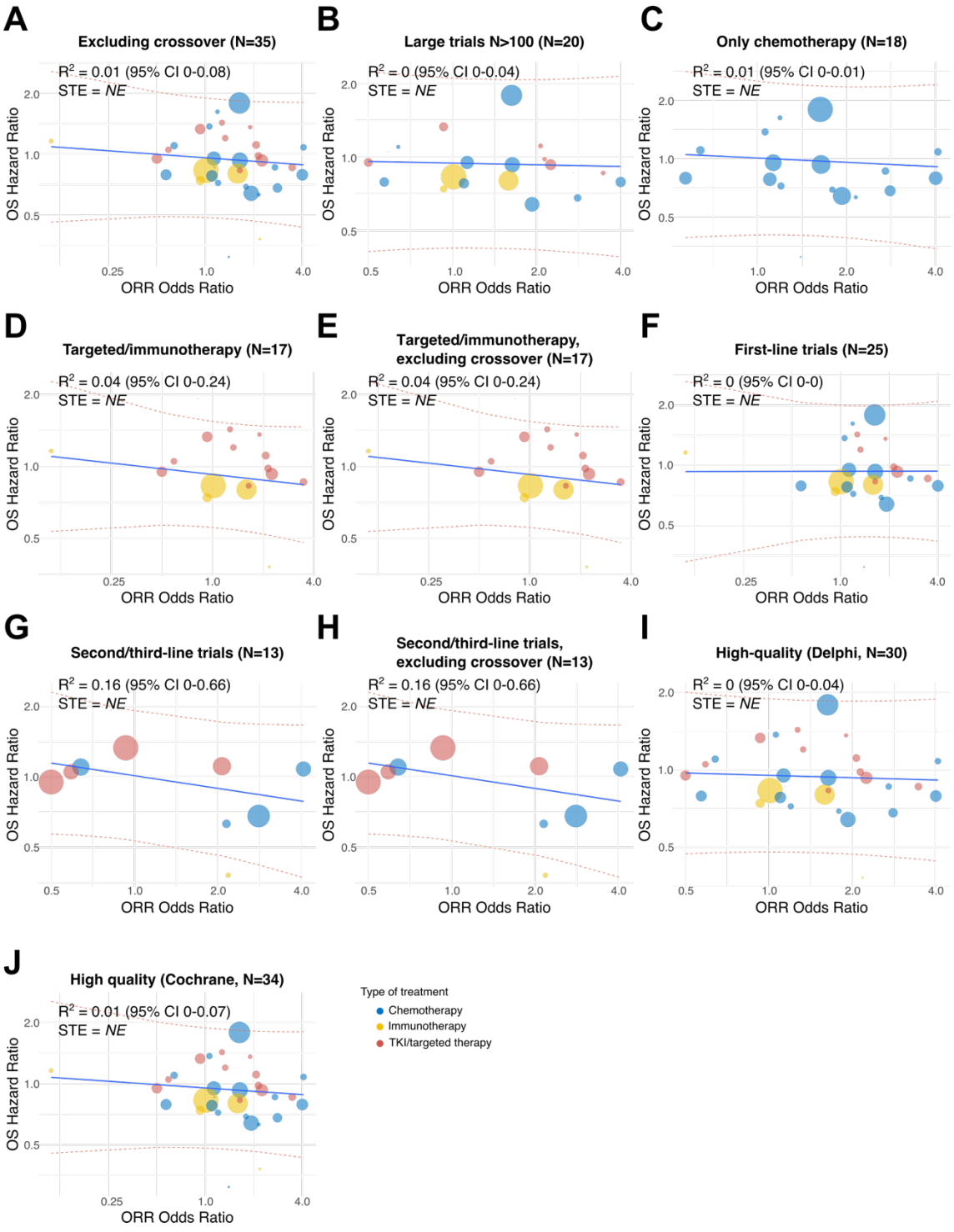


Fig. S6: Bubble plots showing the trial-level correlation for DCR and OS across different subgroups. Every bubble represents a trial, the colour represents the treatment type and the size is proportional to the number of patients included in the trial. The odds ratios are presented in the logarithmic scale. The red lines show the 95% prediction interval for a weight (i.e sample size) of 200. The correlation was estimated by using a linear regression model weighed by trial size. The variation of the weighted treatment effects explained by the model was measured with the coefficient of determination (R^2).
CI, confidence interval; DCR, disease control rate; OS, overall survival; STE, surrogate threshold effect.

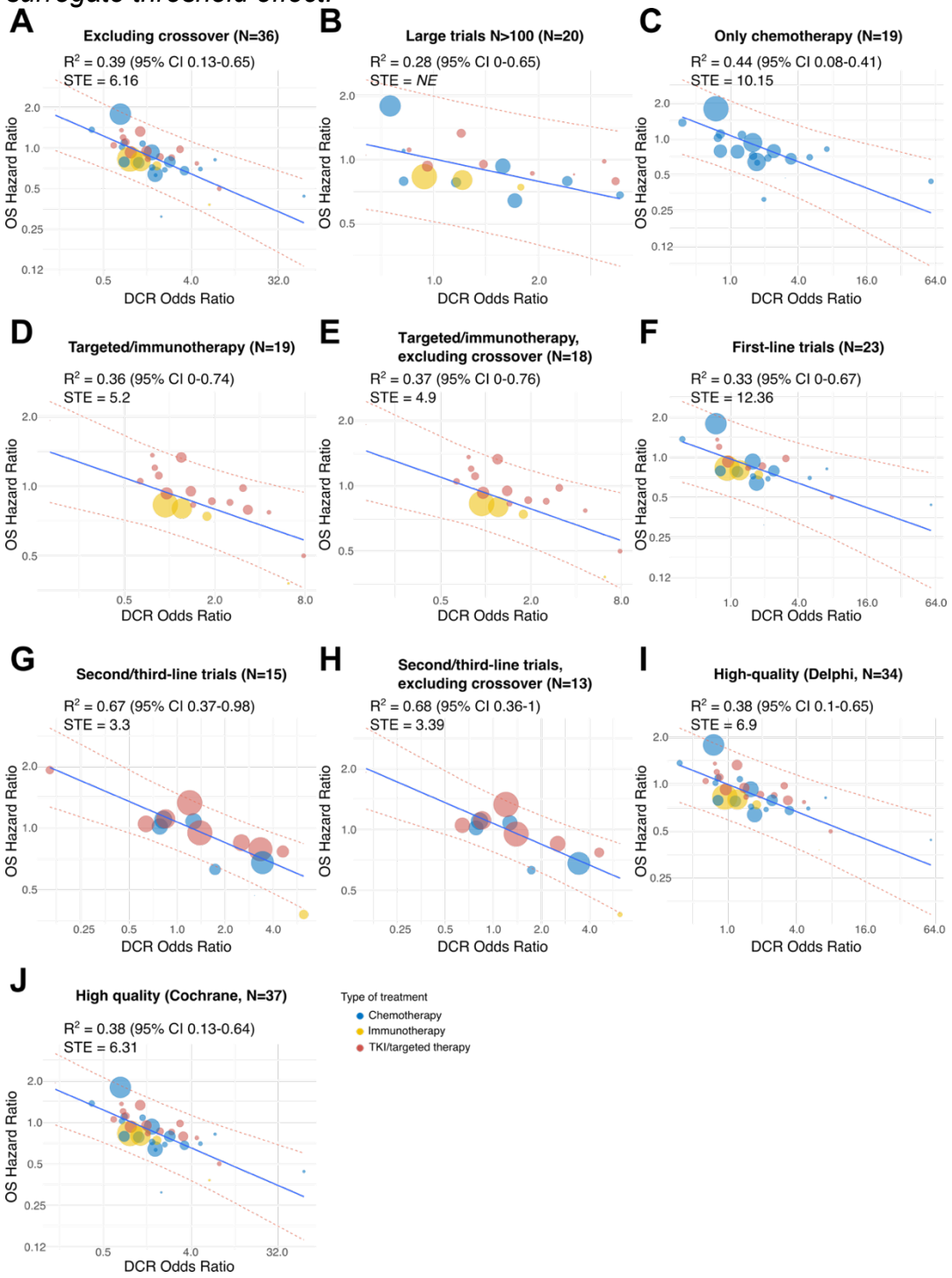


Fig. S7: Sensitivity analysis for PFS based on disease location and stage. Every bubble represents a trial, the colour represents the treatment type and the size is proportional to the number of patients for each category included in the trial. The hazard ratios are presented in the logarithmic scale. The red lines show the 95% prediction interval for a weight (i.e sample size) of 200. The correlation was estimated by using a linear regression model weighed by category size. The variation of the weighted treatment effects explained by the model was measured with the coefficient of determination (R^2).
CI, confidence interval; OS, overall survival; PFS, progression-free survival; STE, surrogate threshold effect.

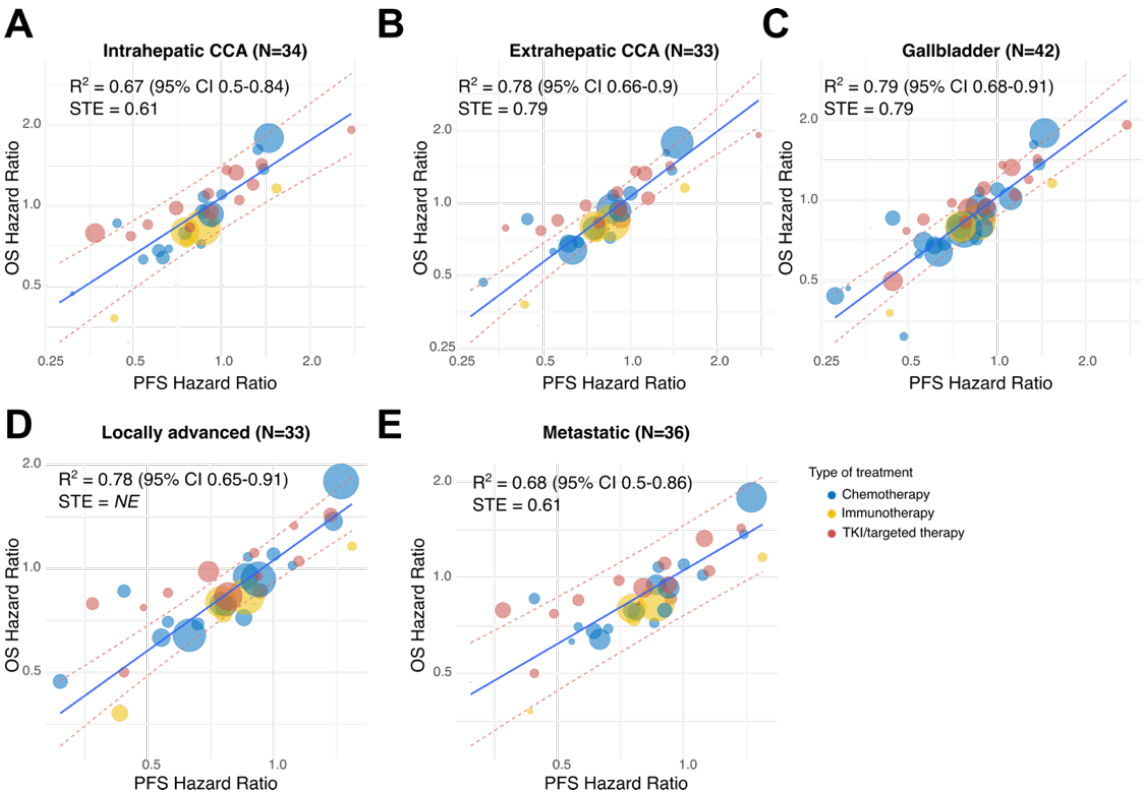


Fig. S8: Sensitivity analysis for ORR based on disease location and stage. Every bubble represents a trial, the colour represents the treatment type and the size is proportional to the number of patients for each category included in the trial. The hazard ratios are presented in the logarithmic scale. The red lines show the 95% prediction interval for a weight (i.e sample size) of 200. The correlation was estimated by using a linear regression model weighed by category size. The variation of the weighted treatment effects explained by the model was measured with the coefficient of determination (R^2).
CI, confidence interval; OS, overall survival; ORR, objective response rate; STE, surrogate threshold effect.

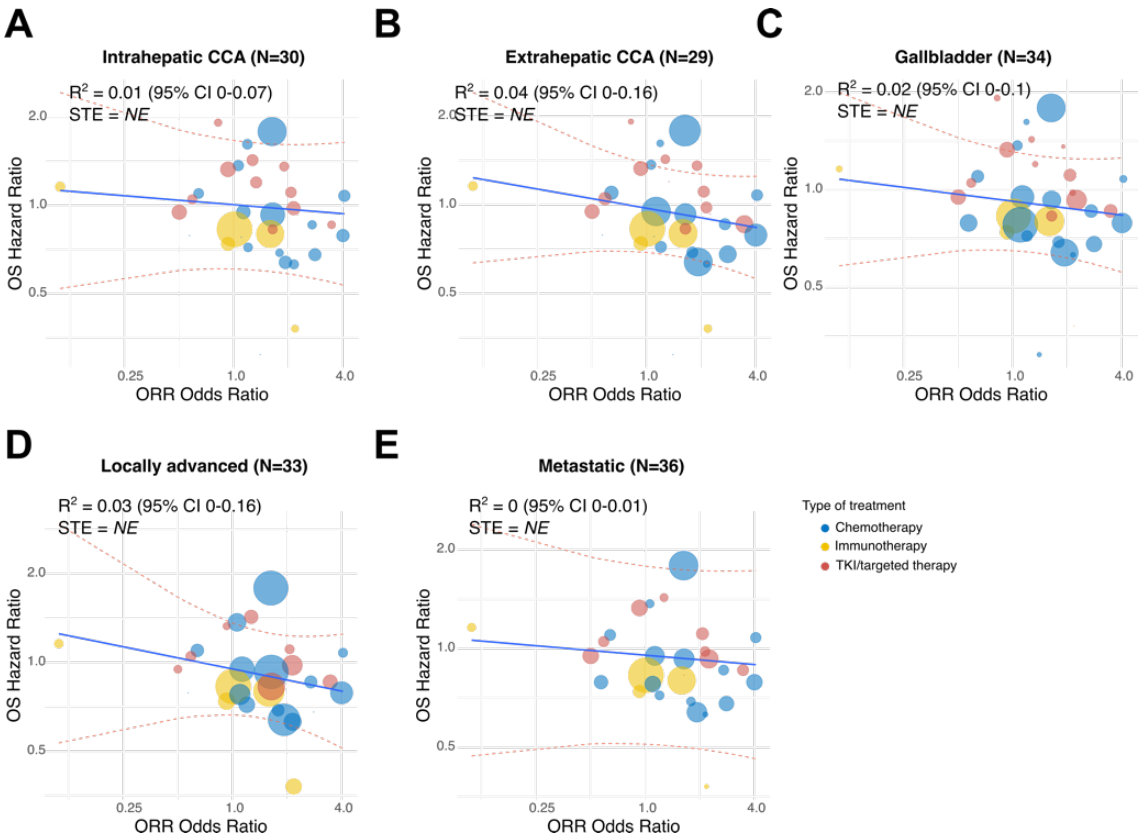


Fig. S9: Sensitivity analysis for DCR based on disease location and stage. Every bubble represents a trial, the colour represents the treatment type and the size is proportional to the number of patients for each category included in the trial. The hazard ratios are presented in the logarithmic scale. The red lines show the 95% prediction interval for a weight (i.e sample size) of 200. The correlation was estimated by using a linear regression model weighed by category size. The variation of the weighted treatment effects explained by the model was measured with the coefficient of determination (R^2).
CI, confidence interval; OS, overall survival; DCR, disease control rate; STE, surrogate threshold effect.

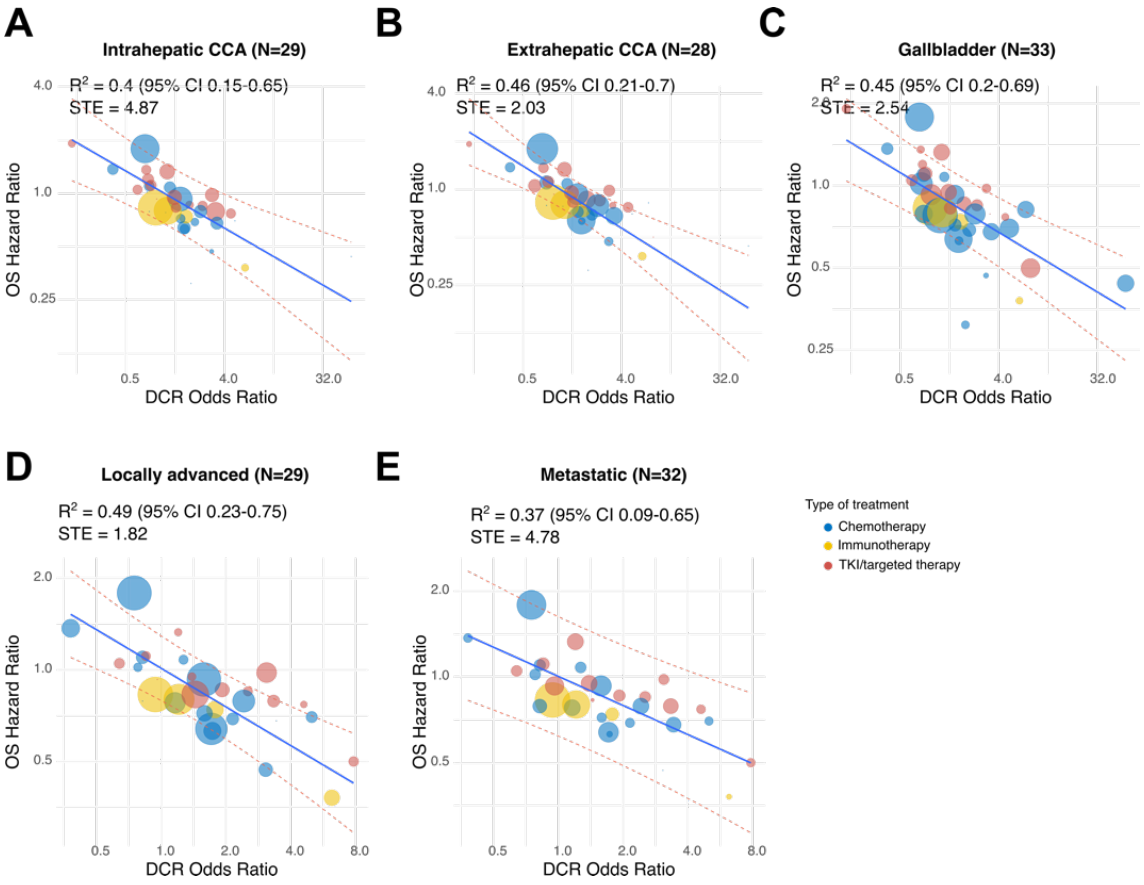


Fig. S10: Leave-one-out cross validation for the correlation analysis of PFS and OS. (A) The red dots are the predicted HR for OS, the black dots show the reported HR for OS and the black lines represent the 95% intervals of HR for OS. (B) Histogram showing the distribution of the R^2 values for each of the models generated after excluding a single trial.
HR, hazard ratio; OS, overall survival.

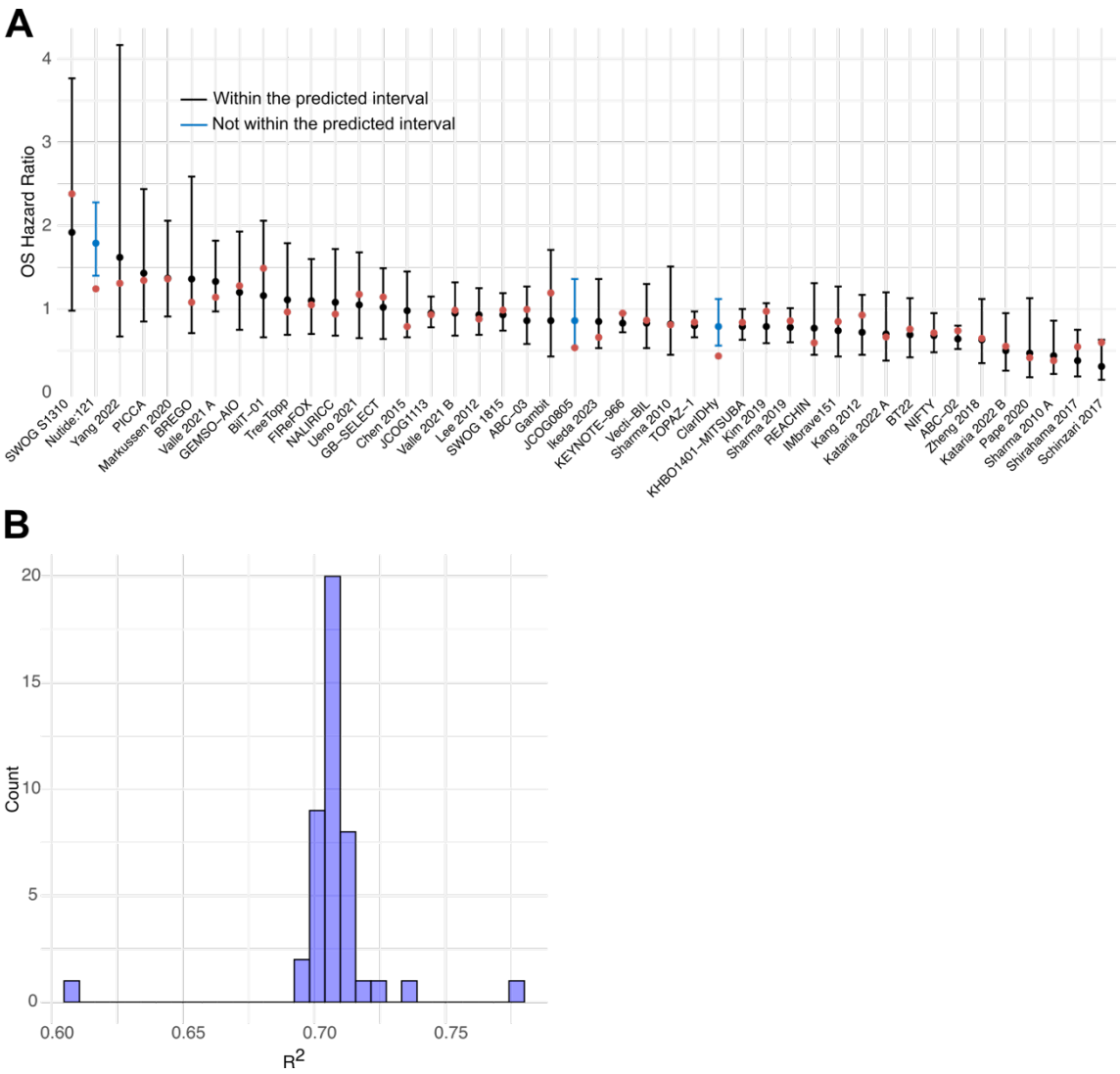
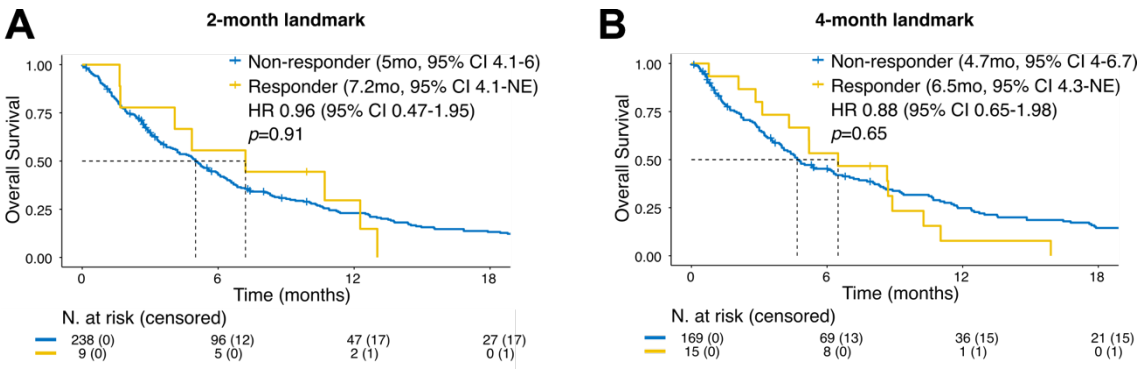


Fig. S11: Impact of response on survival in patients treated with second-line chemotherapy. Kaplan-Meier estimates of overall survival between responders and nonresponders (Condition 2) who were alive and had achieved response at 2 months (A) and 4 months (B). The hazard ratios (HR) were estimated by applying a Cox regression model and the p-values obtained from the Cox regression model.



PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	8-9
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	11-12
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	12
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	14-15
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	14
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Table S1
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	14
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	15
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	15
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	15
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	15
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	15
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	14-15
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	16
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	16
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	16
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	16
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	16
Reporting bias	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	15

Section and Topic	Item #	Checklist item	Location where item is reported
assessment			
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	15
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	18
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	18
Study characteristics	17	Cite each included study and present its characteristics.	Table 2, Table S3
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Fig.S2-4
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Fig. 2
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	18-19
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	18-19
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	18.19, Fig. 2-3, Fig. S5-6
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	18.19, Fig. 2, Fig. S5-9
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	18-19, Fig. 1
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Fig. 2
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	21-23
	23b	Discuss any limitations of the evidence included in the review.	24
	23c	Discuss any limitations of the review processes used.	24
	23d	Discuss implications of the results for practice, policy, and future research.	23-25
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	14
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	14
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	14

Section and Topic	Item #	Checklist item	Location where item is reported
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	6
Competing interests	26	Declare any competing interests of review authors.	4-6
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Supp Mat

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71.

Association of progression-free survival and response rate with overall survival in advanced biliary tract cancer: a trial-level meta-analysis and individual patient-level correlation

Protocol Version 1.1

INDEX

1. BACKGROUND

1.1 Treatment landscape of advanced biliary tract cancer

Biliary tract cancer (BTC) refers to a heterogeneous group of adenocarcinomas arising in the biliary tree which include intrahepatic, perihilar and distal cholangiocarcinomas as well as gallbladder carcinomas[1,2]. The incidence is low but is steadily increasing worldwide, especially for intrahepatic cholangiocarcinomas[3,4]. Most patients will present with or develop unresectable disease or metastasis, for which only systemic treatments have been shown to improve overall survival (OS)[5,6]. The combination of cisplatin with gemcitabine was the first regimen to improve outcomes, providing a median OS of 11.7 months[7,8]. More recently, the combination of this doublet chemotherapy with either durvalumab, an anti-PDL1 antibody, or pembrolizumab, an anti-PD1 antibody, improved outcomes compared with cisplatin-gemcitabine alone[9,10], establishing these combinations as the new standard-of-care. In the second-line setting, the combination of 5-fluouracil with oxaliplatin (FOLFOX regimen) has been shown to improve overall survival[11]. Other combinations, such as liposomal irinotecan and 5FU, have also showed improved benefits in this setting in a randomized phase II trial[12,13]. The identification of unique subgroups of patients harbouring actionable molecular alterations has changed the treatment paradigm in recent years[1,5,6]. The *IDH1* inhibitor ivosidenib was shown to significantly improve progression-free survival (PFS) when compared with placebo in patients with BTC who harboured an *IDH1* mutation[14], although it did not show improved OS outcomes[15]. Additional non-randomised studies have explored the benefits of FGFR inhibitors in patients harbouring a *FGFR2* fusion[16–19], HER2 inhibitors in patients with overexpression of HER2 or amplification of *ERBB2*[20–25], immunotherapy in mismatch repair deficient tumours[26] and vemurafenib or the combination of dabrafenib and trametinib in *BRAF*^{V600E} tumours[27,28], amongst others.

1.2 OS as a primary endpoint in randomized trials in advanced BTC

OS remains the most robust, reliable and clinically meaningful endpoint in randomized controlled trials in advanced BTC. It provides an unbiased assessment of treatment efficacy and safety and is therefore considered the gold-standard endpoint for the design of clinical trials by regulatory agencies[29].

However, under some circumstances, OS may prove to be an impractical primary endpoint[30]. Firstly, cross-over designs, in which patients randomized to the control arm are allowed to receive the experimental treatment after progression, may confound the interpretation of OS[30–34]. For instance, the design of the ClarIDHy trial allowed patients in the placebo arm to cross over to ivosidenib upon progression, which led to non-significant benefit in OS despite providing a HR of 0.37 in PFS. Furthermore, in the era of accelerated drug approvals, the promising results of an early trial may allow clinicians to administer the experimental drug during the execution of the validation trial, leading to inevitable and uncontrolled cross-over. Secondly, imbalances in post-progression management complicate the reliable quantification and analysis of the effect of the experimental therapy on OS[35]. Indeed, the availability of effective subsequent therapies may lead to improved post-progression survival, which may in turn obscure benefits in OS and require an

excessively long follow-up period to detect any statistically significant difference[30,36]. While a potential therapy will improve absolute survival differences regardless of post-trial therapies, the relative difference (measured in terms of hazard ratios) will be diluted by the variability introduced by subsequent lines of treatment[37]. As previously mentioned, the continual development of novel therapies in the BTC field is likely to pose some of these challenges in the near future, making it increasingly elusive to detect OS gains and highlighting the need for surrogate endpoints of OS.

1.3 PFS as an intermediate endpoint in randomized trials in advanced BTC

PFS is a tumour-based intermediate endpoint defined as the time from randomization to disease progression or death. It has several important properties, such as providing a more direct measure of the treatment effect on the tumour burden process, being sensitive to both cytotoxic and cytostatic mechanisms of interventions and incorporating the clinical event of death[34]. It is an attractive endpoint as it is available earlier than OS, less influenced by competing causes of death and by treatments administered after progression[35,38]. Furthermore, PFS may represent clinical benefit by itself; indeed, telling patients that their tumours are not growing may lead to improvements in their quality of life and delaying progression may additionally improve tumour-derived symptoms[39].

However, there are several limitations when using PFS[40]. First, the true progression time lies somewhere between two radiologic assessments and the date at which radiologic evaluation confirms progression is taken as proxy for the true date of progression, which may lead to measurement error[35]. Secondly, informative censoring due to poor drug tolerance may lead to artefactual differences in survival and a biased overestimation of treatment effect[39,41,42]. Thirdly, it has been argued that it is unlikely for therapies administered postprogression to be the explanation for why improvements in PFS fail to improve OS outcomes, as it would require the imbalances in both treatment arms to be imbalanced by chance or have greater activity in the control arm than the experimental arm[43]. Finally, PFS has failed to strongly correlate with OS[44] and quality of life[40,45] in many solid tumours.

To try to reconcile these limitations, clinicians and regulatory agencies highlight the importance of carefully assessing OS and drug tolerance when selecting PFS as the primary endpoint. While acknowledging that the trial may be underpowered to detect statistical differences in OS, careful attention should be given to guarantee a rigorous evaluation of descriptive OS data and ensure no detriment is observed in survival[29,46].

2. SURROGATE ENDPOINTS OF OS IN ADVANCED BTC

Surrogate endpoints are intended to substitute for final patient-relevant outcomes that directly measure how patients feel, function or survive in clinical trials[47]. When using alternative endpoints to OS in clinical trials, a formal statistical validation of surrogacy aims at demonstrating that improvements in this alternative endpoint will predict improvements in OS[30,34]. Three key levels of validity exist when assessing a potential surrogate[48–50]:

- **Level 3: Biological plausibility**: There must be a strong clinical or biological rationale to support the notion that the endpoint can plausibly predict the clinical outcome of interest. No statistical method can be used to formally prove this condition.
- **Level 2: Observational association**: There must be epidemiologic data demonstrating a strong relationship between the surrogate endpoint and final patient relevant outcome. Individual patient data must be used to demonstrate this association.
- **Level 1: Interventional/treatment effect association**: It must be possible to predict the effect of the treatment on the endpoint of interest based on the effect observed on the surrogate endpoint. This is now regarded as the most important criterion for demonstrating the validity of a surrogate endpoint and is the most difficult to establish, as it requires the analysis of multiple randomized clinical trials[51].

Surrogate endpoints for OS are more likely to be formally validated in tumour types or treatment lines for which no effective post-trial therapy exists, due to the previously mentioned reasons[35]. Caution should be exercised when extrapolating the association between OS and a surrogate endpoint when assessed in a distinct treatment line or including only trials assessing drugs with a unique mechanism of action[43]. However, it is important to highlight that confidence in the surrogate endpoint is enhanced when the trial-level regression is conducted over a heterogeneous rather than a homogeneous collection of previously conducted randomized trials, involving a wide range of different interventions, durations of follow-up and treatment lines. This supports the assertion of validity of a surrogate for application in a new trial[49].

Different frameworks have been developed to establish the surrogacy of a potential endpoint[48]. One of the most used is the two-stage meta-analytic framework, that requires individual patient-level data of all included trials in the systematic review to calculate the individual- and trial-level correlation[49,50,52–58]. In this framework, a validated endpoint will meet two conditions: it will demonstrate a strong correlation between the surrogate and definitive endpoint (Condition 1) and a correlation of treatment effects on both endpoints (Condition 2). One of the limitations of this approach is that identified trials whose individual data cannot be retrieved are excluded from the trial-level analysis, which may lead to a selection bias[50]. Because we did not have access to individual-level data from all identified trials, we applied an adaptation of this framework that intended to demonstrate both conditions, as detailed below.

3. HYPOTHESIS AND AIMS

To date, no analysis has formally evaluated the OS surrogacy of PFS in advanced BTC both at the individual-level and trial-level analysis. Despite the aforementioned limitations of PFS, it is a commonly used intermediate endpoint in BTC and has been accepted by regulatory agencies as a primary endpoint in trials evaluating targeted therapies. Hence, this endpoint should be assessed for surrogacy in advanced BTC to ascertain whether changes in PFS accurately predict OS.

4. INDIVIDUAL PATIENT-LEVEL ANALYSIS

4.1 Patients and Datasets

To analyse the individual patient-level association, we intend to enrol patients included in RCTs and in a real-world data cohort. As previously mentioned, one of the limitations of PFS is that it is sensitive to the timing of radiological assessments and measurement errors[40]. Including a pooled cohort of participants in randomized controlled trials and a separate, real-world cohort in which the timing of assessments and response evaluation are done following local practice will enable us to measure the impact of these factors on the strength of the association between PFS and OS.

4.2 Definition of endpoints

For the real-world dataset, we will define OS as the time from treatment initiation to death from any cause and PFS as the time from treatment initiation to progression or death from any cause, whichever occurs first. Patients who do not experience a PFS or OS event will be censored at the date of last follow-up.

For the patients included in RCTs, OS will be defined as the time from randomization to death from any cause and PFS as the time from randomization to progression or death from any cause, whichever occurs first. Patients who do not experience a PFS or OS event will be censored at the date of last follow-up. Response will be assessed following the guidelines used in the trial.

4.3 Statistical analysis

The correlation and 95% confidence intervals (CIs) between OS and PFS will be measured by using the normal score rank correlation, calculated using the iterative multiple imputation approach[59]. Although this approach is semiparametric and does not require any assumptions about the marginal distributions, it uses a Gaussian dependency structure, which may lead to bias from misspecification. Therefore, we will also calculate the rank correlation between OS and PFS using a nonparametric estimator of Spearman's correlation, based on a nonparametric bivariate survival surface estimator[60]. The 95% CIs will be calculated by bootstrap resampling. The nonparametric method does not make assumptions about the underlying correlation structure and is less prone to bias, although the semiparametric method appears more stable than nonparametric estimators.

Finally, we will also use a copula function to model the dependence between OS and PFS by testing different marginal distributions (Weibull, Gompertz and Loglogistic) and copula models to estimate the joint distribution (Frank, Gumbel, Clayton, Joe, AMH)[50]. The best-fitting model according to the AIC will be selected as the optimal model to measure Kendall's τ[50].

To evaluate the association between response and OS, we will perform a responder analysis[52,61,62]. Responders will be defined as patients who achieved a partial or complete response and non-responders as those with stable disease, progressive disease or whose response status is unknown or non-evaluable. OS will be estimated by using Simon-Makuch method and compared using the Mantel-Byar test. HRs and 95% CI will be estimated by using a

Cox regression model with objective response as a time-dependent covariate[61,63]. Multivariate analysis will also be performed by adjusting for important prognostic baseline variables.

5. TRIAL-LEVEL ANALYSIS

5.1 Search Strategy and Trial selection

We will perform a systematic literature review of randomized clinical trials testing chemotherapy alone or combined with other systemic agents in advanced biliary tract cancers. Selected trials will report at least two endpoints of interest (OS, PFS, ORR). Key eligibility criteria following the PICOS recommendations can be found in Table 1.

Table 1: Eligibility criteria following the PICOS framework

PICOS	ELIGIBILITY CRITERIA
POPULATION	Adult patients treated with systemic chemotherapy for locally advanced or metastatic biliary tract cancer (including intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma and gallbladder carcinoma). RCTs including other tumour types will be excluded.
INTERVENTION/COMPARATOR	Systemic therapies, including chemotherapy, targeted therapies or immunotherapies. Both monotherapy and combinations will be included. Combinations with local or locoregional therapies will be excluded.
OUTCOMES	OS, PFS, ORR and/or DCR. Trials not reporting OS or not reporting either PFS or ORR will be excluded.
STUDY DESIGN	Randomized phase II or phase III trials will be included. Sample size will not be considered an eligibility criterion.
LANGUAGE	No language limit will be applied.

We will search Medline through Pubmed, Embase and the Cochrane Central Register of Controlled Trials (CENTRAL) databases. Additionally, we will search references of the selected studies, clinicaltrials.gov and abstract proceedings from the American Society of Clinical Oncology (ASCO), European Society of Medical Oncology (ESMO), ASCO Gastrointestinal Cancers Symposium (ASCO-GI), ESMO World Congress on Gastrointestinal Cancer and ESMO Asia.

All abstracts will be reviewed by two investigators. Any disagreements will be resolved by consensus or through a third, senior reviewer.

We will report the results following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA)[64] and the Reporting of Surrogate Endpoint Evaluation using Meta-analyses (ReSEEM) guidelines[50].

5.2 Bias Assessment

We will generate funnel plots to assess publication bias (taking the 95% confidence intervals to account for the amount of heterogeneity estimated by the model) and use Egger's regression test to assess funnel plot asymmetry.

We will use two methods to determine study methodological quality: The Cochrane Collaboration's risk of bias tool[65] and the Delphi list[66].

5.3 Data Extraction

A single reviewer will extract data from each clinical trial using a customized Excel® sheet. The data collected will be validated by a second reviewer. We will extract the following information for each trial:

- Definition of PFS and OS
- Response evaluation guidelines, proportion of responders
- Median PFS and OS, number of events, HR for PFS and OS
- Median follow-up, years of recruitment
- Number of centres involved (single-centre or multicentre)
- Study phase, blinding, primary endpoint, key secondary endpoints
- Patient characteristics, location in the biliary tract (intrahepatic, extrahepatic, gallbladder)
- Treatment arms, prior chemotherapy for advanced disease, number of patients per arm

5.4 Sensitivity analysis and Subgroup analysis

We will perform the following preplanned sensitivity analyses:

1. Remove trials with a cross-over design, as this may confuse the association between PFS and OS.
2. Remove trials with a sample size of less than 100 patients, as the precision of the effect estimate may be lower in small trials.
3. Remove trials testing targeted therapies, tyrosine-kinase inhibitors or immunotherapy agents, as the effects may vary depending on the type of treatments.
4. Remove trials including patients that have previously received chemotherapy in the advanced setting, as the association between PFS and OS may differ in patients who have previously received chemotherapy.
5. Remove low-quality trials or trials that are at high risk of bias.

5.5 Statistical analysis

All extracted endpoints will be collected as defined by the trial. For trials that do not report hazard ratios, we will estimate these with the methods described by Tierney *et al*[67]. The hazard ratios will be log-transformed and the association will be estimated using a linear regression model weighed by trial size. The variation of the weighted treatment effects explained by the model will be measured with the coefficient of determination R^2.

The surrogate threshold effect (STE) represents the minimum treatment effect of the intermediate endpoint needed to predict a non-zero effect on OS. The STE will be calculated by using the 95% prediction interval at different weights (trial sizes). For each weight, the STE will be defined as the intersection of the upper 95% CI with the horizontal y-axis=0, representing a hazard ratio of 1[68,69].

The surrogate threshold effect proportion (STEP) represents the proportion of the total range of the surrogate that is equal or larger than the STE[70].

We will perform a leave-one-out cross validation to validate the results of the main analysis. Each trial will be left out once and the model will be fitted with the remaining trials. The resulting model will be applied to the left-out trial to predict the effect of treatment on the reference endpoints. The R^2 of the cross-validated model will be calculated as the correlation between the individual predictions made by the model and the actual treatment effects[71].

6. CRITERIA FOR SURROGACY EVALUATION

No consensus has been reached regarding the ideal criteria for surrogacy evaluation[47,50,72]. There is no accepted threshold for quantifying the patient-level correlation and most of the available guidelines only refer to trial-level analyses. Therefore, we will apply two different frameworks to evaluate the potential surrogacy: the German Independent Institute for Quality and Efficiency in Health Care (IQWiG) and the biomarker-surrogacy (BioSurrogate) evaluation schema (BSES3) and ReSEEM (**Table 2**).

Table 2: Statistical evaluation for defining a surrogate endpoint

FRAMEWORK	RECOMMENDATION	
IQWIG[73]	Valid surrogate	Strong correlation: Lower 95% CI of R is ≥ 0.85 (R^2 ≥ 0.72)
	Unclear	Moderate correlation: 0.85 > R > 0.7 (0.72 > R^2 > 0.49) and upper 95% confidence interval of R is ≥ 0.7 (R^2 ≥ 0.49) and lower confidence interval of R is < 0.85 (lower 95% CI limit R^2 < 0.72). The surrogate threshold effect (STE) may be applied.
	Invalid surrogate	Upper 95% CI of R is ≤ 0.7 (R^2 ≤ 0.49)
BSES[70,74]	0 (poor)	Does not meet the criteria for rank 1
	1 (fair)	RCT R^2_{trial} ≥ 0.2 AND STEP ≥ 0.1 AND R^2_{ind} ≥ 0.2 OR cohort data R^2_{ind} ≥ 0.4
	2 (good)	RCT R^2_{trial} ≥ 0.4 AND STEP ≥ 0.2 AND R^2_{ind} ≥ 0.4
	3 (excellent)	RCT R^2_{trial} ≥ 0.6 AND STEP ≥ 0.3 AND R^2_{ind} ≥ 0.6

7. REFERENCES

1. Valle, J. W., Kelley, R. K., Nervi, B., Oh, D.-Y. & Zhu, A. X. Biliary tract cancer. *The Lancet* **397**, 428–444 (2021).
2. Banales, J. M. *et al.* Cholangiocarcinoma 2020: the next horizon in mechanisms and management. *Nat Rev Gastroenterol Hepatol* **17**, 557–588 (2020).
3. Javle, M. *et al.* Temporal Changes in Cholangiocarcinoma Incidence and Mortality in the United States from 2001 to 2017. *Oncologist* **27**, 874–883 (2022).
4. Siegel, R. L., Miller, K. D., Wagle, N. S. & Jemal, A. Cancer statistics, 2023. *CA Cancer J Clin* **73**, 17–48 (2023).
5. Merters, J. & Lamarca, A. Integrating cytotoxic, targeted and immune therapies for cholangiocarcinoma. *J Hepatol* **78**, 652–657 (2023).
6. Ilyas, S. I. *et al.* Cholangiocarcinoma — novel biological insights and therapeutic strategies. *Nat Rev Clin Oncol* **20**, 470–486 (2023).
7. Valle, J. *et al.* Cisplatin plus Gemcitabine versus Gemcitabine for Biliary Tract Cancer. *New England Journal of Medicine* **362**, 1273–1281 (2010).
8. Okusaka, T. *et al.* Gemcitabine alone or in combination with cisplatin in patients with biliary tract cancer: a comparative multicentre study in Japan. *Br J Cancer* **103**, 469–474 (2010).

9. Oh, D.-Y. *et al.* Durvalumab plus Gemcitabine and Cisplatin in Advanced Biliary Tract Cancer. *NEJM Evidence* (2022) doi:10.1056/EVIDoa2200015.
10. Kelley, R. K. *et al.* Pembrolizumab in combination with gemcitabine and cisplatin compared with gemcitabine and cisplatin alone for patients with advanced biliary tract cancer (KEYNOTE-966): a randomised, double-blind, placebo-controlled, phase 3 trial. *The Lancet* **401**, 1853–1865 (2023).
11. Lamarca, A. *et al.* Second-line FOLFOX chemotherapy versus active symptom control for advanced biliary tract cancer (ABC-06): a phase 3, open-label, randomised, controlled trial. *Lancet Oncol* **22**, 690–701 (2021).
12. Yoo, C. *et al.* Liposomal irinotecan plus fluorouracil and leucovorin versus fluorouracil and leucovorin for metastatic biliary tract cancer after progression on gemcitabine plus cisplatin (NIFTY): a multicentre, open-label, randomised, phase 2b study. *Lancet Oncol* **22**, 1560–1572 (2021).
13. Hyung, J. *et al.* Treatment With Liposomal Irinotecan Plus Fluorouracil and Leucovorin for Patients With Previously Treated Metastatic Biliary Tract Cancer. *JAMA Oncol* **9**, 692 (2023).
14. Abou-Alfa, G. K. *et al.* Ivosidenib in IDH1-mutant, chemotherapy-refractory cholangiocarcinoma (ClarIDHy): a multicentre, randomised, double-blind, placebo-controlled, phase 3 study. *Lancet Oncol* **21**, 796–807 (2020).
15. Zhu, A. X. *et al.* Final Overall Survival Efficacy Results of Ivosidenib for Patients With Advanced Cholangiocarcinoma With *IDH1* Mutation. *JAMA Oncol* **7**, 1669 (2021).
16. Abou-Alfa, G. K. *et al.* Pemigatinib for previously treated, locally advanced or metastatic cholangiocarcinoma: a multicentre, open-label, phase 2 study. *Lancet Oncol* **21**, 671–684 (2020).
17. Javle, M. *et al.* Infigratinib (BGJ398) in previously treated patients with advanced or metastatic cholangiocarcinoma with FGFR2 fusions or rearrangements: mature results from a multicentre, open-label, single-arm, phase 2 study. *Lancet Gastroenterol Hepatol* **6**, 803–815 (2021).
18. Goyal, L. *et al.* Futibatinib for *FGFR2* -Rearranged Intrahepatic Cholangiocarcinoma. *New England Journal of Medicine* **388**, 228–239 (2023).
19. Droz Dit Busset, M. *et al.* 47P Derazantinib for patients with intrahepatic cholangiocarcinoma harboring FGFR2 fusions/rearrangements: Primary results from the phase II study FIDES-01. *Annals of Oncology* **32**, S376 (2021).
20. Meric-Bernstam, F. *et al.* Efficacy and safety of trastuzumab deruxtecan (T-DXd) in patients (pts) with HER2-expressing solid tumors: DESTINY-PanTumor02 (DP-02) interim results. *Journal of Clinical Oncology* **41**, LBA3000–LBA3000 (2023).
21. Wang, X. *et al.* Zanidatamab (zani), a HER2-targeted bispecific antibody, in combination with docetaxel as first-line therapy (1L) for patients (pts) with advanced HER2-positive breast cancer (BC): Updated results from a phase 1b/2 study. *Journal of Clinical Oncology* **41**, 1044–1044 (2023).
22. Nakamura, Y. *et al.* Tucatinib and trastuzumab for previously treated HER2-positive metastatic biliary tract cancer (SGNTUC-019): A phase 2 basket study. *Journal of Clinical Oncology* **41**, 4007–4007 (2023).
23. Lee, C. *et al.* Trastuzumab plus FOLFOX for HER2-positive biliary tract cancer refractory to gemcitabine and cisplatin: a multi-institutional phase 2 trial of the Korean Cancer Study Group (KCSG-HB19–14). *Lancet Gastroenterol Hepatol* **8**, 56–65 (2023).
24. Ohba, A. *et al.* Trastuzumab deruxtecan (T-DXd; DS-8201) in patients (pts) with HER2-expressing unresectable or recurrent biliary tract cancer (BTC): An investigator-initiated multicenter phase 2 study (HERB trial). *Journal of Clinical Oncology* **40**, 4006–4006 (2022).
25. Javle, M. *et al.* Pertuzumab and trastuzumab for HER2-positive, metastatic biliary tract cancer (MyPathway): a multicentre, open-label, phase 2a, multiple basket study. *Lancet Oncol* **22**, 1290–1300 (2021).
26. Marabelle, A. *et al.* Efficacy of Pembrolizumab in Patients With Noncolorectal High Microsatellite Instability/Mismatch Repair–Deficient Cancer: Results From the Phase II KEYNOTE-158 Study. *Journal of Clinical Oncology* **38**, 1–10 (2019).
27. Subbiah, V. *et al.* Pan-Cancer Efficacy of Vemurafenib in *BRAF* V600-Mutant Non-Melanoma Cancers. *Cancer Discov* **10**, 657–663 (2020).

28. Wen, P. Y. *et al.* Dabrafenib plus trametinib in patients with BRAFV600E-mutant low-grade and high-grade glioma (ROAR): a multicentre, open-label, single-arm, phase 2, basket trial. *Lancet Oncol* **23**, 53–64 (2022).
29. Merino, M. *et al.* Irreconcilable Differences: The Divorce Between Response Rates, Progression-Free Survival, and Overall Survival. *Journal of Clinical Oncology* **41**, 2706–2712 (2023).
30. Saad, E. D. & Buyse, M. Statistical controversies in clinical research: end points other than overall survival are vital for regulatory approval of anticancer agents. *Annals of Oncology* **27**, 373–378 (2016).
31. Haslam, A. & Prasad, V. When is crossover desirable in cancer drug trials and when is it problematic? *Annals of Oncology* **29**, 1079–1081 (2018).
32. Prasad, V. Double-Crossed: Why Crossover in Clinical Trials May Be Distorting Medical Science. *Journal of the National Comprehensive Cancer Network* **11**, 625–627 (2013).
33. Gyawali, B. Problematic crossovers in cancer drug trials. *Nat Rev Clin Oncol* (2023) doi:10.1038/s41571-023-00805-7.
34. Fleming, T. R., Rothmann, M. D. & Lu, H. L. Issues in Using Progression-Free Survival When Evaluating Oncology Products. *Journal of Clinical Oncology* **27**, 2874–2880 (2009).
35. Saad, E. D. & Buyse, M. Overall Survival: Patient Outcome, Therapeutic Objective, Clinical Trial End Point, or Public Health Measure? *Journal of Clinical Oncology* **30**, 1750–1754 (2012).
36. Broglio, K. R. & Berry, D. A. Detecting an Overall Survival Benefit that Is Derived From Progression-Free Survival. *JNCI: Journal of the National Cancer Institute* **101**, 1642–1649 (2009).
37. Korn, E. L., Freidlin, B. & Abrams, J. S. Overall Survival As the Outcome for Randomized Clinical Trials With Effective Subsequent Therapies. *Journal of Clinical Oncology* **29**, 2439–2442 (2011).
38. Saad, E. D., Katz, A., Hoff, P. M. & Buyse, M. Progression-free survival as surrogate and as true end point: insights from the breast and colorectal cancer literature. *Annals of Oncology* **21**, 7–12 (2010).
39. Tannock, I. F., Pond, G. R. & Booth, C. M. Biased Evaluation in Cancer Drug Trials—How Use of Progression-Free Survival as the Primary End Point Can Mislead. *JAMA Oncol* **8**, 679 (2022).
40. Booth, C. M., Eisenhauer, E. A., Gyawali, B. & Tannock, I. F. Progression-Free Survival Should Not Be Used as a Primary End Point for Registration of Anticancer Drugs. *Journal of Clinical Oncology* (2023) doi:10.1200/JCO.23.01423.
41. Fojo, T. & Simon, R. M. Inappropriate censoring in Kaplan-Meier analyses. *Lancet Oncol* **22**, 1358–1360 (2021).
42. Gilboa, S. *et al.* Informative censoring of surrogate end-point data in phase 3 oncology trials. *Eur J Cancer* **153**, 190–202 (2021).
43. Booth, C. M. & Eisenhauer, E. A. Progression-Free Survival: Meaningful or Simply Measurable? *Journal of Clinical Oncology* **30**, 1030–1033 (2012).
44. Pasalic, D. *et al.* Progression-free survival is a suboptimal predictor for overall survival among metastatic solid tumour clinical trials. *Eur J Cancer* **136**, 176–185 (2020).
45. Samuel, J. N. *et al.* Association of Quality-of-Life Outcomes in Cancer Drug Trials With Survival Outcomes and Drug Class. *JAMA Oncol* **8**, 879 (2022).
46. Garnick, M. B. Preserving the Sanctity of Overall Survival for Drugs Approved on the Basis of Progression-Free Survival: Tivozanib As a Case Study. *Journal of Clinical Oncology* **31**, 3746–3748 (2013).
47. Ciani, O. *et al.* Validation of Surrogate Endpoints in Advanced Solid Tumors: Systematic Review of Statistical Methods, Results, and Implications for Policy Makers. *Int J Technol Assess Health Care* **30**, 312–324 (2014).
48. Weir, C. J. & Taylor, R. S. Informed decision-making: Statistical methodology for surrogacy evaluation and its role in licensing and reimbursement assessments. *Pharm Stat* **21**, 740–756 (2022).
49. Inker, L. A. *et al.* A meta-analysis of GFR slope as a surrogate endpoint for kidney failure. *Nat Med* **29**, 1867–1876 (2023).
50. Xie, W. *et al.* A Systematic Review and Recommendation for Reporting of Surrogate Endpoint Evaluation Using Meta-analyses. *JNCI Cancer Spectr* **3**, (2019).

51. Buyse, M., Saad, E. D., Burzykowski, T., Regan, M. M. & Sweeney, C. S. Surrogacy Beyond Prognosis: The Importance of "Trial-Level" Surrogacy. *Oncologist* **27**, 266–271 (2022).
52. Norsworthy, K. J. *et al.* Response Rate, Event-Free Survival, and Overall Survival in Newly Diagnosed Acute Myeloid Leukemia: US Food and Drug Administration Trial-Level and Patient-Level Analyses. *Journal of Clinical Oncology* **40**, 847–854 (2022).
53. Buyse, M. *et al.* Progression-Free Survival Is a Surrogate for Survival in Advanced Colorectal Cancer. *Journal of Clinical Oncology* **25**, 5218–5224 (2007).
54. Xie, W. *et al.* Metastasis-Free Survival Is a Strong Surrogate of Overall Survival in Localized Prostate Cancer. *Journal of Clinical Oncology* **35**, 3097–3104 (2017).
55. Roy, S. *et al.* Biochemical Recurrence Surrogacy for Clinical Outcomes After Radiotherapy for Adenocarcinoma of the Prostate. *Journal of Clinical Oncology* (2023) doi:10.1200/JCO.23.00617.
56. Burzykowski, T., Molenberghs, G. & Buyse, M. The Validation of Surrogate End Points by using Data from Randomized Clinical Trials: A Case-Study in Advanced Colorectal Cancer. *J R Stat Soc Ser A Stat Soc* **167**, 103–124 (2004).
57. Buyse, M., Burzykowski, T., Michiels, S. & Carroll, K. Individual- and trial-level surrogacy in colorectal cancer. *Stat Methods Med Res* **17**, 467–475 (2008).
58. Gharzai, L. A. *et al.* Meta-Analysis of Candidate Surrogate End Points in Advanced Prostate Cancer. *NEJM Evidence* **2**, (2023).
59. Schemper, M., Kaider, A., Wakounig, S. & Heinze, G. Estimating the correlation of bivariate failure times under censoring. *Stat Med* **32**, 4781–4790 (2013).
60. Eden, S. K., Li, C. & Shepherd, B. E. Nonparametric estimation of Spearman's rank correlation with bivariate survival data. *Biometrics* **78**, 421–434 (2022).
61. Kudo, M. *et al.* Overall survival and objective response in advanced unresectable hepatocellular carcinoma: A subanalysis of the REFLECT study. *J Hepatol* **78**, 133–141 (2023).
62. Blumenthal, G. M. *et al.* Overall Response Rate, Progression-Free Survival, and Overall Survival With Targeted and Standard Therapies in Advanced Non–Small-Cell Lung Cancer: US Food and Drug Administration Trial-Level and Patient-Level Analyses. *Journal of Clinical Oncology* **33**, 1008–1014 (2015).
63. Simon, R. & Makuch, R. W. A non-parametric graphical representation of the relationship between survival and the occurrence of an event: Application to responder versus non-responder bias. *Stat Med* **3**, 35–44 (1984).
64. Page, M. J. *et al.* The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* n71 (2021) doi:10.1136/bmj.n71.
65. Higgins JPT *et al.* Cochrane Handbook for Systematic Reviews of Interventions version 6.4 (updated August 2023). *Cochrane* (2023).
66. Verhagen, A. P. *et al.* The Delphi List: a criteria list for quality assessment of randomized clinical trials for conducting systematic reviews developed by Delphi consensus. *J Clin Epidemiol* **51**, 1235–1241 (1998).
67. Tierney, J. F., Stewart, L. A., Ghersi, D., Burdett, S. & Sydes, M. R. Practical methods for incorporating summary time-to-event data into meta-analysis. *Trials* **8**, 16 (2007).
68. Johnson, K. R. *et al.* Response rate or time to progression as predictors of survival in trials of metastatic colorectal cancer or non-small-cell lung cancer: a meta-analysis. *Lancet Oncol* **7**, 741–746 (2006).
69. Burzykowski, T. & Buyse, M. Surrogate threshold effect: an alternative measure for meta-analytic surrogate endpoint validation. *Pharm Stat* **5**, 173–186 (2006).
70. Lassere, M. N., Johnson, K. R., Schiff, M. & Rees, D. Is blood pressure reduction a valid surrogate endpoint for stroke prevention? an analysis incorporating a systematic review of randomised controlled trials, a by-trial weighted errors-in-variables regression, the surrogate threshold effect (STE) and the biomarker-surrogacy (BioSurrogate) evaluation schema (BSES). *BMC Med Res Methodol* **12**, 27 (2012).
71. Conforti, F. *et al.* Evaluation of pathological complete response as surrogate endpoint in neoadjuvant randomised clinical trials of early stage breast cancer: systematic review and meta-analysis. *BMJ* e066381 (2021) doi:10.1136/bmj-2021-066381.
72. Belin, L., Tan, A., De Rycke, Y. & Dechartres, A. Progression-free survival as a surrogate for overall survival in oncology trials: a methodological systematic review. *Br J Cancer* **122**, 1707–1714 (2020).

73. Institute for Quality and Efficiency in Health Care (IQWiG). Validity of surrogate endpoints in oncology: Executive summary of rapid report A10-05, Version 1.1. *Institute for Quality and Efficiency in Health Care: Executive Summaries* (2011).
74. Lassere, M. N. The Biomarker-Surrogacy Evaluation Schema: a review of the biomarker-surrogate literature and a proposal for a criterion-based, quantitative, multidimensional hierarchical levels of evidence schema for evaluating the status of biomarkers as surrogate endpoints. *Stat Methods Med Res* **17**, 303–340 (2008).

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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:

This study does not refer to an animal trial or involve the use of drugs and chemicals. Additionally, it does not encompass genomic and proteomic data, DNA and protein sequencing, microarray data, or include a list of antibodies and primers.

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

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

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

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.

ICMJE DISCLOSURE FORM

Date: 4/10/2025

Your Name: Florian Castet

Manuscript Title: Association of candidate surrogate endpoints with overall survival in advanced biliary tract cancer: a trial- and patient-level analysis

Manuscript Number (if known): JHEPAT-D-24-03000

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related to the content of your manuscript. "Related" means any relation with for-profit or not-for-profit third parties whose interests may be affected by the content of the manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

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3	Royalties or licenses	☒ **None**	

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
4	Consulting fees	☒ **None**	
5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	☐ **None**	
		AstraZeneca, Eisai, Roche, Servier	
6	Payment for expert testimony	☒ **None**	
7	Support for attending meetings and/or travel	☐ **None**	
		Roche and Servier	
8	Patents planned, issued or pending	☒ **None**	
9	Participation on a Data Safety Monitoring Board or Advisory Board	☒ **None**	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	☒ **None**	

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
11	Stock or stock options	☒ **None**	
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	☒ **None**	
13	Other financial or non-financial interests	☒ **None**	

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☒ I certify that I have answered every question and have not altered the wording of any of the questions on this form.

ICMJE DISCLOSURE FORM

Date: 4/10/2025

Your Name: Carles Fabregat-Franco

Manuscript Title: Association of candidate surrogate endpoints with overall survival in advanced biliary tract cancer: a trial- and patient-level analysis

Manuscript Number (if known): JHEPAT-D-24-03000

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ICMJE DISCLOSURE FORM

Date: 4/10/2025

Your Name: John Bridgewater

Manuscript Title: Association of candidate surrogate endpoints with overall survival in advanced biliary tract cancer: a trial- and patient-level analysis

Manuscript Number (if known): JHEPAT-D-24-03000

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7	Support for attending meetings and/or travel	☒ **None**	
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ICMJE DISCLOSURE FORM

Date: 4/10/2025

Your Name: Jin Won Kim

Manuscript Title: Association of candidate surrogate endpoints with overall survival in advanced biliary tract cancer: a trial- and patient-level analysis

Manuscript Number (if known): JHEPAT-D-24-03000

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6	Payment for expert testimony	☒ **None**	
7	Support for attending meetings and/or travel	☒ **None**	
8	Patents planned, issued or pending	☒ **None**	
9	Participation on a Data Safety Monitoring Board or Advisory Board	☒ **None**	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	☒ **None**	

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11	Stock or stock options	☒ **None**	
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	☒ **None**	
13	Other financial or non-financial interests	☒ **None**	

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ICMJE DISCLOSURE FORM

Date: 4/10/2025

Your Name: Margherita Rimini

Manuscript Title: Association of candidate surrogate endpoints with overall survival in advanced biliary tract cancer: a trial- and patient-level analysis

Manuscript Number (if known): JHEPAT-D-24-03000

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ICMJE DISCLOSURE FORM

Date: 4/10/2025

Your Name: Adelaida La Casta

Manuscript Title: Association of candidate surrogate endpoints with overall survival in advanced biliary tract cancer: a trial- and patient-level analysis

Manuscript Number (if known): JHEPAT-D-24-03000

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7	Support for attending meetings and/or travel	☒ **None**	
8	Patents planned, issued or pending	☒ **None**	
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ICMJE DISCLOSURE FORM

Date: 4/10/2025

Your Name: Angela Lamarca

Manuscript Title: Association of candidate surrogate endpoints with overall survival in advanced biliary tract cancer: a trial- and patient-level analysis

Manuscript Number (if known): JHEPAT-D-24-03000

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2	Grants or contracts from any entity (if not indicated in item #1 above).	☐ **None**	
		QED, Merck, Boehringer Ingelheim, Servier, AstraZeneca, GenFit, Panbela Therapeutics, Novocure GmbH, Camurus AB, Albireo Pharma, Taiho, TransThera, Jazz Therapeutics and Roche	

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3	Royalties or licenses	☒ **None**	
4	Consulting fees	☐ **None**	
		EISAI, Nutricia, Ipsen, QED, Roche, Servier, Boston Scientific, Albireo Pharma, AstraZeneca, Boehringer Ingelheim, GENFIT, TransThera Biosciences, Taiho and MSD	
5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	☐ **None**	
		Merck, Pfizer, Ipsen, Incyte, AAA/Novartis, QED, Servier, Astra Zeneca, EISAI, Roche, Advanz Pharma and MSD	
6	Payment for expert testimony	☒ **None**	
7	Support for attending meetings and/or travel	☐ **None**	
		Ipsen, Pfizer, Bayer, AAA, SirtEx, Novartis, Mylan, Delcath Advanz Pharma and Roche	
8	Patents planned, issued or pending	☒ **None**	
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ICMJE DISCLOSURE FORM

Date: 4/10/2025

Your Name: Minsu Kang

Manuscript Title: Association of candidate surrogate endpoints with overall survival in advanced biliary tract cancer: a trial- and patient-level analysis

Manuscript Number (if known): JHEPAT-D-24-03000

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ICMJE DISCLOSURE FORM

Date: 4/10/2025

Your Name: Francesca Salani

Manuscript Title: Association of candidate surrogate endpoints with overall survival in advanced biliary tract cancer: a trial- and patient-level analysis

Manuscript Number (if known): JHEPAT-D-24-03000

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			Click the tab key to add additional rows.
Time frame: past 36 months			
2	Grants or contracts from any entity (if not indicated in item #1 above).	☒ **None**	
3	Royalties or licenses	☒ **None**	

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
4	Consulting fees	☒ **None**	
5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	☐ **None**	
		Daiichi Sankyo	
6	Payment for expert testimony	☒ **None**	
7	Support for attending meetings and/or travel	☐ **None**	
		Leo Pharma	
8	Patents planned, issued or pending	☒ **None**	
9	Participation on a Data Safety Monitoring Board or Advisory Board	☒ **None**	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	☒ **None**	

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
11	Stock or stock options	☒ **None**	
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	☒ **None**	
13	Other financial or non-financial interests	☒ **None**	

Please place an "X" next to the following statement to indicate your agreement:

☒ I certify that I have answered every question and have not altered the wording of any of the questions on this form.

ICMJE DISCLOSURE FORM

Date: 4/10/2025

Your Name: Alfredo Castillo

Manuscript Title: Association of candidate surrogate endpoints with overall survival in advanced biliary tract cancer: a trial- and patient-level analysis

Manuscript Number (if known): JHEPAT-D-24-03000

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related to the content of your manuscript. "Related" means any relation with for-profit or not-for-profit third parties whose interests may be affected by the content of the manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

The author's relationships/activities/interests should be defined broadly. For example, if your manuscript pertains to the epidemiology of hypertension, you should declare all relationships with manufacturers of antihypertensive medication, even if that medication is not mentioned in the manuscript.

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		Name all entities with whom you have this relationship or indicate none (add rows as needed)	**Specifications/Comments (e.g., if payments were made to you or to your institution)**
Time frame: Since the initial planning of the work			
1	All support for the present manuscript (e.g., funding, provision of study materials, medical writing, article processing charges, etc.) **No time limit for this item.**	☒ **None**	
			Click the tab key to add additional rows.
Time frame: past 36 months			
2	Grants or contracts from any entity (if not indicated in item #1 above).	☒ **None**	
3	Royalties or licenses	☒ **None**	

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
4	Consulting fees	☒ **None**	
5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	☒ **None**	
6	Payment for expert testimony	☒ **None**	
7	Support for attending meetings and/or travel	☒ **None**	
8	Patents planned, issued or pending	☒ **None**	
9	Participation on a Data Safety Monitoring Board or Advisory Board	☒ **None**	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	☒ **None**	

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
11	Stock or stock options	☒ **None**	
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	☒ **None**	
13	Other financial or non-financial interests	☒ **None**	

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☒ I certify that I have answered every question and have not altered the wording of any of the questions on this form.

ICMJE DISCLOSURE FORM

Date: 4/10/2025

Your Name: Andre Lopes

Manuscript Title: Association of candidate surrogate endpoints with overall survival in advanced biliary tract cancer: a trial- and patient-level analysis

Manuscript Number (if known): JHEPAT-D-24-03000

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related to the content of your manuscript. "Related" means any relation with for-profit or not-for-profit third parties whose interests may be affected by the content of the manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

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Time frame: past 36 months			
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3	Royalties or licenses	☒ **None**	

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4	Consulting fees	☒ **None**	
5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	☒ **None**	
6	Payment for expert testimony	☒ **None**	
7	Support for attending meetings and/or travel	☒ **None**	
8	Patents planned, issued or pending	☒ **None**	
9	Participation on a Data Safety Monitoring Board or Advisory Board	☒ **None**	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	☒ **None**	

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
11	Stock or stock options	☒ **None**	
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	☒ **None**	
13	Other financial or non-financial interests	☒ **None**	

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ICMJE DISCLOSURE FORM

Date: 4/10/2025

Your Name: Jaewon Hyung

Manuscript Title: Association of candidate surrogate endpoints with overall survival in advanced biliary tract cancer: a trial- and patient-level analysis

Manuscript Number (if known): JHEPAT-D-24-03000

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Time frame: past 36 months			
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3	Royalties or licenses	☒ **None**	

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4	Consulting fees	☒ **None**	
5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	☒ **None**	
6	Payment for expert testimony	☒ **None**	
7	Support for attending meetings and/or travel	☒ **None**	
8	Patents planned, issued or pending	☒ **None**	
9	Participation on a Data Safety Monitoring Board or Advisory Board	☒ **None**	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	☒ **None**	

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
11	Stock or stock options	☒ **None**	
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	☒ **None**	
13	Other financial or non-financial interests	☒ **None**	

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ICMJE DISCLOSURE FORM

Date: 4/10/2025

Your Name: Lorenza Rimassa

Manuscript Title: Association of candidate surrogate endpoints with overall survival in advanced biliary tract cancer: a trial- and patient-level analysis

Manuscript Number (if known): JHEPAT-D-24-03000

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related to the content of your manuscript. "Related" means any relation with for-profit or not-for-profit third parties whose interests may be affected by the content of the manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

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Time frame: Since the initial planning of the work			
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			Click the tab key to add additional rows.
Time frame: past 36 months			
2	Grants or contracts from any entity (if not indicated in item #1 above).	☐ **None**	
		Agios, AstraZeneca, BeiGene, Eisai, Exelixis, Fibrogen, Incyte, Ipsen, Lilly, MSD, Nerviano Medical Sciences, Roche, Servier, Taiho Oncology, TransThera Sciences, Zymeworks	
3	Royalties or licenses	☒ **None**	

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
4	Consulting fees	☐ **None**	
		AbbVie, AstraZeneca, Basilea, Bayer, BMS, Elevar Therapeutics, Exelixis, Genenta, Hengrui, Incyte, Ipsen, IQVIA, Jazz Pharmaceuticals, MSD, Nerviano Medical Sciences, Roche, Servier, Taiho Oncology, Zymeworks	
5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	☐ **None**	
		AstraZeneca, Bayer, BMS, Guerbet, Incyte, Ipsen, Roche, Servier	
6	Payment for expert testimony	☒ **None**	
7	Support for attending meetings and/or travel	☐ **None**	
		AstraZeneca	
8	Patents planned, issued or pending	☒ **None**	
9	Participation on a Data Safety Monitoring Board or Advisory Board	☒ **None**	
10	Leadership or fiduciary role in other board, society, committee or	☒ **None**	

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
	advocacy group, paid or unpaid		
11	Stock or stock options	☒ **None**	
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	☒ **None**	
13	Other financial or non-financial interests	☒ **None**	

Please place an "X" next to the following statement to indicate your agreement:

☒ I certify that I have answered every question and have not altered the wording of any of the questions on this form.

ICMJE DISCLOSURE FORM

Date: 4/10/2025

Your Name: Jorge Adeva

Manuscript Title: Association of candidate surrogate endpoints with overall survival in advanced biliary tract cancer: a trial- and patient-level analysis

Manuscript Number (if known): JHEPAT-D-24-03000

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related to the content of your manuscript. "Related" means any relation with for-profit or not-for-profit third parties whose interests may be affected by the content of the manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

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		Name all entities with whom you have this relationship or indicate none (add rows as needed)	**Specifications/Comments (e.g., if payments were made to you or to your institution)**
Time frame: Since the initial planning of the work			
1	All support for the present manuscript (e.g., funding, provision of study materials, medical writing, article processing charges, etc.) **No time limit for this item.**	☒ **None**	
			Click the tab key to add additional rows.
Time frame: past 36 months			
2	Grants or contracts from any entity (if not indicated in item #1 above).	☒ **None**	
3	Royalties or licenses	☒ **None**	

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
4	Consulting fees	☐ **None**	
		AstraZeneca, Jazz Pharmaceuticals, MSD, Roche, Servier, Taiho Oncology, Zymeworks	
5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	☐ **None**	
		AstraZeneca, Roche, Servier	
6	Payment for expert testimony	☒ **None**	
7	Support for attending meetings and/or travel	☐ **None**	
		AstraZeneca, Roche, Servier	
8	Patents planned, issued or pending	☒ **None**	
9	Participation on a Data Safety Monitoring Board or Advisory Board	☒ **None**	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	☒ **None**	

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
11	Stock or stock options	☒ **None**	
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	☒ **None**	
13	Other financial or non-financial interests	☒ **None**	

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ICMJE DISCLOSURE FORM

Date: 4/10/2025

Your Name: Daniel López-Valbuena

Manuscript Title: Association of candidate surrogate endpoints with overall survival in advanced biliary tract cancer: a trial- and patient-level analysis

Manuscript Number (if known): JHEPAT-D-24-03000

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related to the content of your manuscript. "Related" means any relation with for-profit or not-for-profit third parties whose interests may be affected by the content of the manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

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Time frame: past 36 months			
2	Grants or contracts from any entity (if not indicated in item #1 above).	☒ **None**	
3	Royalties or licenses	☒ **None**	

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4	Consulting fees	☒ **None**	
5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	☒ **None**	
6	Payment for expert testimony	☒ **None**	
7	Support for attending meetings and/or travel	☒ **None**	
8	Patents planned, issued or pending	☒ **None**	
9	Participation on a Data Safety Monitoring Board or Advisory Board	☒ **None**	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	☒ **None**	

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
11	Stock or stock options	☒ **None**	
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	☒ **None**	
13	Other financial or non-financial interests	☒ **None**	

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ICMJE DISCLOSURE FORM

Date: 4/10/2025

Your Name: Míriam Basagaña-Farres

Manuscript Title: Association of candidate surrogate endpoints with overall survival in advanced biliary tract cancer: a trial- and patient-level analysis

Manuscript Number (if known): JHEPAT-D-24-03000

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related to the content of your manuscript. "Related" means any relation with for-profit or not-for-profit third parties whose interests may be affected by the content of the manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

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Time frame: past 36 months			
2	Grants or contracts from any entity (if not indicated in item #1 above).	☒ **None**	
3	Royalties or licenses	☒ **None**	

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5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	☒ **None**	
6	Payment for expert testimony	☒ **None**	
7	Support for attending meetings and/or travel	☒ **None**	
8	Patents planned, issued or pending	☒ **None**	
9	Participation on a Data Safety Monitoring Board or Advisory Board	☒ **None**	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	☒ **None**	

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
11	Stock or stock options	☒ **None**	
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	☒ **None**	
13	Other financial or non-financial interests	☒ **None**	

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ICMJE DISCLOSURE FORM

Date: 4/10/2025

Your Name: Simran Vaja

Manuscript Title: Association of candidate surrogate endpoints with overall survival in advanced biliary tract cancer: a trial- and patient-level analysis

Manuscript Number (if known): JHEPAT-D-24-03000

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related to the content of your manuscript. "Related" means any relation with for-profit or not-for-profit third parties whose interests may be affected by the content of the manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

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Time frame: past 36 months			
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3	Royalties or licenses	☒ **None**	

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4	Consulting fees	☒ **None**	
5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	☒ **None**	
6	Payment for expert testimony	☒ **None**	
7	Support for attending meetings and/or travel	☒ **None**	
8	Patents planned, issued or pending	☒ **None**	
9	Participation on a Data Safety Monitoring Board or Advisory Board	☒ **None**	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	☒ **None**	

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11	Stock or stock options	☒ **None**	
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	☒ **None**	
13	Other financial or non-financial interests	☒ **None**	

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ICMJE DISCLOSURE FORM

Date: 4/10/2025

Your Name: Ka Man Mak

Manuscript Title: Association of candidate surrogate endpoints with overall survival in advanced biliary tract cancer: a trial- and patient-level analysis

Manuscript Number (if known): JHEPAT-D-24-03000

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3	Royalties or licenses	☒ **None**	

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5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	☒ **None**	
6	Payment for expert testimony	☒ **None**	
7	Support for attending meetings and/or travel	☒ **None**	
8	Patents planned, issued or pending	☒ **None**	
9	Participation on a Data Safety Monitoring Board or Advisory Board	☒ **None**	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	☒ **None**	

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
11	Stock or stock options	☒ **None**	
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	☒ **None**	
13	Other financial or non-financial interests	☒ **None**	

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ICMJE DISCLOSURE FORM

Date: 4/10/2025

Your Name: Tian V Tian

Manuscript Title: Association of candidate surrogate endpoints with overall survival in advanced biliary tract cancer: a trial- and patient-level analysis

Manuscript Number (if known): JHEPAT-D-24-03000

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			Click the tab key to add additional rows.
Time frame: past 36 months			
2	Grants or contracts from any entity (if not indicated in item #1 above).	☐ **None**	
		AstraZeneca, LOXO Oncology, Servier, Alentis, and Incyte	
3	Royalties or licenses	☒ **None**	

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ICMJE DISCLOSURE FORM

Date: 4/10/2025

Your Name: Andrés Muñoz

Manuscript Title: Association of candidate surrogate endpoints with overall survival in advanced biliary tract cancer: a trial- and patient-level analysis

Manuscript Number (if known): JHEPAT-D-24-03000

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8	Patents planned, issued or pending	☐ **None**	
		Risk assessment model in venous thromboembolism in cancer patients	
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		Rovi, Menarini, Stada, Medscape	

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Date: 4/10/2025

Your Name: Andrea Casadei-Gardini

Manuscript Title: Association of candidate surrogate endpoints with overall survival in advanced biliary tract cancer: a trial- and patient-level analysis

Manuscript Number (if known): JHEPAT-D-24-03000

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		AstraZeneca, Eisai	
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		AstraZeneca	
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ICMJE DISCLOSURE FORM

Date: 4/10/2025

Your Name: Changhoon Yoo

Manuscript Title: Association of candidate surrogate endpoints with overall survival in advanced biliary tract cancer: a trial- and patient-level analysis

Manuscript Number (if known): JHEPAT-D-24-03000

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ICMJE DISCLOSURE FORM

Date: 4/10/2025

Your Name: Juan W Valle

Manuscript Title: Association of candidate surrogate endpoints with overall survival in advanced biliary tract cancer: a trial- and patient-level analysis

Manuscript Number (if known): JHEPAT-D-24-03000

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Date: 4/10/2025

Your Name: Teresa Macarulla

Manuscript Title: Association of candidate surrogate endpoints with overall survival in advanced biliary tract cancer: a trial- and patient-level analysis

Manuscript Number (if known): JHEPAT-D-24-03000

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		MSD, Novocure, QED Therapeutics, Roche Farma, Sanofi-Aventis, Servier, Zymeworks	
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		Ability Pharmaceuticals SL, Arcus Bioscience Inc., AstraZeneca, Basilea Pharma, Baxter, BioLineRX Ltd, Celgene, Eisai, Incyte, Ipsen Bioscience Inc	
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		Janssen, Lilly, Esteve, Daïchi, Biontech, Novartis, Jazz Pharmaceuticals	
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Research Article
Hepatic and Biliary Cancer

JOURNAL
OF HEPATOLOGY

Association of candidate surrogate endpoints with overall survival in advanced biliary tract cancer

Authors

Florian Castet, Carles Fabregat-Franco, John Bridgewater, …, Changhoon Yoo, Juan W. Valle, Teresa Macarulla

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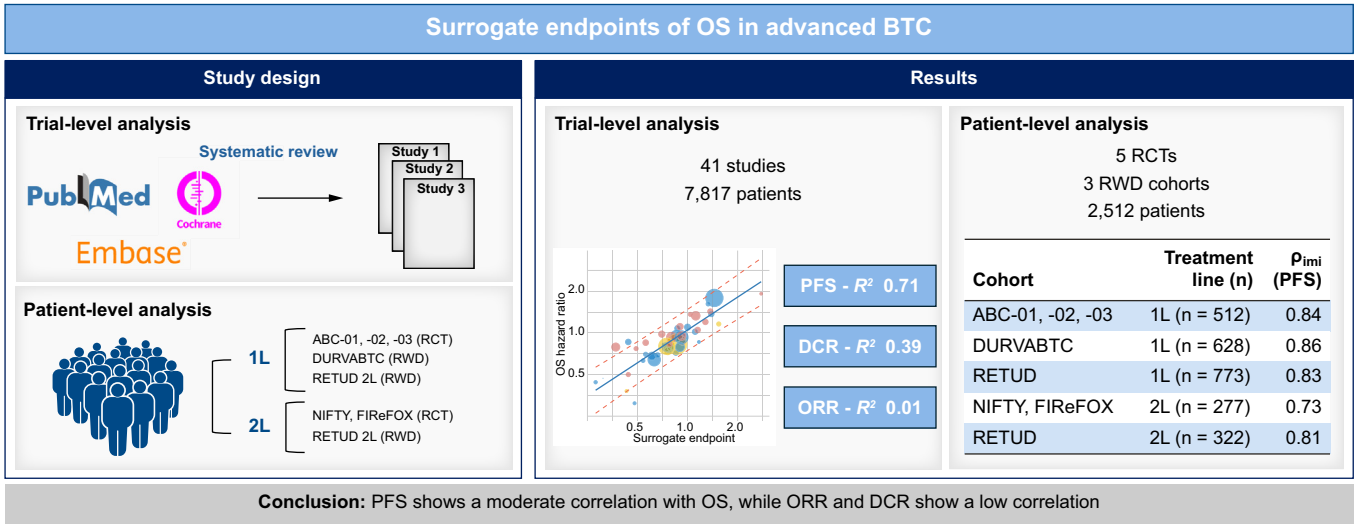
Graphical abstract



Highlights

- PFS showed a moderate correlation with OS at the trial- and patient-level.
- A PFS hazard ratio of 0.61 in a hypothetical trial of 200 patients would likely lead to an OS benefit.
- Disease control rate and response rate showed a low correlation at the trial-level.
- Patients who responded to first- or second-line chemotherapy did not show significantly improved OS.

Impact and implications

The use of validated surrogate endpoints in biliary tract cancer trials may decrease costs and improve study feasibility, particularly with agents that only target small subsets of patients or in trials that incorporate a crossover design. A formal statistical validation of surrogacy requires patient-level and trial-level data. This is the first comprehensive analysis to incorporate novel agents (including immunotherapies and targeted agents), include patient-level data and rigorously and homogeneously extract appropriate measures of treatment effect for endpoint correlation. These results show a moderate correlation for progression-free survival both at the trial- and patient-level and a low correlation for disease control rate and response rate. This information will aid clinicians in appropriately interpreting contemporary clinical trials and guide clinical researchers and trial sponsors involved in clinical trial design. Furthermore, it has important implications for the regulatory approval process and may aid agencies in appropriately evaluating novel drugs.

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Research Article
Hepatic and Biliary Cancer

JOURNAL
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Association of candidate surrogate endpoints with overall survival in advanced biliary tract cancer

Florian Castet[1], Carles Fabregat-Franco[2], John Bridgewater[3], Jin Won Kim[4], Margherita Rimini[5], Adelaida La Casta[6], Angela Lamarca[7,8], Minsu Kang[4], Francesca Salani[9], Alfredo Castillo[10], Andre Lopes[11], Jaewon Hyung[12], Lorenza Rimassa[13,14], Jorge Adeva[15], Daniel López-Valbuena[1], Míriam Basagaña-Farres[16], Simran Vaja[11], Ka Man Mak[11], Tian V. Tian[1], Andrés Muñoz[17], on behalf of the Spanish Cooperative Group for the Treatment of Digestive Tumors (TTD), Andrea Casadei-Gardini[5], on behalf of the DURVABTC Group, Changhoon Yoo[12], Juan W. Valle[18,19], Teresa Macarulla[1,*]

Journal of Hepatology **2025**. vol. ■ | 1–14

Background & Aims: Surrogate endpoints are increasingly used in biliary tract cancer (BTC) trials. While this may expedite drug approval and decrease costs, surrogate endpoints may not always correlate with an overall survival (OS) advantage. We aimed to explore the association of progression-free survival (PFS), objective response rate (ORR) and disease control rate (DCR) with OS at the trial- and patient-level.

Methods: For the trial-level analysis, we performed a systematic review of Pubmed/MEDLINE, Embase, Cochrane, clinicaltrials.gov and conference proceedings for phase II-III trials in advanced BTC. We used a weighted linear regression to measure the correlation of OS with PFS, ORR and DCR. For the patient-level analysis, we analyzed patients included in five randomized trials and three real-world datasets. The protocol is registered with PROSPERO, CRD42023398279.

Results: For the trial-level analysis, we included 41 studies, involving 88 treatment arms and 7,817 patients. The coefficient of determination (R^2) of the model was 0.71 (95% CI 0.56-0.86) for PFS, 0.01 (0-0.08) for ORR and 0.39 (0.14-0.64) for DCR. Predefined subgroup analysis showed consistent results. For the patient-level analysis, we included a total of 2,506 patients, 783 in randomized trials (first-line 512, second-line 271) and 1,723 in routine clinical care (first-line chemotherapy 773, first-line chemotherapy-durvalumab 628, second-line chemotherapy 322). Across the distinct datasets, the correlation coefficient ranged from 0.73 to 0.86 for PFS. A responder analysis found no association between response and survival.

Conclusion: PFS shows a moderate correlation with OS both at the trial- and patient-level, while ORR and DCR show a low correlation. Whilst PFS is currently the best candidate surrogate marker for OS, our results highlight the need for novel endpoints in this field.

Introduction

Biliary tract cancers (BTCs) are a heterogeneous group of aggressive neoplasms arising in the biliary tree.[1] Around 60% of tumors are diagnosed at advanced stages and more than 70% of tumors treated with local curative treatments will eventually relapse,[2] resulting in a dismal median survival of about 1 year despite optimal systemic treatment.[3,4]

In this setting, overall survival (OS) is the most robust, reliable and clinically meaningful endpoint for the design of randomized-controlled trials (RCTs).[5] The relatively low follow-up necessary to reach sufficient events, coupled with the scarcity of effective treatment options beyond first-line therapy, make OS an ideal endpoint and less prone to biases arising from post-progression treatment imbalances and biological differences in molecular subgroups.[6,7] However, some circumstances may hinder the interpretation of OS, such as crossover designs or conditional accelerated approval programs, where the experimental drug is made available to clinicians during the execution of the validation trial, leading to uncontrolled post-progression crossover.

Surrogate endpoints are intended to substitute for final patient-relevant outcomes that directly measure how patients feel, function or survive in clinical trials.[8] The use of surrogates is cost-effective and may overcome some of the challenges associated with OS. The use of these endpoints in oncology trials has increased dramatically in recent years, best reflected by the fact that 78% of drug approvals by the US FDA between 2005 and 2023 were based on surrogate endpoints.[9] However, only 32% of approved indications based on

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surrogate endpoints eventually demonstrated an improvement in OS,[10] highlighting the need for appropriate validation of these endpoints.

Previous studies have explored the association of progression-free survival (PFS) and objective response rate (ORR) with OS in BTC, although the results have been conflicting, the statistical methodology has been suboptimal, and only trial-level information has been included.[11–14] Despite the lack of robust data supporting the use of surrogate endpoints in BTC, 25% of randomized phase II-III trials used ORR as a primary endpoint and 44% used PFS.[15] In addition, the FDA has granted accelerated approval for pemigatinib and futibatinib based on ORR and duration of response for *FGFR2*-rearranged tumors and regular approval to ivosidenib based on PFS for *IDH1*-mutant tumors.[16]

To address these issues and explore the feasibility of using surrogate endpoints in advanced BTC, we performed a comprehensive analysis evaluating the association of PFS, ORR and disease control rate (DCR) at a trial-level through a meta-analysis of RCTs and at a patient-level through an analysis of five cohorts comprising both patients treated within the context of a RCT and in the real-world setting.

Patients and methods

Theoretical framework

One of the most used methodologies for evaluating potential surrogate endpoints is the two-stage meta-analytic framework, which requires individual patient-level data from all trials included in the systematic review to calculate the individual- and trial-level correlation.[17] In this framework, a validated endpoint will meet two conditions: demonstrate a correlation of treatment effects on both endpoints (Condition 1) and a strong correlation between the surrogate and definitive endpoint (Condition 2). One of the major limitations of this approach is that identified trials whose individual data cannot be retrieved are excluded from the trial-level analysis, which leads to a selection bias.[18,19] To address this potential limitation and because we did not have access to individual-level data from all identified trials in the systematic review, we applied an adaptation of this framework that intended to demonstrate both conditions.

For Condition 1 (trial-level), we performed a systematic review and correlation analyses of all trials based on aggregate-level data, as detailed below. For Condition 2 (patient-level), we analyzed two cohorts of patients included in RCTs evaluating first-line (ABC-01,[20] ABC-02[21] and ABC-03[22]) and second-line chemotherapy (NIFTY[23] and FIRe-FOX[24]). Given the complementary information provided by real-world data (RWD),[25] especially in the context of PFS, which is sensitive to the timing of assessments and response evaluation,[26] we also included a cohort of patients treated in the real-world setting with first-line chemotherapy, another cohort treated with cisplatin-gemcitabine and durvalumab and a final cohort of patients treated with second-line chemotherapy.

Protocol and registration

The protocol of the study was registered on the International Prospective Register of Systematic Reviews in February 2023 (PROSPERO registration ID CRD42023398279). Following a protocol amendment in October 2023, incorporating the patient-level data and an improvement in the search strategy, an updated systematic review and a new analysis were performed (see Protocol). We followed the PRISMA reporting guidelines.[27] The study was approved by the Vall d'Hebron Research Ethics Committee (PR(AG) 29/2024).

Search strategy

We searched Medline through Pubmed, Embase, Cochrane Library and ClinicalTrials.gov databases from inception to October 2023 (Table S1). Additionally, we searched references of the selected studies and abstract proceedings from the American Society of Clinical Oncology (ASCO), European Society of Medical Oncology (ESMO), ASCO Gastrointestinal Cancers Symposium (ASCO-GI), ESMO World Congress on Gastrointestinal Cancer and ESMO Asia.

The title and abstract of non-English studies were translated into English for the first screening step. The full text of those studies considered eligible for further evaluation was then translated. Of note, we identified no non-English study that required full-text evaluation.

All abstracts were reviewed and independently evaluated by two investigators through the Rayyan interface. Any disagreements were resolved by consensus with a third reviewer.

Eligibility criteria

Eligible studies were comparative phase II-III RCTs assessing systemic agents in the treatment of advanced BTC and included OS, PFS and/or ORR/DCR as an endpoint (Table S2). Studies that assessed locoregional or maintenance therapies, involved tumors other than BTC (except for periampullary carcinomas), were non-randomized, non-comparative or included patients in the (neo)adjuvant settings were excluded. The most recent and updated version of the trial was included in the final analysis.

Data extraction and quality assessment

We extracted the following data from the available reports: trial and baseline patient characteristics, number of patients included, endpoints, intervention details, median follow-up, response assessment criteria, OS hazard ratio (HR), PFS HR, ORR and DCR.

We generated funnel plots to assess publication bias (taking the 95% CIs to account for the heterogeneity estimated by the model) and used Egger's regression test to assess funnel plot asymmetry. Additionally, a *p* curve analysis was used to assess any further publication bias.

To assess the methodological quality of the included studies, we used two distinct tools: the Cochrane Handbook for Systematic Reviews of Interventions Risk of Bias tool (RoB version 2.0)[28] and the Delphi list.[29] Reports with a low or moderate risk of bias according to Cochrane's RoB or a score ≥5 points in the Delphi list were considered high quality.

A description of patients and datasets used for the individual-level correlation can be found in the supplementary materials and methods.

Statistical analyses

Condition 1 (Trial-level): All extracted endpoints were collected as defined by the trial. For trials that did not report HR, we estimated these with the methods described by Tierney *et al.* The odds ratio (OR) estimates for ORR and DCR were obtained from logistic regression models, including patients with measurable disease and considering non-evaluable patients as non-responders. The HR and OR were log-transformed and the associations estimated using a linear regression model weighed by trial size. The variation of the weighted treatment effects explained by the model was measured with the coefficient of determination (R^2).

The surrogate threshold effect (STE) represents the minimum treatment effect of the intermediate endpoint needed to predict a non-zero effect on OS and is calculated based on the prediction interval. The 95% prediction intervals were constructed for the regression line of the treatment effect on OS *vs*. the surrogate with a weight (*i.e*. trial size) of 200. The STE was defined as the intersection of the upper 95% prediction interval with the horizontal y-axis = 0, representing a hazard ratio of 1.[30,31]

We analyzed predefined subgroups according to the presence of crossover, trial size, type of treatment, disease setting/line of treatment and quality of the trials. We further performed two non-preplanned sensitivity analyses based on disease location and stage by assigning each trial a weight proportional to the number of included patients for each category. Additionally, we performed a leave-one-out cross-validation, whereby each trial was left out once, and the model was refitted with the remaining trials. The resulting model was then applied to the left-out trial to predict the effect of treatment on the reference endpoints. The R^2 of the cross-validated model was calculated as the correlation between the individual predictions made by the model and the actual treatment effects.[32]

Condition 2 (Patient-level): The correlation between OS and PFS was measured by using the normal score rank correlation, calculated by the iterative multiple imputation approach.[33] Although this approach is semiparametric and does not require any assumptions about the marginal distributions, it uses a Gaussian dependency structure. Therefore, we also calculated the rank correlation between OS and PFS using a non-parametric estimator of Spearman's correlation, based on a non-parametric bivariate survival surface estimator.[34] The 95% CIs were calculated by bootstrap resampling 1,000 times.

To evaluate the association between response and OS, we performed a responder analysis.[35–37] Responders were defined as patients who achieved a partial or complete response and non-responders as those with stable disease, progressive disease or whose response status was unknown or non-evaluable. To adjust for immortal-time bias, a landmark analysis was performed[38] at 3-month and 6-month landmark times for first-line trials and 2-month and 4-month times for second-line trials. Only the datasets of patients included in randomized trials were used for this analysis, as no longitudinal response assessment was available for the RWD cohorts.

We scored the strength following the criteria used by Prasad *et al.*:[39] low correlation ($r \leq 0.7$), moderate strength correlation ($r > 0.7$ to $r < 0.85$), and high correlation ($r \geq 0.85$).

All statistical analyses were completed using R version 4.1.2 (R Foundation).

Results

Condition 1: Trial-level association

Of the 8,576 records identified, a total of 41 randomized phase II and phase III clinical trials were eligible, including 44 treatment comparisons, 88 treatment arms and 7,817 patients (Fig. 1; Tables 1, 2 and S3). Most studies were phase II trials (70.7%), included first-line combinations (65.9%), tested chemotherapy (53.7%) or targeted/tyrosine kinase inhibitor (36.6%) agents, and were multicenter (80.5%), while only 2 (4.9%) allowed for crossover. The median follow-up was 10.85 months (IQR 10.1-15.7 months), although 17 (41.5%) trials did not report this information. Twenty trials (48.8%) used PFS as a primary endpoint and 16 (39%) used OS. Eleven (26.8%) were double blind and the remaining 30 trials were open-label.

We found no evidence of publication bias by applying the two distinct detection methods for OS, PFS and ORR (Fig. S1). A funnel plot asymmetry was detected for DCR, although the *p*-curve analysis showed that evidential value was present. The overall risk of bias was low or moderate, and only two studies were found to be at high risk of bias (Fig. S2 and S3). When applying the Delphi assessment criteria,[29] 35 studies were found to be of high quality, and six had a score below 5 points (Fig. S4).

The correlation between PFS and OS showed an R^2 of 0.71 (95% CI 0.56-0.86) and the STE was 0.61 (Fig. 2A), meaning that a HR of 0.61 in a hypothetical trial of 200 patients would likely lead to a non-zero effect on OS. Importantly, the correlations with ORR and DCR were low or non-existent, with R^2 values of 0.01 (95% CI 0-0.08) and 0.39 (95% CI 0.14-0.64), respectively (Fig. 2B,C). Prespecified subgroup analyses based on the line of treatment, presence of crossover, study phase, type of systemic treatment, sample size and trial quality confirmed these findings (Figs 2D, 3, S5 and S6). Non-preplanned sensitivity analyses showed consistent results for distinct disease locations and stages (Fig. S7–S9). The correlation of ORR and DCR with OS remained low across all subgroups. We further calculated the STE for all surrogate endpoints based on different hypothetical sample sizes (Table S4).

Finally, we performed a leave-one-out cross-validation procedure to confirm the correlation observed between OS and PFS. The R^2 ranged from 0.61 to 0.78. All trial HR estimates for OS fell within the predicted intervals except for three (Fig. S10). Two of these were highly influential trials in the cross-validation: the ClarIDHy trial,[40] whose exclusion from the model led to an R^2 of 0.78, and the NuTide:121,[41] whose exclusion led to an R^2 of 0.61. The R^2 remained consistent after individually excluding the remaining trials, with R^2 values that ranged from 0.7 to 0.73 (Fig. S10B).

Condition 2: Patient-level association

We analyzed five datasets involving 2,506 patients diagnosed with advanced BTC who received systemic treatments: a pooled population of 512 patients included in the ABC-01,[20] -02[21] and -03[22] trials, a RWD dataset of 628 patients treated with first-line cisplatin-gemcitabine and durvalumab, a RWD dataset of 773 patients treated with first-line chemotherapy, a pooled population of 271 patients included in the NIFTY[23] and

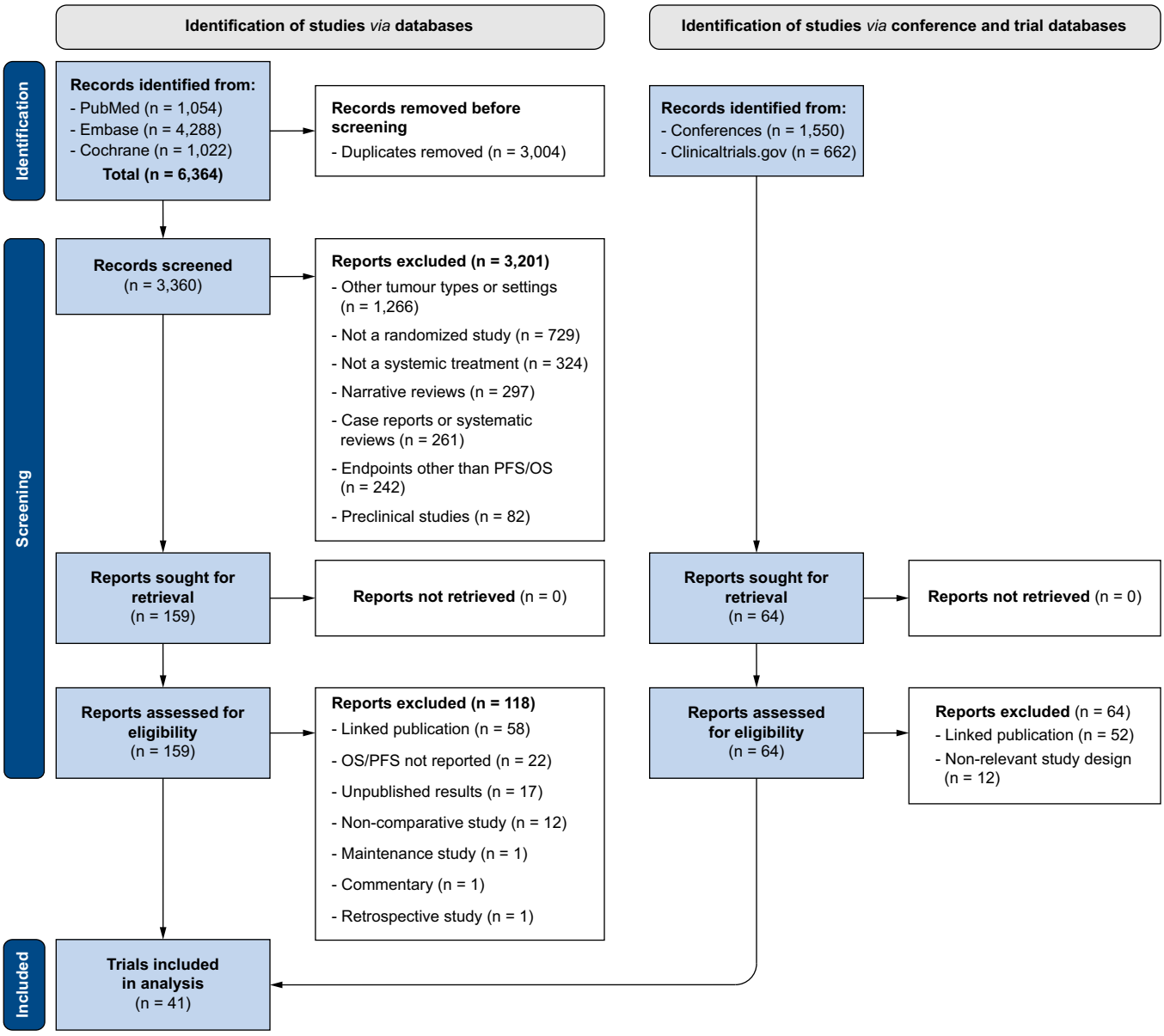

Fig. 1. PRISMA flowchart reporting the results of the systematic review.

FIReFOX[24] trials and a RWD dataset of 322 patients treated with standard second-line chemotherapy (Table S5–S8).

We estimated the correlation between PFS and OS at the patient-level using two distinct methods. We applied the multiple imputation approach[33] and found a rank correlation ranging between 0.73 and 0.86 across all five datasets (Table 3). Only the pooled population of NIFTY[23] and FIReFOX[24] trials showed a slightly lower correlation of 0.73, while all other datasets showed a rank correlation above 0.8. We also calculated the correlation using a more conservative, non-parametric estimator of Spearman's correlation.[34] This approach rendered similar results, although the correlation estimated by this method tended to be lower in all datasets, with a rank correlation that ranged between 0.68 and 0.82 (Table S9). We found consistent results across distinct disease locations and stages (Table S10 and S11).

Finally, to estimate the association between ORR and OS, we performed a responder analysis.[35–37] We only included datasets of patients treated in RCTs, as longitudinal response data was not available in the RWD. In the first-line setting, 370 patients had measurable disease and were included in this analysis. The ORR was 23% and the DCR was 77.8%. Responders did not experience better survival, either at the 3-month or 6-month landmark times (Fig. 4). In the second-line setting, 256 patients were included in the analysis. The ORR was 9.4% and the DCR was 64.1%. Similar to the first-line setting, responders did not experience better survival (Fig. S11). However, given the low response rate in the second-

Table 1. Characteristics of the trials, treatment comparisons and patients included in the studies.

	Patients (n = 7,817)	Trials (n = 41)	Comparisons (n = 44)[1]
Age, median (IQR)	63 (60.5–64)	-	-
Missing	151 (1.9%)		
Sex, n (%)		-	-
Males	3,952 (50.6%)		
Females	3,818 (48.8%)		
Missing	47 (0.6%)		
Tumor location, n (%)			
Intrahepatic	3,445 (44.1%)	37 (90.2%)	38 (86.4%)
Extrahepatic	1,410 (18%)	36 (87.8%)	37 (84.1%)
Gallbladder	2,272 (29.1%)	40 (97.6%)	43 (97.7%)
Ampullary	192 (2.5%)	17 (41.5%)	18 (40.9%)
Other	36 (0.5%)	-	-
Missing	462 (5.9%)	-	-
Disease stage, n (%)			
Locally advanced	1,457 (18.6%)	38[2] (95%)	41[2] (95.3%)
Metastatic	5,810 (74.3%)	41 (100%)	44 (100%)
Missing	550 (7%)	-	-
ECOG status, n (%)			
0	3,194 (40.9%)	40 (97.6%)	42 (95.5%)
1	3,569 (45.7%)	40 (97.6%)	42 (95.5%)
2-3	311 (4%)	14 (34.1%)	16 (36.4%)
Missing	743 (9.5%)	-	-
Number of centers, n (%)			
Multicenter	7,088 (90.7%)	33 (80.5%)	34 (77.3%)
Single-center	634 (8.1%)	6 (14.6%)	8 (18.2%)
Missing	95 (1.2%)	2 (4.9%)	2 (4.5%)
Treatment line, n (%)			
First line	6,164 (78.9%)	27 (65.9%)	29 (65.9%)
Beyond first line	1,653 (21.1%)	14 (34.1%)	15 (34.1%)
Systemic agents, n (%)			
Chemotherapy	5,295 (67.7%)	22[3] (53.7%)	23 (52.3%)
Immunotherapy	1,153 (14.7%)	5 (12.2%)	5 (11.4%)
Targeted therapy	1,066 (13.6%)	15[3] (36.6%)	16 (36.4%)
Placebo/BSC	303 (3.9%)	-	-
Clinical trial phase, n (%)			
Phase II	2,814 (36%)	29 (70.7%)	31 (70.5%)
Phase III	5,003 (64%)	12 (29.3%)	13 (29.5%)
Crossover, n (%)	53 (0.7%)	2 (4.9%)	2 (4.5%)
Follow-up (months), median (IQR)	-	10.85 (10.1–15.7)	-
Missing		17 (41.5%)	

BSC, best supportive care; ECOG, Eastern Cooperative Oncology Group.
[1]Three trials[54–56] contained three arms, leading to two comparisons.
[2]One trial[57] did not specify whether locally advanced patients were included.
[3]One trial[55] had two experimental arms, one including chemotherapy and another targeted therapy.

line setting, the number of responders at each landmark time is low and precludes any definitive conclusions.

Discussion

Inappropriate validation of intermediate endpoints may lead to the approval of potentially ineffective or even harmful treatments.[10] Previous studies have evaluated the association of PFS and response with OS at the trial-level in the context of first-[12,14] and second-line treatment of BTC.[11,13] Our analysis can be distinguished from these studies in several important ways: First, it is the only one, to our knowledge, that has included trial- and patient-level data. Second, it includes contemporary trials testing distinct systemic agents, including immunotherapies and targeted agents. Third, we rigorously extracted and calculated the HR for time-to-event endpoints and OR for binomial endpoints to ensure homogeneous analyses of these variables and appropriate measures of treatment effect. Finally, we also included RWD to complement the RCT information.

This comprehensive analysis suggests that the correlation for PFS is moderate both at the trial- and patient-level but is low for ORR and DCR in advanced BTC. Whether the strength of the correlation is sufficient to justify the use of PFS as a surrogate endpoint is arguable and controversial. For instance, PFS would meet the surrogacy criteria established by the BSES[42,43] and ReSEEM[17] guidelines, while the IQWiG[44] guidelines would consider the evidence "Unclear". Regulatory agencies have not established criteria for defining surrogate endpoints. We believe that PFS could be used as a primary endpoint in advanced BTC in circumstances when OS may be confounded, such as crossover designs or accelerated approval programs that may lead to uncontrolled post-progression crossover in the confirmatory trial. In these circumstances, a careful evaluation of OS should continue to be mandatory to ensure no detrimental effect is observed.[5,45] The magnitude of the benefit in PFS should also be considered. Our analysis of the STE shows that a magnitude of 0.61 (0.67 after excluding crossover trials) in PFS would likely lead to an OS

Table 2. Characteristics and design of the trials included in the systematic review.

Trial[1]	Treatments	Phase	N	Blinding	Primary Endpoint	Response evaluation	Timing of scans
ABC-02	CG Gemcitabine	III	410	Open-label	OS	RECIST 1.0	Q12w
ABC-03	CG+cediranib CG+placebo	II	124	Double blind	PFS	RECIST 1.1	Q12w
BilT-01	Nivo-ipi CG-nivo	II	68	Open-label	PFS 6 months	RECIST 1.1/irRECIST	Q8w
BREGO	mGEMOX+regorafenib mGEMOX	II	66	Open-label	NA	RECIST 1.0	NA
BT22	CG Gemcitabine	II	83	Open-label	OS 1 year	NA	Q8w
Chen 2015	GEMOX+cetuximab GEMOX	II	122	Open-label	ORR	RECIST 1.1	Q8w
ClarIDHy	Ivosidenib Placebo	III	187	Double blind	PFS	RECIST 1.1	Q6w
FIReFOX	mFOLFIRI mFOLFOX	II	118	Open-label	OS 6 months	RECIST 1.1	Q6w
Gambit	Irinotecan+Cisplatin CG	II	47	Open-label	ORR	RECIST 1.1	NA
GB-SELECT	CAPIRI Irinotecan	II	98	Open-label	OS 6 months	RECIST 1.1	Q8w
GEMSO-AIO	Gemcitabine+sorafenib Gemcitabine	II	97	Double blind	PFS	RECIST 1.0	Q8w
Ikeda 2023	Nanvuranlat Placebo	II	104	Double blind	PFS	RECIST 1.1	NA
IMbrave151	CG+atezolizumab+bevacizumab CG+atezolizumab+placebo	II	162	Double blind	PFS	RECIST 1.1	Q9w
JCOG0805	SG S1	II	101	Open-label	OS 1 year	RECIST 1.0	Q6w
JCOG1113	SG CG	III	354	Open-label	OS	RECIST 1.1	Q6w
Kang 2012	SG CG	II	96	Open-label	PFS 6 months	RECIST 1.0	Q6w
Kataria 2022	Capecitabine BSC	II/III	69	Open-label	OS	RECIST 1.1	NA
Kataria 2022	Erlotinib BSC	II/III	69	Open-label	OS	RECIST 1.1	NA
KEYNOTE-966	CG+pembrolizumab CG-placebo	III	1,069	Double blind	OS	RECIST 1.1	Q6w
KHBO1401-MITSUBA	CG CGS	III	246	Open-label	OS	RECIST 1.1	Q12w
Kim 2019	CAPOX GEMOX	III	222	Open-label	PFS	RECIST 1.1	Q6w
Lee 2012	GEMOX+erlotinib GEMOX	III	268	Open-label	PFS	RECIST 1.0	Q6w
Markussen 2020	GEMOX-capecitabine CG	II	96	Open-label	PFS	RECIST 1.1	Q12w
NALIRICC	5FU-nalIRI 5FU	II	100	Open-label	PFS	RECIST 1.1	Q6w
NIFTY	5FU-nalIRI 5FU	II	174	Open-label	PFS	RECIST 1.1	Q6w

(*continued on next page*)

Table 2. (*continued*)

Trial[1]	Treatments	Phase	N	Blinding	Primary Endpoint	Response evaluation	Timing of scans
Nutide:121	Cisplatin+NUC1031 CG	III	773	Open-label	OS, ORR	RECIST 1.1	Q9w
Pape 2020	CAP7.1 BSC	II	27	Open-label	DCR	RECIST 1.1	Q8w
PICCA	CG+panitumumab CG	II	90	Open-label	PFS 6 months	RECIST 1.0	Q6w
REACHIN	Regorafenib Placebo	II	66	Double blind	PFS	RECIST 1.1	Q6w
Schinzari 2017	FOLFOX4 De Gramont	II	48	Open-label	OS	RECIST 1.1	Q8w
Sharma 2010	mGEMOX BSC	II	53	Open-label	OS, ORR, toxicity	RECIST 1.0	Q6w
Sharma 2010	FUFA BSC	II	55	Open-label	OS, ORR, toxicity	RECIST 1.0	Q6w
Sharma 2019	mGEMOX CG	III	243	Open-label	OS	RECIST 1.1	NA
Shirahama 2017	PPV+CPA PPV	II	49	Open-label	Immune response	RECIST 1.0	Q8w
SWOG 1815	CG+Nab/paclitaxel CG	III	441	Open-label	OS	RECIST 1.1	Q9w
SWOG S1310	Trametinib 5FU/capecitabine	II	44	Open-label	OS	RECIST 1.1	Q6w
TOPAZ-1	CG+durvalumab CG	III	685	Double blind	OS	RECIST 1.1	Q6w
TreeTopp	Varlitinib+capecitabine Placebo+capecitabine	II	127	Double blind	ORR, PFS	RECIST 1.1	Q6w
Ueno 2021	Reminostat+S1 Placebo+S1	II	101	Double blind	PFS	RECIST 1.1	Q6w
Valle 2021	Ramucirumab Placebo	II	207	Double blind	PFS	RECIST 1.1	Q6w
Valle 2021	Merestinib Placebo	II	203	Double blind	PFS	RECIST 1.1	Q6w
Vecti-BIL	GEMOX+panitumumab GEMOX	II	89	Open-label	PFS	RECIST 1.1	Q8w
Yang 2022	Cisplatin+Nab/paclitaxel CG	II	67	Open-label	PFS	NA	NA
Zheng 2018	XELIRI Irinotecan	II	60	Open-label	PFS	RECIST 1.1	Q6w

BSC, best supportive care; CG, cisplatin + gemcitabine; DCR, disease control rate; NA, not available; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.
[1]A complete list of the studies referenced in the table is found in the Supplementary Materials.

Surrogate endpoints of OS in BTC

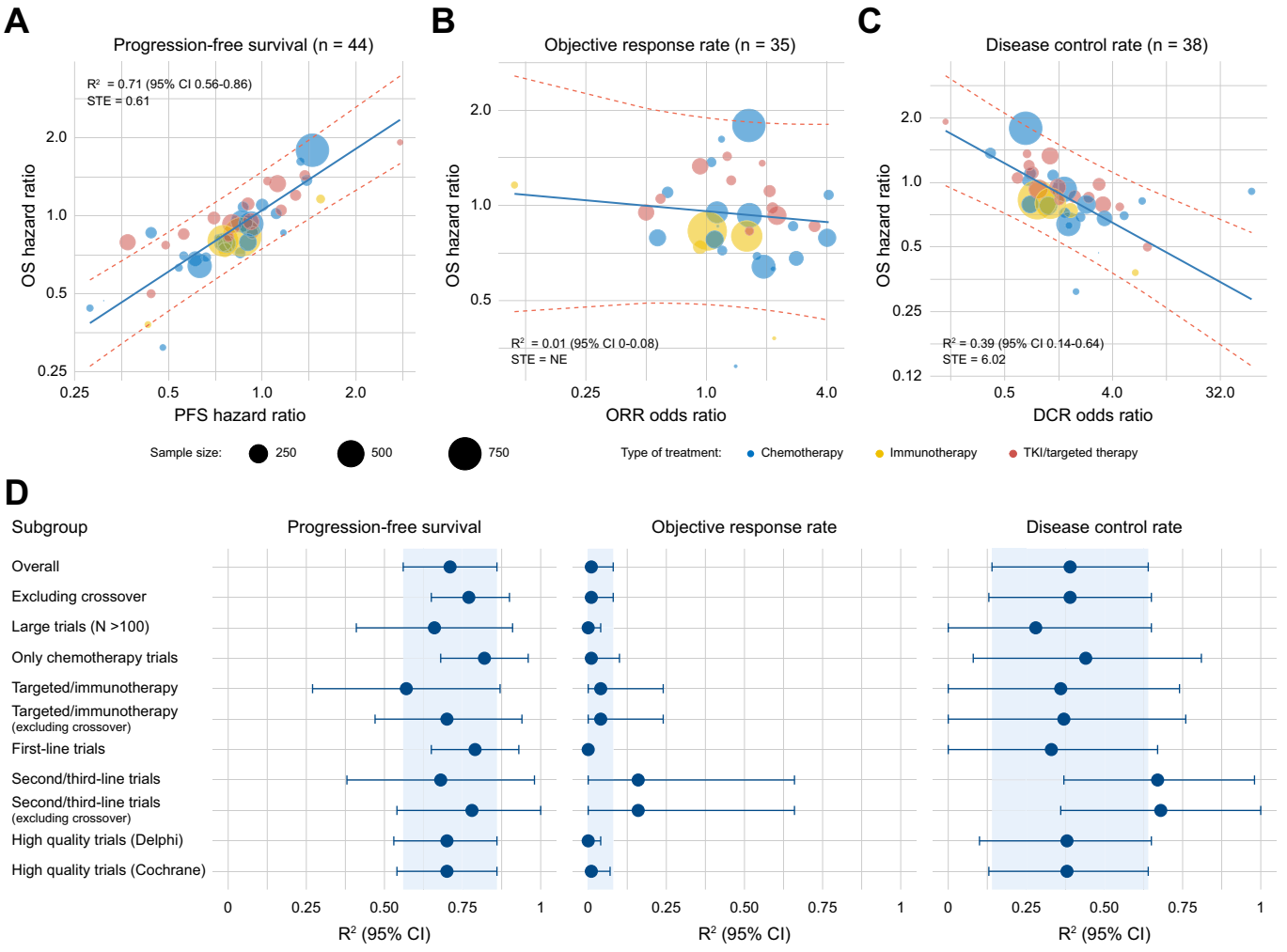

Fig. 2. Trial-level correlation of PFS, ORR and DCR with OS (Condition 1). Bubble plot assessing the correlation of (A) PFS, (B) ORR and (C) DCR with OS. Every bubble represents a trial, the color represents the treatment type and the size is proportional to the number of patients included in the trial. The hazard ratios and odds ratios are presented in the logarithmic scale. The red lines show the 95% prediction interval for a weight (*i.e.* sample size) of 200. (D) Subgroup analysis assessing the coefficient of determination across different subgroups according to the indicated criteria (left column). The shaded blue rectangles indicate the reference R^2 and its 95% CI of the global correlation. The correlation was estimated by using a linear regression model weighed by trial size. The variation of the weighted treatment effects explained by the model was measured with the coefficient of determination (R^2). DCR, disease control rate; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; STE, surrogate threshold effect.

benefit in a 200-patient randomized trial, which may be informative for interpreting and designing future studies. In addition, the use of a STE may provide a more reasonable standard for evaluating the magnitude of a treatment benefit in BTC when using PFS as a surrogate endpoint, such as the ones proposed by the ESMO Magnitude of Clinical Benefit Scale guidelines.[46] However, our data also highlight the importance of further refining and developing novel endpoints. In the case of PFS, for example, the use of time to treatment failure, which incorporates treatment discontinuation due to toxicity as an event to avoid informative censoring[26,47–49] or considering the pattern of progression may help to better capture OS.[50]

The results of our study do not support the use of either ORR or DCR as surrogate endpoints in this setting. Several factors may account for this finding. First, BTCs are frequently infiltrative and irregular, making it challenging to radiologically monitor the disease.[51] Second, patients who do not achieve a response might not be uniformly disadvantaged, especially when receiving non-cytotoxic agents, as these may confer improved survival by restraining tumor progression without inducing radiological responses.[3,40] Third, BTCs are densely fibrotic tumors in which treatment-induced tumor death may not necessarily lead to tumor shrinkage. Other parameters, such as metabolic changes, may be more accurate in discriminating response.[52] Finally, the low ORR observed with most systemic therapies in BTC may decrease the prognostic discrimination of response and lead to this poor correlation.

Several limitations should be considered when interpreting this study. First, the systematic review included a heterogeneous group of trials involving different study lines, treatment regimens and patient populations. Nonetheless, this high heterogeneity is necessary to support the assertion of the validity of a surrogate for application in a new trial.[53] Additionally, we conducted several predefined subgroup and sensitivity analyses which showed consistent levels of correlation. Second,

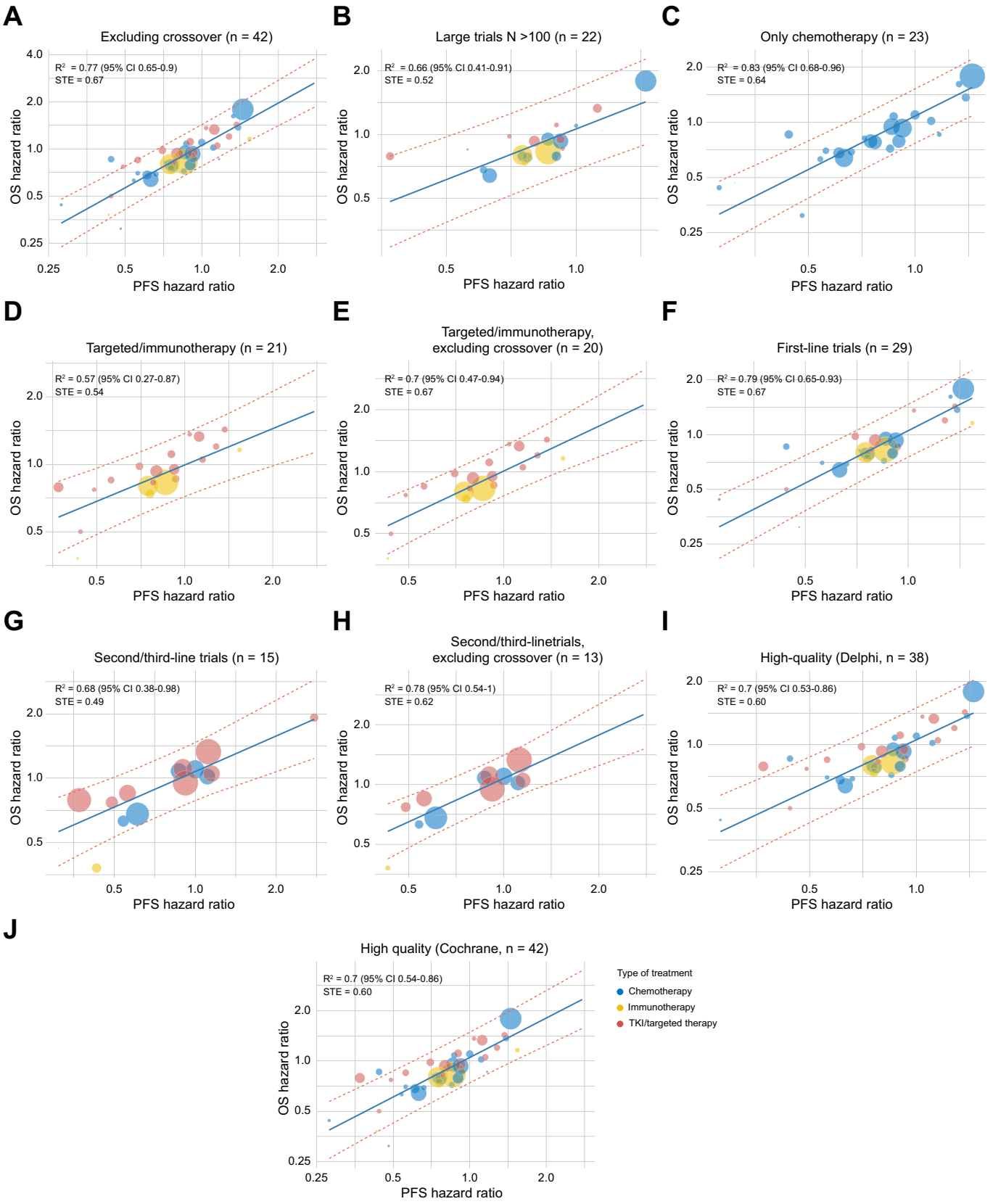

Fig. 3. Bubble plots showing the trial-level correlation for PFS and OS across different subgroups. Every bubble represents a trial, the color represents the treatment type and the size is proportional to the number of patients included in the trial. The hazard ratios are presented in the logarithmic scale. The red lines show the 95% prediction interval for a weight (*i.e.* sample size) of 200. The correlation was estimated by using a linear regression model weighed by trial size. The variation of the weighted treatment effects explained by the model was measured with the coefficient of determination (R^2). OS, overall survival; PFS, progression-free survival; STE, surrogate threshold effect.

Table 3. Patient-level correlation of PFS with OS across the different datasets using the iterative imputation method.

Cohort	Setting	Treatment line	N (events)	Follow-up (95% CI)	Median OS (95% CI)	Median PFS (95% CI)	ρ_{imi} (95% CI)
ABC-01, -02, -03	RCT	First line	512 (497)	51 (41.1-NA)	10.2 (9-11.5)	6.5 (6-7.4)	0.84 (0.81-0.86)
DURVABTC	RWD	First line	628 (190)	8.4 (7.8-9.4)	14.9 (13.4-17.8)	8.2 (7.5-8.9)	0.86 (0.81-0.9)
RETUD	RWD	First line	773 (623)	32 (25.3-37.3)	9.7 (8.7-10.4)	5 (4.5-5.4)	0.83 (0.8-0.85)
NIFTY, FIReFOX	RCT	Second line	277 (236)	33 (27-37.2)	6.3 (5.5-7.4)	2.6 (2.4-2.9)	0.73 (0.67-0.79)
RETUD	RWD	Second line	322 (279)	24.8 (22.3-NA)	5.2 (4.8-6)	2.8 (2.5-3)	0.81 (0.78-0.83)

The correlation coefficient ρ_{imi} was measured by using a normal score rank correlation calculated by the iterative multiple imputation approach.
Follow-up, OS, and PFS measured in months.
NA, not available; OS, overall survival; PFS, progression-free survival; RCT, randomized-controlled trial; RWD, real-world data.

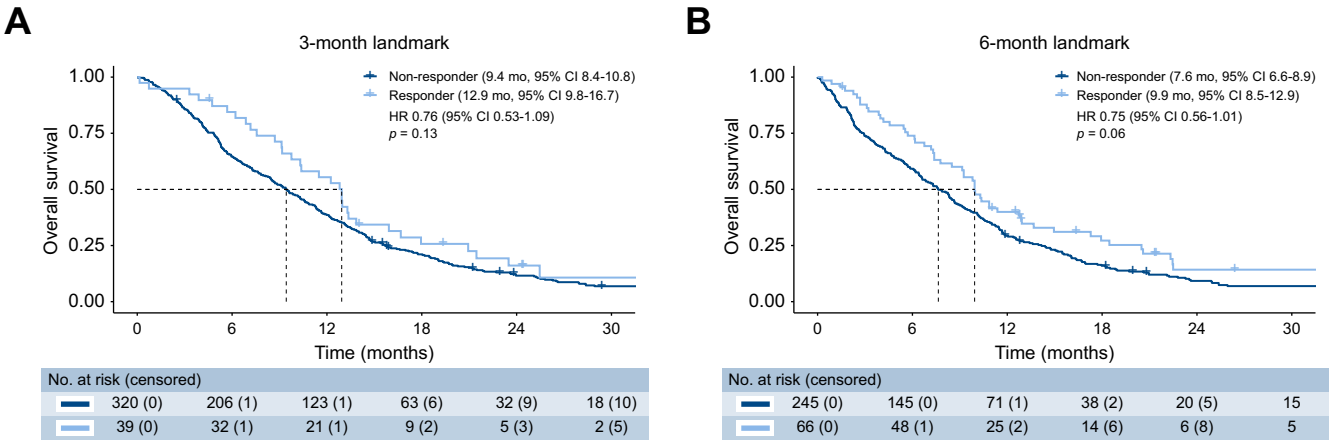

Fig. 4. Impact of response on survival in patients treated with first-line chemotherapy. Kaplan-Meier estimates of overall survival between responders and non-responders (Condition 2) who were alive and had achieved response at (A) 3-month and (B) 6-month landmark times. The HRs were estimated by applying a Cox regression model and the *p* values obtained from the Cox regression model. HR, hazard ratios.

the trial-level correlation was performed with aggregate data rather than patient-level data. We intentionally modelled the trial-level and individual-level correlation separately to ensure a broad inclusion of trials in the first condition and decrease the risk of selection bias. Third, most of the trials explored chemotherapy or tyrosine kinase inhibitors. The meta-analysis will have to be updated when further randomized studies exploring immunotherapy combinations and targeted therapies (especially FGFR inhibitors) become available. Importantly, the association of ORR/DCR and PFS with OS will have to be confirmed in individual-level data for patients treated with these therapies. Fourth, trials did not uniformly time the radiological assessments nor use a uniform definition for response evaluation. Although this may influence PFS and ORR/DCR, it is reflective of the current scenario of RCTs and highlights the need to establish a uniform set of criteria for defining and evaluating PFS in future trials.

In conclusion, our results caution against the routine use of surrogate endpoints in randomized trials testing systemic agents in advanced BTC and highlight the need for further developments to better capture OS. However, until better surrogate endpoints are developed and validated, PFS should be prioritized over ORR and DCR. Furthermore, validation in RCTs including targeted therapies and immunotherapies will be necessary to confidently extrapolate these results to trials assessing these therapies.

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Abbreviations

ASCO, American Society of Clinical Oncology; BTC, biliary tract cancer; DCR, disease control rate; ESMO, European Society of Medical Oncology; HR, hazard ratio; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RCT, randomized-controlled trial; RWD, real-world data; STE, surrogate threshold effect.

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Conflict of interest

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

Authors' contributions

FC: acquisition of data; data analysis and interpretation; manuscript writing, study concept and design. ***CFF***: acquisition of data; interpretation of data; critical revision of the manuscript. ***JB***: acquisition of data; interpretation of data; critical revision of the manuscript. ***JWK***: acquisition of data; interpretation of data; critical revision of the manuscript. ***MR***: acquisition of data; interpretation of data; critical revision of the manuscript. ***ALC***: acquisition of data; interpretation of data; critical revision of the manuscript. ***AL***: acquisition of data; interpretation of data; critical revision of the manuscript. ***MK***: acquisition of data; interpretation of data; critical revision of the manuscript. ***FS***: acquisition of data; interpretation of data; critical revision of the manuscript. ***AC***: acquisition of data; interpretation of data; critical revision of the manuscript. ***AL***: acquisition of data; interpretation of data; critical revision of the manuscript. ***JH***: acquisition of data; interpretation of data; critical revision of the manuscript. ***LR***: acquisition of data; interpretation of data; critical revision of the manuscript. ***JA***: acquisition of data; interpretation of data; critical revision of the manuscript. ***DLV***: acquisition of data; interpretation of data; critical revision of the manuscript. ***MBF***: acquisition of data; critical revision of the manuscript. ***SV***: acquisition of data; data analysis and interpretation; critical revision of the manuscript. ***KMK***: acquisition of data; critical revision of the manuscript. ***TVT***: data analysis and interpretation; critical revision of the manuscript. ***AM***: acquisition of data; interpretation of data; critical revision of the manuscript. ***ACG***: acquisition of data; interpretation of data; critical revision of the manuscript. ***CY***: acquisition of data; interpretation of data; critical revision of the manuscript. ***JWV***: acquisition of data; interpretation of data; critical revision of the manuscript. ***TM*** acquisition of data; data analysis and interpretation; manuscript writing, study concept and design.

Data availability statement

All trial-level data are presented in the Article or Supplementary Materials. Study protocol is available on PROSPERO, registration number CRD42023398279. Participant-level information cannot be shared due to confidentiality agreements. Requests for raw, individual-level data should be directed to the study Sponsors. All the codes used in the analysis can be provided to qualified researchers upon reasonable request to the corresponding author.

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Supplementary data

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References

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[1] Valle JW, Kelley RK, Nervi B, et al. Biliary tract cancer. Lancet 2021;397:428–444. https://doi.org/10.1016/S0140-6736(21)00153-7.

[2] Izquierdo-Sanchez L, Lamarca A, La Casta A, et al. Cholangiocarcinoma landscape in Europe: diagnostic, prognostic and therapeutic insights from the ENSCCA Registry. J Hepatol 2022;76:1109–1121. https://doi.org/10.1016/j.jhep.2021.12.010.

[3] Oh D-Y, Ruth He A, Qin S, et al. Durvalumab plus gemcitabine and cisplatin in advanced biliary tract cancer. NEJM Evid 2022;1. https://doi.org/10.1056/EVIDoa2200015.
[4] Kelley RK, Ueno M, Yoo C, et al. Pembrolizumab in combination with gemcitabine and cisplatin compared with gemcitabine and cisplatin alone for patients with advanced biliary tract cancer (KEYNOTE-966): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2023;401:1853–1865. https://doi.org/10.1016/S0140-6736(23)00727-4.
[5] Merino M, Kasamon Y, Theoret M, et al. Irreconcilable differences: the divorce between response rates, progression-free survival, and overall survival. J Clin Oncol 2023;41:2706–2712. https://doi.org/10.1200/JCO.23.00225.
[6] Saad ED, Buyse M. Statistical controversies in clinical research: end points other than overall survival are vital for regulatory approval of anticancer agents. Ann Oncol 2016;27:373–378. https://doi.org/10.1093/annonc/mdv562.
[7] Korn EL, Freidlin B, Abrams JS. Overall survival as the outcome for randomized clinical trials with effective subsequent therapies. J Clin Oncol 2011;29:2439–2442. https://doi.org/10.1200/JCO.2011.34.6056.
[8] Ciani O, Davis S, Tappenden P, et al. Validation of surrogate endpoints in advanced solid tumors: systematic review of statistical methods, results, and implications for policy makers. Int J Technol Assess Health Care 2014;30:312–324. https://doi.org/10.1017/S0266462314000300.
[9] Elbaz J, Haslam A, Prasad V. An empirical analysis of overall survival in drug approvals by the US FDA (2006–2023). Cancer Med 2024;13. https://doi.org/10.1002/cam4.7190.
[10] Naci H, Zhang Y, Woloshin S, et al. Overall survival benefits of cancer drugs initially approved by the US Food and Drug Administration on the basis of immature survival data: a retrospective analysis. Lancet Oncol 2024;25:760–769. https://doi.org/10.1016/S1470-2045(24)00152-9.
[11] Neuzillet C, Malka D, Lièvre A, et al. Correlation between efficacy endpoints in patients with advanced biliary tract cancer treated by systemic second-line therapies: analysis of aggregated data from a systematic literature review. Clin Res Hepatol Gastroenterol 2022;46:102010. https://doi.org/10.1016/j.clinre.2022.102010.
[12] Moriwaki T, Yamamoto Y, Gosho M, et al. Correlations of survival with progression-free survival, response rate, and disease control rate in advanced biliary tract cancer: a meta-analysis of randomised trials of first-line chemotherapy. Br J Cancer 2016;114:881–888. https://doi.org/10.1038/bjc.2016.83.
[13] Lamarca A, Hubner RA, David Ryder W, et al. Second-line chemotherapy in advanced biliary cancer: a systematic review. Ann Oncol 2014;25:2328–2338. https://doi.org/10.1093/annonc/mdu162.
[14] Eckel F, Schmid RM. Chemotherapy in advanced biliary tract carcinoma: a pooled analysis of clinical trials. Br J Cancer 2007;96:896–902. https://doi.org/10.1038/sj.bjc.6603648.
[15] Belin L, Tan A, De Rycke Y, et al. Progression-free survival as a surrogate for overall survival in oncology trials: a methodological systematic review. Br J Cancer 2020;122:1707–1714. https://doi.org/10.1038/s41416-020-0805-y.
[16] Lamarca A, Macarulla T. Facts and hopes in the systemic therapy of biliary tract carcinomas. Clin Cancer Res 2024. https://doi.org/10.1158/1078-0432.CCR-22-2438.
[17] Xie W, Halabi S, Tierney JF, et al. A systematic review and recommendation for reporting of surrogate endpoint evaluation using meta-analyses. JNCI Cancer Spectr 2019;3. https://doi.org/10.1093/jncics/pkz002.
[18] Gharzai LA, Jiang R, Wallington D, et al. Intermediate clinical endpoints for surrogacy in localised prostate cancer: an aggregate meta-analysis. Lancet Oncol 2021;22:402–410. https://doi.org/10.1016/S1470-2045(20)30730-0.
[19] Kemp R, Prasad V. Surrogate endpoints in oncology: when are they acceptable for regulatory and clinical decisions, and are they currently overused? BMC Med 2017;15:134. https://doi.org/10.1186/s12916-017-0902-9.
[20] Valle JW, Wasan H, Johnson P, et al. Gemcitabine alone or in combination with cisplatin in patients with advanced or metastatic cholangiocarcinomas or other biliary tract tumours: a multicentre randomised phase II study – the UK ABC-01 Study. Br J Cancer 2009;101:621–627. https://doi.org/10.1038/sj.bjc.6605211.
[21] Valle J, Wasan H, Palmer DH, et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Engl J Med 2010;362:1273–1281. https://doi.org/10.1056/NEJMoa0908721.
[22] Valle JW, Wasan H, Lopes A, et al. Cediranib or placebo in combination with cisplatin and gemcitabine chemotherapy for patients with advanced biliary tract cancer (ABC-03): a randomised phase 2 trial. Lancet Oncol 2015;16:967–978. https://doi.org/10.1016/S1470-2045(15)00139-4.
[23] Yoo C, Kim K, Jeong JH, et al. Liposomal irinotecan plus fluorouracil and leucovorin versus fluorouracil and leucovorin for metastatic biliary tract cancer after progression on gemcitabine plus cisplatin (NIFTY): a multicentre, open-label, randomised, phase 2b study. Lancet Oncol 2021;22:1560–1572. https://doi.org/10.1016/S1470-2045(21)00486-1.
[24] **Choi IS**, **Kim KH**, Lee JH, et al. A randomised phase II study of oxaliplatin/5-FU (mFOLFOX) versus irinotecan/5-FU (mFOLFIRI) chemotherapy in locally advanced or metastatic biliary tract cancer refractory to first-line gemcitabine/cisplatin chemotherapy. Eur J Cancer 2021;154:288–295. https://doi.org/10.1016/j.ejca.2021.06.019.
[25] Ramsey SD, Onar-Thomas A, Wheeler SB. Real-world database studies in oncology: a call for standards. J Clin Oncol 2024;42:977–980. https://doi.org/10.1200/JCO.23.02399.
[26] Booth CM, Eisenhauer EA, Gyawali B, et al. Progression-free survival should not Be used as a primary end point for registration of anticancer drugs. J Clin Oncol 2023. https://doi.org/10.1200/JCO.23.01423.
[27] Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021:n71. https://doi.org/10.1136/bmj.n71.
[28] Higgins JPT, Thomas J, Chandler J, et al. Cochrane Handbook for systematic reviews of interventions version 6.4. Cochrane; 2023 (updated August 2023).
[29] Verhagen AP, de Vet HCW, de Bie RA, et al. The Delphi List: a criteria list for quality assessment of randomized clinical trials for conducting systematic reviews developed by Delphi consensus. J Clin Epidemiol 1998;51:1235–1241. https://doi.org/10.1016/S0895-4356(98)00131-0.
[30] Johnson KR, Ringland C, Stokes BJ, et al. Response rate or time to progression as predictors of survival in trials of metastatic colorectal cancer or non-small-cell lung cancer: a meta-analysis. Lancet Oncol 2006;7:741–746. https://doi.org/10.1016/S1470-2045(06)70800-2.
[31] Burzykowski T, Buyse M. Surrogate threshold effect: an alternative measure for meta-analytic surrogate endpoint validation. Pharm Stat 2006;5:173–186. https://doi.org/10.1002/pst.207.
[32] Conforti F, Pala L, Sala I, et al. Evaluation of pathological complete response as surrogate endpoint in neoadjuvant randomised clinical trials of early stage breast cancer: systematic review and meta-analysis. BMJ 2021:e066381. https://doi.org/10.1136/bmj-2021-066381.
[33] Schemper M, Kaider A, Wakounig S, et al. Estimating the correlation of bivariate failure times under censoring. Stat Med 2013;32:4781–4790. https://doi.org/10.1002/sim.5874.
[34] Eden SK, Li C, Shepherd BE. Nonparametric estimation of Spearman's rank correlation with bivariate survival data. Biometrics 2022;78:421–434. https://doi.org/10.1111/biom.13453.
[35] Norsworthy KJ, Gao X, Ko C-W, et al. Response rate, event-free survival, and overall survival in newly diagnosed acute myeloid leukemia: US food and drug administration trial-level and patient-level analyses. J Clin Oncol 2022;40:847–854. https://doi.org/10.1200/JCO.21.01548.
[36] Blumenthal GM, Karuri SW, Zhang H, et al. Overall response rate, progression-free survival, and overall survival with targeted and standard therapies in advanced non–small-cell lung cancer: US food and drug administration trial-level and patient-level analyses. J Clin Oncol 2015;33:1008–1014. https://doi.org/10.1200/JCO.2014.59.0489.
[37] Simon R, Makuch RW. A non-parametric graphical representation of the relationship between survival and the occurrence of an event: application to responder versus non-responder bias. Stat Med 1984;3:35–44. https://doi.org/10.1002/sim.4780030106.
[38] Anderson JR, Cain KC, Gelber RD. Analysis of survival by tumor response. J Clin Oncol 1983;1:710–719. https://doi.org/10.1200/JCO.1983.1.11.710.
[39] Prasad V, Kim C, Burotto M, et al. The strength of association between surrogate end points and survival in oncology. JAMA Intern Med 2015;175:1389. https://doi.org/10.1001/jamainternmed.2015.2829.
[40] Abou-Alfa GK, Macarulla T, Javle MM, et al. Ivosidenib in IDH1-mutant, chemotherapy-refractory cholangiocarcinoma (ClarIDHy): a multicentre, randomised, double-blind, placebo-controlled, phase 3 study. Lancet Oncol 2020;21:796–807. https://doi.org/10.1016/S1470-2045(20)30157-1.
[41] Knox J, Bazin I, Oh D, et al. O-2 Phase III study of NUC-1031 + cisplatin vs gemcitabine + cisplatin for first-line treatment of patients with advanced biliary tract cancer (NuTide:121). Ann Oncol 2023;34:S180–S181. https://doi.org/10.1016/j.annonc.2023.04.017.
[42] Lassere MN, Johnson KR, Schiff M, et al. Is blood pressure reduction a valid surrogate endpoint for stroke prevention? an analysis incorporating a systematic review of randomised controlled trials, a by-trial weighted errors-in-

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[43] Lassere MN. The Biomarker-Surrogacy Evaluation Schema: a review of the biomarker-surrogate literature and a proposal for a criterion-based, quantitative, multidimensional hierarchical levels of evidence schema for evaluating the status of biomarkers as surrogate endpoints. Stat Methods Med Res 2008;17:303–340. https://doi.org/10.1177/0962280207082719.

[44] Institute for Quality and Efficiency in Health Care (IQWiG). Validity of surrogate endpoints in oncology: executive summary of rapid report A10-05, Version 1.1. Inst Qual Efficiency Health Care Executive Summ 2011.

[45] Garnick MB. Preserving the sanctity of overall survival for drugs approved on the basis of progression-free survival: tivozanib as a case study. J Clin Oncol 2013;31:3746–3748. https://doi.org/10.1200/JCO.2013.51.4869.

[46] Cherny NI, Dafni U, Bogaerts J, et al. ESMO-magnitude of clinical benefit Scale version 1.1. Ann Oncol 2017;28:2340–2366. https://doi.org/10.1093/annonc/mdx310.

[47] Tannock IF, Pond GR, Booth CM. Biased evaluation in cancer drug trials—how use of progression-free survival as the primary end point can mislead. JAMA Oncol 2022;8:679. https://doi.org/10.1001/jamaoncol.2021.8206.

[48] Fojo T, Simon RM. Inappropriate censoring in Kaplan-Meier analyses. Lancet Oncol 2021;22:1358–1360. https://doi.org/10.1016/S1470-2045(21)00473-3.

[49] Gilboa S, Pras Y, Mataraso A, et al. Informative censoring of surrogate endpoint data in phase 3 oncology trials. Eur J Cancer 2021;153:190–202. https://doi.org/10.1016/j.ejca.2021.04.044.

[50] Walia A, Tuia J, Prasad V. Progression-free survival, disease-free survival and other composite end points in oncology: improved reporting is needed. Nat Rev Clin Oncol 2023;20:885–895. https://doi.org/10.1038/s41571-023-00823-5.

[51] Harry VN, Semple SI, Parkin DE, et al. Use of new imaging techniques to predict tumour response to therapy. Lancet Oncol 2010;11:92–102. https://doi.org/10.1016/S1470-2045(09)70190-1.

[52] Sahani DV, Hayano K, Galluzzo A, et al. Measuring treatment response to systemic therapy and predicting outcome in biliary tract cancer: comparing tumor size, volume, density, and metabolism. AJR Am J Roentgenol 2015;204:776–781. https://doi.org/10.2214/AJR.14.13223.

[53] Inker LA, Collier W, Greene T, et al. A meta-analysis of GFR slope as a surrogate endpoint for kidney failure. Nat Med 2023;29:1867–1876. https://doi.org/10.1038/s41591-023-02418-0.

[54] Valle JW, Vogel A, Denlinger CS, et al. Addition of ramucirumab or merestinib to standard first-line chemotherapy for locally advanced or metastatic biliary tract cancer: a randomised, double-blind, multicentre, phase 2 study. Lancet Oncol 2021;22:1468–1482. https://doi.org/10.1016/S1470-2045(21)00409-5.

[55] Kataria B, Sharma A, Pramanik R, et al. PD-9 Three-arm phase II/III randomized controlled trial in patients with unresectable/metastatic gall bladder cancer with poor performance status: Erlotinib or capecitabine v/s best supportive care. Ann Oncol 2022;33:S242. https://doi.org/10.1016/j.annonc.2022.04.087.

[56] Sharma A, Dwary AD, Mohanti BK, et al. Best supportive care compared with chemotherapy for unresectable gall bladder cancer: a randomized controlled study. J Clin Oncol 2010;28:4581–4586. https://doi.org/10.1200/JCO.2010.29.3605.

[57] Assenat E, Blanc JF, Bouattour M, et al. 48P (BREGO) Regorafenib combined with modified m-GEMOX in patients with advanced biliary tract cancer (BTC): a phase II randomized trial. Ann Oncol 2021;32:S376–S377. https://doi.org/10.1016/j.annonc.2021.08.327.

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Supplemental information

Association of candidate surrogate endpoints with overall survival in advanced biliary tract cancer

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Supplementary materials and methods

Patients and datasets

The following cohorts were included in the study:

First-line RCT cohort: We included a pooled population of patients enrolled in the first-line trials ABC-01[1], ABC-02[2] and ABC-03[3]. The ABC-01 study was a phase II study that enrolled 86 patients who were randomized to cisplatin-gemcitabine or gemcitabine. Response evaluation was performed locally every 12 weeks following the RECIST 1.0 criteria[4]. The ABC-02 was a phase III trial that enrolled 410 patients who were randomized to cisplatin-gemcitabine or gemcitabine. Response evaluation was performed locally every 12 weeks following the RECIST 1.0 criteria. The ABC-03 study was a randomized phase II trial that tested the combination of cisplatin-gemcitabine-cediranib or cisplatin-gemcitabine-placebo in 124 patients. Response evaluation was performed locally every 12 weeks following the RECIST 1.1 criteria[5]. Patients with periampullary carcinoma were excluded. Overall, the pooled population included 512 patients (81, 307 and 124 patients from the ABC-01, -02, and -03 studies, respectively; although the ABC-02 clinical trial reported a total of 388 patients (excluding periampullary carcinomas), 81 had been patients previously recruited into the ABC-01).

Second line RCT cohort: We included a pooled population of patients included in the second-line NIFTY[6,7] and FIReFOX[8] trials. NIFTY was a randomized phase II trial that enrolled 174 patients who received 5FU/LV or the combination of 5FU/LV with nal-irinotecan. Response evaluation was performed centrally every 6 weeks following the RECIST 1.1 criteria. FIReFOX was a phase

II trial that randomized 118 patients to either modified FOLFOX or modified FOLFIRI. Response evaluation was performed locally every 6 weeks following the RECIST 1.1 criteria. After excluding patients with periampullary carcinoma, a total of 271 patients were included.

DURVABTC RWD cohort: In this cohort, we included patients diagnosed with advanced BTC and treated with a combination of cisplatin-gemcitabine and durvalumab at 39 sites in 11 countries[9]. Patient data were retrospectively collected and included sociodemographic, clinical features, tumor characteristics, treatment outcomes and survival data. Response evaluation followed local practice guidelines.

RETUD cohorts: We included all patients diagnosed with advanced BTC included in the RETUD registry who received first-line and/or second-line systemic chemotherapy[10]. The RETUD registry is a Spanish epidemiological cohort study that involves 33 sites and has included consecutive cases of histologically confirmed BTC since January 2017. Data are managed through a secured web-based data platform available to researchers, that includes filters and a query-generating system to guarantee reliability and control of missing and inconsistent data. Patient data include sociodemographic, clinical features, tumour characteristics, treatment outcomes and survival data. Response evaluation follows local practice guidelines.

Definition of endpoints

For the real-world datasets, we defined OS as the time from treatment initiation to death from any cause and PFS as the time from treatment initiation to progression or death from any cause, whichever occurred first. Patients who did not experience a PFS or OS event were censored at the date of last follow-up.

For the patients included in RCTs, OS was defined as the time from randomization to death from any cause and PFS as the time from randomization to progression or death from any cause, whichever occurred first. Patients who did not experience a PFS or OS event were censored at the date of last follow-up. Response was assessed following the guidelines originally used in the trial.

Supplementary tables

Table S1: Search strategy for the systematic review performed on PubMed.

Database: PubMed			
Search	**Date**	**Search terms**	**Number of results**
#1	17/10/2023	"Antineoplastic Combined Chemotherapy Protocols"[MeSH Terms]	160620
#2	17/10/2023	"chemother*"[Title/Abstract]	507165
#3	17/10/2023	"systemic therap*"[Title/Abstract]	22708
#4	17/10/2023	"systemic treatmen*"[Title/Abstract]	15211
#5	17/10/2023	"targeted therap*"[Title/Abstract]	74645
#6	17/10/2023	Drug Combinations[MeSH Terms]	100753
#7	17/10/2023	Drug Administration Schedule[MeSH Terms]	105693
#8	17/10/2023	**#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7**	834067
#9	17/10/2023	Cholangiocarcinoma[MeSH Terms]	12457
#10	17/10/2023	Cholangiocarcinoma[Title/Abstract]	17935
#11	17/10/2023	Biliary Tract Neoplasms[MeSH Terms]	33773
#12	17/10/2023	"gallbladder cancer"[Title/Abstract]	4680
#13	17/10/2023	"bile duct neoplasms"[Title/Abstract]	350
#14	17/10/2023	"biliary tract carcinoma"[Title/Abstract]	352
#15	17/10/2023	"biliary tract cancer*"[Title/Abstract]	2615
#16	17/10/2023	"biliary cancer"[Title/Abstract]	699
#17	17/10/2023	"biliary duct carcinoma"[Title/Abstract]	28
#18	17/10/2023	**#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17**	43852
#19	17/10/2023	Double-Blind Method[MeSH Terms]	176240
#20	17/10/2023	"clinical trial"[Text Word]	800820
#21	17/10/2023	"randomized"[Text Word]	1037166
#22	17/10/2023	"randomized controlled trial"[Text Word]	646296
#23	17/10/2023	"randomised"[Text Word]	133649
#24	17/10/2023	"randomised controlled trial"[Text Word]	32188
#25	17/10/2023	"phase 2 clinical trial"[Text Word]	874
#26	17/10/2023	"phase 2 trial"[Text Word]	2997
#27	17/10/2023	"phase 2 study"[Text Word]	3121
#28	17/10/2023	"phase 2 clinical study"[Text Word]	88
#29	17/10/2023	"phase ii clinical trial"[Text Word]	3037
#30	17/10/2023	"phase ii trial"[Text Word]	12094
#31	17/10/2023	"phase ii clinical study"[Text Word]	385
#32	17/10/2023	"phase ii study"[Text Word]	15067
#33	17/10/2023	"phase 2"[Text Word]	25708
#34	17/10/2023	"phase ii"[Text Word]	88693
#35	17/10/2023	"phase 2a clinical trial"[Text Word]	47
#36	17/10/2023	"phase 2a trial"[Text Word]	133

#37	17/10/2023	"phase 2a study"[Text Word]	188
#38	17/10/2023	"phase 2a clinical study"[Text Word]	9
#39	17/10/2023	"phase iia clinical trial"[Text Word]	90
#40	17/10/2023	"phase iia trial"[Text Word]	170
#41	17/10/2023	"phase iia clinical study"[Text Word]	20
#42	17/10/2023	"phase iia study"[Text Word]	202
#43	17/10/2023	"phase 2a"[Text Word]	741
#44	17/10/2023	"phase iia"[Text Word]	883
#45	17/10/2023	"phase 2b clinical trial"[Text Word]	40
#46	17/10/2023	"phase 2b trial"[Text Word]	199
#47	17/10/2023	"phase 2b study"[Text Word]	229
#48	17/10/2023	"phase 2b clinical study"[Text Word]	6
#49	17/10/2023	"phase iib clinical trial"[Text Word]	117
#50	17/10/2023	"phase iib trial"[Text Word]	257
#51	17/10/2023	"phase iib clinical study"[Text Word]	10
#52	17/10/2023	"phase iib study"[Text Word]	231
#53	17/10/2023	"phase 2b"[Text Word]	1043
#54	17/10/2023	"phase iib"[Text Word]	1305
#55	17/10/2023	"phase 1/2"[Text Word]	1681
#56	17/10/2023	"phase i/ii"[Text Word]	8371
#57	17/10/2023	"phase 1/2 clinical study"[Text Word]	27
#58	17/10/2023	"phase i/ii clinical study"[Text Word]	100
#59	17/10/2023	"phase 1/2 clinical trial"[Text Word]	144
#60	17/10/2023	"phase i/ii clinical trial"[Text Word]	756
#61	17/10/2023	"phase 2/3 clinical study"[Text Word]	5
#62	17/10/2023	"phase ii/iii clinical study"[Text Word]	7
#63	17/10/2023	"phase 2/3 clinical trial"[Text Word]	43
#64	17/10/2023	"phase ii/iii clinical trial"[Text Word]	84
#65	17/10/2023	"phase iii randomized trial"[Text Word]	545
#66	17/10/2023	"phase ii randomized trial"[Text Word]	237
#67	17/10/2023	"randomized phase ii trial"[Text Word]	1238
#68	17/10/2023	"randomized phase iii trial"[Text Word]))	1411
#69	17/10/2023	**#19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68**	1583403
#70	17/10/2023	**#8 AND #16 AND #69**	1054

Table S2: Eligibility criteria following the PICOS framework

PICOS	Eligibility criteria
Population	Adult patients treated with systemic chemotherapy for locally advanced or metastatic biliary tract cancer (including intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma and gallbladder carcinoma). RCTs including other tumour types will be excluded.
intervention/comparator	Systemic therapies, including chemotherapy, targeted therapies or immunotherapies. Both monotherapy and combinations will be included. Combinations with local or locoregional therapies will be excluded.
Outcomes	OS, PFS, ORR and/or DCR. Trials not reporting OS or not reporting either PFS or ORR will be excluded.
Study Design	Randomized phase II or phase III trials will be included. Sample size will not be considered an eligibility criterion.
Language	No language limit will be applied.

DCR, disease control rate; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RCTs, randomized controlled trials.

Table S3: Characteristics and design of the trials included in the systematic review.

Trial	Treatments	Phase	N	N[a] of centres	Recruitment period	Stratification factors	Blinding	Primary Endpoint	Secondary endpoint	Response evaluation	Timing of scans
ABC-02[2]	CG Gemcitabine	III	410	37	February 2002 - October 2008	Primary tumour site Extent of disease Performance status Previous therapy Recruiting centre	Open-label	OS	PFS, ORR, AEs	RECIST 1.0	Q12w
ABC-03[3]	CG+cediranib CG+placebo	II	124	14	April 2011 - September 2012	Primary tumour site Extent of disease Performance status Previous therapy Recruiting centre	Double blind	PFS	OS, ORR, AEs, QoL	RECIST 1.1	Q12w
BilT-01[11]	Nivo-ipi CG-nivo	II	68	6	September 2017 - June 2019	None	Open-label	PFS 6 months	ORR, PFS, OS, AEs	RECIST 1.1/irRECIST	Q8w
BREGO[12]	mGEMOX+regorafenib mGEMOX	II	66	NA	NA	Primary tumour site Recruiting centre	Open-label	NA	NA	RECIST 1.0	NA
BT22[13]	CG Gemcitabine	II	83	9	September 2006 - October 2008	Primary tumour site Presence of primary tumour	Open-label	OS 1 year	PFS, ORR, safety	NA	Q8w
Chen 2015[14]	GEMOX+cetuximab GEMOX	II	122	12	December 2010 - May 2012	KRAS status Performance status Primary tumour site	Open-label	ORR	DCR, PFS, OS safety	RECIST 1.1	Q8w
ClarIDHy[15]	Ivosidenib Placebo	III	187	49	February 2017 - March 2019	Number of previous lines	Double blind	PFS	OS, ORR, PFS investigator, safety, tolerability, QoL	RECIST 1.1	Q6w
FIReFOX[16]	mFOLFIRI mFOLFOX	II	118	NA	August 2015 - Novembre 2019	Primary tumour site Performance status	Open-label	OS 6 months	ORR, DCR, PFS, safety	RECIST 1.1	Q6w
Gambit[17]	Irinotecan+Cisplatin CG	II	47	NA	January 2013 - April 2018	NA	Open-label	ORR	PFS, OS, DCR, safety	RECIST 1.1	NA

GB-SELECT[18]	CAPIRI Irinotecan	II	98	2	August 2018 - January 2020	None	Open-label	OS 6 months	PFS, ORR, DCR, QoL	RECIST 1.1	Q8w
GEMSO-AIO[19]	Gemcitabine+sorafenib Gemcitabine	II	97	11	NA	None	Double blind	PFS	Safety, OS, ORR, SD duration, PFS 1 year, QoL	RECIST 1.0	Q8w
Ikeda 2023[20]	Nanvuranlat Placebo	II	104	14	NA	Primary tumour site Prior resection	Double blind	PFS	OS, DCR	RECIST 1.1	NA
IMbrave151[21]	CG+atezolizumab+bevacizumab CG+atezolizumab+placebo	II	162	NA	NA	Primary tumour site Extent of disease Geographic region	Double blind	PFS	ORR, DoR, DCR, OS, safety, PRO/QoL	RECIST 1.1	Q9w
JCOG0805[22]	SG S1	II	101	19	February 2009 - April 2010	Primary tumour site Extent of disease Recruiting centre	Open-label	OS 1 year	PFS, ORR, AEs, SAEs	RECIST 1.0	Q6w
JCOG1113[23]	SG CG	III	354	33	May 2013 - March 2016	Primary tumour site Prior resection Recruiting centre	Open-label	OS	PFS, ORR, AEs, SAEs	RECIST 1.1	Q6w
Kang 2012[24]	SG CG	II	96	1	March 2008 - March 2009	Primary tumour site Extent of disease	Open-label	PFS 6 months	OS, ORR, toxicity	RECIST 1.0	Q6w
Kataria 2022[25]	Capecitabine BSC	II/III	69	1	December 2017 - January 2021	None	Open-label	OS	PFS, ORR, QoL	RECIST 1.1	NA
Kataria 2022[25]	Erlotinib BSC	II/III	69	1	December 2017 - January 2021	None	Open-label	OS	PFS, ORR, QoL	RECIST 1.1	NA
KEYNOTE-966[26]	CG+pembrolizumab CG-placebo	III	1069	175	October 2019 - June 2021	Primary tumour site Extent of disease Geographic region	Double blind	OS	PFS, ORR, DoR, safety	RECIST 1.1	Q6w
KHBO1401-MITSUBA[27]	CG CGS	III	246	39	July 2014 - February 2016	Primary tumour site Performance status Prior resection	Open-label	OS	PFS, ORR, safety	RECIST 1.1	Q12w
Kim 2019[28]	CAPOX GEMOX	III	222	10	December 2011 - June 2016	Recruiting centre	Open-label	PFS	OS, ORR, safety	RECIST 1.1	Q6w
Lee 2012[29]	GEMOX+erlotinib GEMOX	III	268	11	February 2009 - August 2010	Recruiting centre Presence of measurable disease	Open-label	PFS	OS, ORR, QoL, safety	RECIST 1.0	Q6w

Markussen 2020[30]	GEMOX-capecitabine CG	II	96	2	July 2014 - Novembre 2017	Performance status	Open-label	PFS	OS, ORR, toxicity	RECIST 1.1	Q12w
NALIRICC[31]	5FU-nalIRI 5FU	II	100	17	NA	Primary tumour site	Open-label	PFS	OS, ORR, AEs, QoL	RECIST 1.1	Q6w
NIFTY[32]	5FU-nalIRI 5FU	II	174	5	September 2018 - February 2020	Primary tumour site Prior resection Recruiting centre	Open-label	PFS	OS, ORR, safety, QoL	RECIST 1.1	Q6w
Nutide:121[33]	Cisplatin+ NUC1031 CG	III	773	125	December 2019 - March 2022	Primary tumour site Extent of disease Measurable disease Geographic region	Open-label	OS, ORR	PFS, Safety	RECIST 1.1	Q9w
Pape 2020[34]	CAP7.1 BSC	II	27	NA	NA	None	Open-label	DCR	PFS, TTF, OS, safety	RECIST 1.1	Q8w
PICCA[35]	CG+ panitumumab CG	II	90	17	July 2011 - December 2015	Primary tumour site Leucocyte count Alkaline phosphatase	Open-label	PFS 6 months	ORR, OS, toxicity	RECIST 1.0	Q6w
REACHIN[36]	Regorafenib Placebo	II	66	12	May 2014 - February 2018	None	Double blind	PFS	OS, ORR, DCR, safety	RECIST 1.1	Q6w
Schinzari 2017[37]	FOLFOX4 De Gramont	II	48	NA	January 2008 - June 2010	None	Open-label	OS	PFS, ORR	RECIST 1.1	Q8w
Sharma 2010[38]	mGEMOX BSC	II	53	1	June 2006 - October 2008	None	Open-label	OS, ORR, toxicity	PFS	RECIST 1.0	Q6w
Sharma 2010[38]	FUFA BSC	II	55	1	June 2006 - October 2008	None	Open-label	OS, ORR, toxicity	PFS	RECIST 1.0	Q6w
Sharma 2019[39]	mGEMOX CG	III	243	1	February 2011 - July 2015	None	Open-label	OS	PFS, ORR	RECIST 1.1	NA
Shirahama 2017[40]	PPV+CPA PPV	II	49	1	November 2011 - December 2014	Extent of disease Performance status	Open-label	Immune response	OS, PFS, safety	RECIST 1.0	Q8w
SWOG 1815[41]	CG+Nab/paclitaxel CG	III	441	NA	February 2019 - February 2021	Primary tumour site Extent of disease Performance status	Open-label	OS	ORR, PFS, DCR, safety	RECIST 1.1	Q9w
SWOG S1310[42]	Trametinib 5FU/capecitabine	II	44	NA	February 2014 - March 2015	Primary tumour site Chemotherapy regimen	Open-label	OS	PFS, ORR	RECIST 1.1	Q6w

TOPAZ-1[43]	CG+durvalumab CG	III	685	105	April 2019 - December 2020	Primary tumour site Disease status	Double blind	OS	PFS, ORR, DoR, DCR	RECIST 1.1	Q6w
TreeTopp[44]	Varlitinib+ capecitabine Placebo+ capecitabine	II	127	56	May 2018 - December 2019	Primary tumour site Geographic region	Double blind	ORR, PFS	OS, AEs	RECIST 1.1	Q6w
Ueno 2021[45]	Reminostat+S1 Placebo+S1	II	101	21	March 2018 - February 2019	Primary tumour site Prior resection Performance status Recruiting centre	Double blind	PFS	OS, ORR, DCR, safety	RECIST 1.1	Q6w
Valle 2021[46]	Ramucirumab Placebo	II	207	81	May 2016 - August 2017	Primary tumour site Extent of disease Geographic region	Double blind	PFS	OS, ORR, DCR, QoL, safety	RECIST 1.1	Q6w
Valle 2021[46]	Merestinib Placebo	II	203	81	May 2016 - August 2017	Primary tumour site Extent of disease Geographic region	Double blind	PFS	OS, ORR, DCR, QoL, safety	RECIST 1.1	Q6w
Vecti-BIL[47]	GEMOX+ panitumumab GEMOX	II	89	12	June 2010 - September 2013	Primary tumour site Performance status	Open-label	PFS	OS, ORR, safety	RECIST 1.1	Q8w
Yang 2022[48]	Cisplatin+ Nab/paclitaxel CG	II	67	NA	NA	NA	Open-label	PFS	OS, ORR, safety	NA	NA
Zheng 2018[49]	XELIRI Irinotecan	II	60	1	September 2015 - September 2017	None	Open-label	PFS	OS	RECIST 1.1	Q6w

AEs, adverse events; BSC, best supportive care; CG, cisplatin + gemcitabine; DCR, disease control rate; DoR, duration of response; NA, not available; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; QoL, quality of life; SAE, serious adverse events; SD, stable disease; TTF, time to treatment failure.

Table S4: Estimated STE for PFS, DCR and ORR in different hypothetical trials with varying sample sizes.

Hypothetical trial size	PFS STE (HR)	DCR STE (OR)	ORR STE (OR)
***N* = 50**	0.39	37.78	NE
***N* = 100**	0.51	12.85	NE
***N* = 150**	0.57	7.99	NE
***N* = 200**	0.61	6.02	NE
***N* = 400**	0.69	3.55	NE
***N* = 600**	0.73	2.82	NE
***N* = 800**	0.75	2.46	NE
***N* = 1000**	0.77	2.25	NE
***N* = 1200**	0.78	2.1	NE

The STE was defined as the intersection of the upper 95% prediction interval with the horizontal y-axis=0 of the linear regression model, representing a hazard ratio of 1.
DCR, disease control rate; HR, hazard ratio; OR, odds ratio; ORR, objective response rate; PFS, progression free survival; STE, surrogate threshold effect.

Table S5: Baseline characteristics of patients included in the ABC-01, ABC-02 and ABC-03 trials.

	Cohort (N=512)
Age (median, IQR)	64 (58-70)
Sex (N, %)	
Male	238 (46.5%)
Female	274 (53.5%)
Location (N, %)	
Intrahepatic	123 (24%)
Hiliar	53 (10.4%)
Distal	141 (27.5%)
Gallbladder	122 (23.8%)
Cholangiocarcinoma NOS	20 (3.9%)
Missing	53 (10.4%)
Stage (N, %)	
Locally advanced	121 (23.6%)
Metastatic	391 (76.4%)
CA19.9 (UI/mL, median IQR)	105 (24.4-776.5)
Grade of differentiation	
Well	42 (8.2%)
Moderate	158 (30.9%)
Poor	93 (18.2%)
Not specified	219 (42.8%)
Histology	
Adenocarcinoma	464 (90.6%)
Adenosquamous	4 (0.8%)
Carcinoma NOS	32 (6.3%)
Other	12 (2.3%)
ECOG-PS (N, %)	
0	177 (34.6%)
1	283 (55.3%)
2	51 (10%)
Missing	1 (0.2%)
Prior surgery (N, %)	191 (37.3%)
Missing	40 (7.8%)
Prior biliary stenting (N, %)	227 (44.3%)
Missing	43 (8.3%)
Treatment received (N, %)	
Cisplatin-gemcitabine	195 (38.1%)
Cisplatin-gemcitabine-placebo	62 (12.1%)
Cisplatin-gemcitabine-cediranib	62 (12.1%)
Gemcitabine	193 (37.7%)

ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range.

Table S6: Baseline characteristics of patients included in the NIFTY and FIReFOX trials (FAS population).

	Cohort (N=271)
Age, median (range)	64 (26-84)
Sex (N, %)	
Male	164 (60.5%)
Female	107 (39.5%)
Tumour location (N, %)	
Intrahepatic	116 (42.8%)
Extrahepatic	72 (26.6%)
Gallbladder	83 (30.6%)
Disease setting (N, %)	
Initially metastatic	232 (85.6%)
Recurrence after curative surgery	39 (14.4%)
ECOG performance Status (N, %)	
0	43 (15.9%)
1	228 (84.1%)
First-line CG duration (N, %)	
< 3 months	68 (25.1%)
≥ 3 months	203 (74.9%)
First-line CG duration (N, %)	
< 6 months	170 (62.7%)
≥ 6 months	101 (37.3%)
Baseline serum CA 19-9 (N, %)	
< 172 IU/mL	127 (46.9%)
≥ 172 IU/mL	144 (53.1%)
Baseline serum CA 19-9 (N, %)	
< 400 IU/mL	152 (56.1%)
≥ 400 IU/mL	119 (43.9%)
Post study treatment	
Yes	108 (39.9%)
No	163 (60.1%)

CG, cisplatin-gemcitabine; ECOG, Eastern Cooperative Oncology Group; FAS, full analysis set.

Table S7: Baseline characteristics of patients included in the first-line RWD of cisplatin-gemcitabine combined with durvalumab cohort.

	Cohort (N=628)
Age (median, IQR)	68 (59-74)
Sex (N, %)	
Male	334 (53.2%)
Female	294 (46.8%)
Location (N, %)	
Intrahepatic	335 (53.3%)
Hiliar	105 (16.7%)
Distal	58 (9.2%)
Gallbladder	130 (20.7%)
Stage (N, %)	
Locally advanced	144 (22.9%)
Metastatic	483 (76.9%)
MIssing	1 (0.2%)
CA19.9 (UI/mL, median IQR)	105 (24.4-776.5)
Etiology (N, %)	
HBV	38 (6.1%)
HCV	21 (3.3%)
Non-viral	371 (59.1%)
Unknown	198 (31.5%)
ECOG-PS (N, %)	
0	304 (48.4%)
1	303 (48.2%)
2	18 (2.9%)
3-4	3 (4.8%)
Prior surgery (N, %)	172 (27.4%)
Prior adjuvant treatment (N, %)	106 (61.6%)

CG-Durva, cisplatin-gemcitabine-durvalumab; ECOG, Eastern Cooperative Oncology Group; HBV, Hepatitis B virus; HCV, Hepatitis C virus; IQR, interquartile range; RWD, real-world data.

Table S8: Baseline characteristics of patients included in the first-line and second-line RETUD RWD chemotherapy cohorts.

	First-line cohort (N=773)	Second-line cohort (N=322)
Age (median, IQR)	68 (60-74)	65 (56-72)
Sex (N, %)		
Male	418 (54.1%)	166 (51.6%)
Female	355 (45.9%)	156 (48.4%)
Location (N, %)		
Intrahepatic	460 (59.5%)	200 (62.1%)
Hiliar	97 (12.5%)	35 (10.9%)
Distal	115 (14.9%)	44 (13.7%)
Gallbladder	101 (13.1%)	43 (13.4%)
Stage at diagnosis (N, %)		
Resectable	145 (18.8%)	59 (18.3%)
Locally advanced	169 (21.9%)	60 (18.6%)
Metastatic	459 (59.4%)	203 (63%)
Metastatic location (N, %)		
Liver	388 (50.2%)	173 (53.7%)
Lung	154 (19.9%)	65 (20.2%)
Bone	69 (8.9%)	36 (11.2%)
ECOG-PS (N, %)		
0	150 (19.4%)	86 (26.7%)
1	315 (40.8%)	147 (45.7%)
2	97 (12.5%)	15 (4.7%)
3-4	7 (0.9%)	2 (0.6%)
Missing	204 (26.4%)	72 (22.4%)
Prior surgery (N, %)	204 (26.4%)	90 (28%)
Chemotherapy regimen (N, %)	Cisplatin-Gemcitabine: 504 (65.2%) GEMOX: 60 (7.8%) Gemcitabine: 118 (15.3%) Other: 91 (11.8%)	FOLFOX: 90 (28%) CAPOX: 46 (14.3%) Capecitabine: 60 (18.6%) Irinotecan-based: 39 (12.1%) Other: 87 (27%)

ChT, chemotherapy; ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; RWD, real-world data.

Table S9: Patient-level correlation of PFS with OS across the different datasets using Spearman's non-parametric correlation estimate for bivariate survival data.

Cohort	Setting	Treatment line	N (events)	Follow-up (mo, 95% CI)	Median OS (mo, 95% CI)	Median PFS (mo, 95% CI)	ρ_s (95% CI)
Pooled ABC-01, -02, -03	RCT	First line	512 (497)	51 (41.1-NA)	10.2 (9-11.5)	6.5 (6-7.4)	0.82 (0.78-0.86)
CG-Durva	RWD	First line	628 (190)	8.4 (7.8-9.4)	14.9 (13.4-17.8)	8.2 (7.5-8.9)	0.69 (0.6-0.76)
RETUD	RWD	First line	773 (623)	32 (25.3-37.3)	9.7 (8.7-10.4)	5 (4.5-5.4)	0.79 (0.75-0.83)
NIFTY, FIReFOX	RCT	Second line	277 (236)	33 (27-37.2)	6.3 (5.5-7.4)	2.6 (2.4-2.9)	0.7 (0.63-0.78)
RETUD	RWD	Second line	322 (279)	24.8 (22.3-NA)	5.2 (4.8-6)	2.8 (2.5-3)	0.77 (0.71-0.83)

The ρ_s between OS and PFS was calculated by using a nonparametric estimator of Spearman's correlation, based on a nonparametric bivariate survival surface estimator.
CI, confidence interval; mo, months; NA, not available; RCT, randomized controlled trial; RWD, real-world data.

Table S10: Patient-level correlation of PFS with OS stratified according to tumour location

INTRAHEPATIC CHOLANGIOCARCINOMA								
Cohort	**Setting**	**Treatment line**	**N (events)**	**Follow-up (mo, 95% CI)**	**Median OS (mo, 95% CI)**	**Median PFS (mo, 95% CI)**	**ρ_{imi} (95% CI)**	**ρ_s (95% CI)**
ABC-01, -02, -03	RCT	First line	123 (110)	58.3 (33.4-NA)	12.4 (9.9-15.1)	7.9 (5.9-8.5)	0.82 (0.75-0.87)	0.79 (0.7-0.89)
DURVABTC	RWD	First line	335 (117)	8.5 (7.8-10.6)	14.8 (11.3-16.3)	7.8 (7.1-8.9)	0.87 (0.82-0.9)	0.76 (0.65-0.85)
RETUD	RWD	First line	460 (389)	32.7 (26.5-NA)	9.1 (8.1-10.2)	4.8 (3.9-5.3)	0.83 (0.79-0.86)	0.79 (0.74-0.84)
NIFTY, FIReFOX	RCT	Second line	116 (104)	33 (26.3-NA)	5.6 (4.8-6.7)	2 (1.5-2.7)	0.76 (0.67-0.83)	0.72 (0.63-0.82)
RETUD	RWD	Second line	200 (177)	25.5 (22.3-NA)	5.5 (4.9-6.7)	2.8 (2.5-3.1)	0.82 (0.79-0.85)	0.79 (0.72-0.86)
EXTRAHEPATIC CHOLANGIOCARCINOMA								
Cohort	**Setting**	**Treatment line**	**N (events)**	**Follow-up (mo, 95% CI)**	**Median OS (mo, 95% CI)**	**Median PFS (mo, 95% CI)**	**ρ_{imi} (95% CI)**	**ρ_s (95% CI)**
ABC-01, -02, -03	RCT	First line	194 (178)	51 (27.4-NA)	10.7 (8.8-12.6)	6.9 (6.3-8.3)	0.87 (0.82-0.9)	0.84 (0.78-0.91)
DURVABTC	RWD	First line	163 (37)	9.4 (7.9-10.7)	NA (13.6-NA)	9.4 (8.6-10)	0.86 (0.66-0.95)	0.66 (0.54-0.79)
RETUD	RWD	First line	212 (162)	35 (20.3-51.2)	10.6 (8.6-11.7)	5.3 (4.2-6.3)	0.84 (0.79-0.87)	0.79 (0.72-0.87)
NIFTY, FIReFOX	RCT	Second line	72 (61)	25.8 (24.8-NA)	7 (4.8-8.4)	2.9 (2.5-4.1)	0.69 (0.54-0.8)	0.7 (0.53-0.87)
RETUD	RWD	Second line	79 (66)	22.5 (14.6-NA)	4.7 (4.4-7)	2.6 (2.1-3.3)	0.76 (0.7-0.8)	0.73 (0.61-0.87)
GALLBLADDER CARCINOMA								
Cohort	**Setting**	**Treatment line**	**N (events)**	**Follow-up (mo, 95% CI)**	**Median OS (mo, 95% CI)**	**Median PFS (mo, 95% CI)**	**ρ_{imi} (95% CI)**	**ρ_s (95% CI)**
ABC-01, -02, -03	RCT	First line	122 (120)	42 (42-NA)	8.5 (7.3-11.4)	5.7 (5-7.3)	0.81 (0.74-0.87)	0.82 (0.73-0.9)
DURVABTC	RWD	First line	130 (36)	7 (6.2-8.8)	15 (10.2-NA)	7.3 (6.5-8.5)	0.8 (0.58-0.91)	0.6 (0.42-0.8)
RETUD	RWD	First line	101 (72)	15.8 (12.9-NA)	9.9 (8.7-13.2)	5.3 (4.3-7)	0.83 (0.75-0.89)	0.81 (0.71-0.93)
NIFTY, FIReFOX	RCT	Second line	83 (69)	34.2 (27-NA)	7.3 (6.8-10.3)	3.1 (2.6-4.4)	0.71 (0.55-0.81)	0.66 (0.53-0.8)
RETUD	RWD	Second line	43 (36)	NA (8-NA)	4.3 (3.3-6.8)	2.7 (2.5-3.8)	0.88 (0.85-0.91)	0.83 (0.7-0.97)

The correlation coefficient ρ_{imi} was measured by using a normal score rank correlation calculated by the iterative multiple imputation approach.The ρ_s was calculated by using a nonparametric estimator of Spearman's correlation, based on a nonparametric bivariate survival surface estimator.
CI, confidence interval; mo, months; NA, not available; OS, overall survival; PFS, progression-free survival; RCT, randomized controlled trial; RWD, real-world data.

Table S11: Patient-level correlation of PFS with OS stratified according to disease stage.

LOCALLY ADVANCED								
Cohort	**Setting**	**Treatment line**	**N (events)**	**Follow-up (mo, 95% CI)**	**Median OS (mo, 95% CI)**	**Median PFS (mo, 95% CI)**	**ρ_{imi} (95% CI)**	**ρ_s (95% CI)**
ABC-01, -02, -03	RCT	First line	121 (108)	58.3 (41.5-NA)	13.3 (10.3-15.6)	6.9 (5.9-9)	0.87 (0.82-0.91)	0.85 (0.78-0.93)
DURVABTC	RWD	First line	144 (25)	9.3 (8-10.7)	23.3 (18.4-NA)	9.5 (8.5-12.2)	0.73 (0.42-0.8)	0.47 (0.21-0.77)
RETUD	RWD	First line	166 (114)	19.5 (17-31.1)	10.2 (8.7-12.1)	6.4 (5-7.3)	0.83 (0.77-0.88)	0.79 (0.7-0.89)
NIFTY, FIReFOX	RCT	Second line	39 (34)	34.2 (34.2-NA)	7.6 (4.7-13.4)	3 (2.4-4.7)	0.82 (0.67-0.91)	0.77 (0.62-0.96)
RETUD	RWD	Second line	51 (41)	24.8 (24.8-NA)	4.6 (3.5-7.9)	2.8 (2.3-4.4)	0.88 (0.85-0.9)	0.85 (0.73-0.99)
METASTATIC								
Cohort	**Setting**	**Treatment line**	**N (events)**	**Follow-up (mo, 95% CI)**	**Median OS (mo, 95% CI)**	**Median PFS (mo, 95% CI)**	**ρ_{imi} (95% CI)**	**ρ_s (95% CI)**
ABC-01, -02, -03	RCT	First line	391 (370)	42 (33.4-NA)	9.6 (8.6-10.7)	6.4 (5.5-7.3)	0.82 (0.79-0.85)	0.81 (0.77-0.86)
DURVABTC	RWD	First line	483 (165)	8 (7.6-9.5)	13.3 (11.3-15.6)	7.5 (6.9-8.5)	0.86 (0.79-0.91)	0.74 (0.66-0.81)
RETUD	RWD	First line	607 (509)	35 (26.9-46.1)	9.6 (8.6-10.3)	4.7 (4.1-5.3)	0.83 (0.8-0.85)	0.79 (0.75-0.83)
NIFTY, FIReFOX	RCT	Second line	232 (200)	28.9 (26.3-NA)	6.2 (5.4-7.2)	2.6 (2.2-2.8)	0.71 (0.64-0.77)	0.69 (0.61-0.77)
RETUD	RWD	Second line	271 (238)	23.7 (22.3-NA)	5.3 (4.9-6.2)	2.8 (2.5-3)	0.8 (0.77-0.82)	0.75 (0.69-0.82)

The correlation coefficient ρ_{imi} was measured by using a normal score rank correlation calculated by the iterative multiple imputation approach.The ρ_s was calculated by using a nonparametric estimator of Spearman's correlation, based on a nonparametric bivariate survival surface estimator.
CI, confidence interval; mo, months; NA, not available; OS, overall survival; PFS, progression-free survival; RCT, randomized controlled trial; RWD, real-world data.

Supplementary references

Author names in bold designate shared co-first authorship

[1] Valle JW, Wasan H, Johnson P, et al. Gemcitabine alone or in combination with cisplatin in patients with advanced or metastatic cholangiocarcinomas or other biliary tract tumours: a multicentre randomised phase II study – The UK ABC-01 Study. Br J Cancer 2009;101:621–7. https://doi.org/10.1038/sj.bjc.6605211.

[2] Valle J, Wasan H, Palmer DH, et al. Cisplatin plus Gemcitabine versus Gemcitabine for Biliary Tract Cancer. N Engl J Med 2010;362:1273–81. https://doi.org/10.1056/NEJMoa0908721.

[3] Valle JW, Wasan H, Lopes A, et al. Cediranib or placebo in combination with cisplatin and gemcitabine chemotherapy for patients with advanced biliary tract cancer (ABC-03): a randomised phase 2 trial. Lancet Oncol 2015;16:967–78. https://doi.org/10.1016/S1470-2045(15)00139-4.

[4] Therasse P, Arbuck SG, Eisenhauer EA, et al. New Guidelines to Evaluate the Response to Treatment in Solid Tumors. JNCI: J Natl Cancer Inst 2000;92:205–16. https://doi.org/10.1093/jnci/92.3.205.

[5] Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228–47. https://doi.org/10.1016/j.ejca.2008.10.026.

[6] Yoo C, Kim K, Jeong JH, et al. Liposomal irinotecan plus fluorouracil and leucovorin versus fluorouracil and leucovorin for metastatic biliary tract cancer after progression on gemcitabine plus cisplatin (NIFTY): a multicentre, open-label, randomised, phase 2b study. Lancet Oncol 2021;22:1560–72. https://doi.org/10.1016/S1470-2045(21)00486-1.

[7] Hyung J, Kim I, Kim K, et al. Treatment With Liposomal Irinotecan Plus Fluorouracil and Leucovorin for Patients With Previously Treated Metastatic Biliary Tract Cancer. JAMA Oncol 2023;9:692. https://doi.org/10.1001/jamaoncol.2023.0016.

[8] **Choi IS, Kim KH**, Lee JH, et al. A randomised phase II study of oxaliplatin/5-FU (mFOLFOX) versus irinotecan/5-FU (mFOLFIRI) chemotherapy in locally advanced or metastatic biliary tract cancer refractory to first-line gemcitabine/cisplatin chemotherapy. Eur J Cancer 2021;154:288–95. https://doi.org/10.1016/j.ejca.2021.06.019.

[9] **Rimini M, Fornaro L,** Rizzato MD, et al. Durvalumab plus gemcitabine and cisplatin in advanced biliary tract cancer: A large real-life worldwide population. Eur J Cancer 2024;208:114199. https://doi.org/10.1016/j.ejca.2024.114199.

[10] Macarulla T, Barrero M, Adeva J, et al. Epidemiological biliary tract cancer characterization: A patient cohort from the Spanish RETUD registry. J Clin Oncol 2022;40:480–480. https://doi.org/10.1200/JCO.2022.40.4_suppl.480.

[11] Sahai V, Griffith KA, Beg MS, et al. A randomized phase 2 trial of nivolumab, gemcitabine, and cisplatin or nivolumab and ipilimumab in previously untreated advanced biliary cancer: BilT-01. Cancer 2022;128:3523–30. https://doi.org/10.1002/cncr.34394.

[12] Assenat E, Blanc JF, Bouattour M, et al. 48P (BREGO) Regorafenib combined with modified m-GEMOX in patients with advanced biliary tract

cancer (BTC): A phase II randomized trial. Ann Oncol 2021;32:S376–7. https://doi.org/10.1016/j.annonc.2021.08.327.
[13] Okusaka T, Nakachi K, Fukutomi A, et al. Gemcitabine alone or in combination with cisplatin in patients with biliary tract cancer: a comparative multicentre study in Japan. Br J Cancer 2010;103:469–74. https://doi.org/10.1038/sj.bjc.6605779.
[14] **Chen JS, Hsu C, Chiang NJ, Tsai CS**, et al. A KRAS mutation status-stratified randomized phase II trial of gemcitabine and oxaliplatin alone or in combination with cetuximab in advanced biliary tract cancer. Ann Oncol 2015;26:943–9. https://doi.org/10.1093/annonc/mdv035.
[15] Zhu AX, Macarulla T, Javle MM, et al. Final Overall Survival Efficacy Results of Ivosidenib for Patients With Advanced Cholangiocarcinoma With *IDH1* Mutation. JAMA Oncol 2021;7:1669. https://doi.org/10.1001/jamaoncol.2021.3836.
[16] **Choi IS, Kim KH**, Lee JH, et al. A randomised phase II study of oxaliplatin/5-FU (mFOLFOX) versus irinotecan/5-FU (mFOLFIRI) chemotherapy in locally advanced or metastatic biliary tract cancer refractory to first-line gemcitabine/cisplatin chemotherapy. Eur J Cancer 2021;154:288–95. https://doi.org/10.1016/j.ejca.2021.06.019.
[17] dos Santos LV, Pinto GSF, Ferraz MWS, et al. Cisplatin plus irinotecan versus cisplatin plus gemcitabine in the treatment of advanced or metastatic gallbladder or biliary tract cancer: Results of a randomized phase II trial (NCT01859728)– the Gambit trial. J Clin Oncol 2020;38:529–529. https://doi.org/10.1200/JCO.2020.38.4_suppl.529.
[18] Ramaswamy A, Ostwal V, Sharma A, et al. Efficacy of Capecitabine Plus Irinotecan vs Irinotecan Monotherapy as Second-line Treatment in Patients With Advanced Gallbladder Cancer. JAMA Oncol 2021;7:436. https://doi.org/10.1001/jamaoncol.2020.6166.
[19] Moehler M, Maderer A, Schimanski C, et al. Gemcitabine plus sorafenib versus gemcitabine alone in advanced biliary tract cancer: A double-blind placebo-controlled multicentre phase II AIO study with biomarker and serum programme. Eur J Cancer 2014;50:3125–35. https://doi.org/10.1016/j.ejca.2014.09.013.
[20] Ikeda M, Ueno M, Furukawa M, et al. Subgroup analysis of double-blind, placebo-controlled Ph. 2 study of nanvuranlat in treatment of pre-treated, advanced, refractory biliary tract cancer (BTC): Patients with high LAT1 expression and response to nanvuranlat. J Clin Oncol 2023;41:4011–4011. https://doi.org/10.1200/JCO.2023.41.16_suppl.4011.
[21] El-Khoueiry AB, Ren Z, Chon H, et al. IMbrave151: A phase 2, randomized, double-blind, placebo-controlled study of atezolizumab with or without bevacizumab in combination with cisplatin plus gemcitabine in patients with untreated, advanced biliary tract cancer. J Clin Oncol 2023;41:491–491. https://doi.org/10.1200/JCO.2023.41.4_suppl.491.
[22] Morizane C, Okusaka T, Mizusawa J, et al. Randomized phase II study of gemcitabine plus S-1 versus S-1 in advanced biliary tract cancer: A Japan Clinical Oncology Group trial (JCOG 0805). Cancer Sci 2013;104:1211–6. https://doi.org/10.1111/cas.12218.
[23] Morizane C, Okusaka T, Mizusawa J, et al. Combination gemcitabine plus S-1 versus gemcitabine plus cisplatin for advanced/recurrent biliary tract

cancer: the FUGA-BT (JCOG1113) randomized phase III clinical trial. Ann Oncol 2019;30:1950–8. https://doi.org/10.1093/annonc/mdz402.
[24] Kang MJ, Lee J-L, Kim TW, et al. Randomized phase II trial of S-1 and cisplatin versus gemcitabine and cisplatin in patients with advanced biliary tract adenocarcinoma. Acta Oncol (Madr) 2012;51:860–6. https://doi.org/10.3109/0284186X.2012.682628.
[25] Kataria B, Sharma A, Pramanik R, et al. PD-9 Three-arm phase II/III randomized controlled trial in patients with unresectable/metastatic gall bladder cancer with poor performance status: Erlotinib or capecitabine v/s best supportive care. Ann Oncol 2022;33:S242. https://doi.org/10.1016/j.annonc.2022.04.087.
[26] Kelley RK, Ueno M, Yoo C, et al. Pembrolizumab in combination with gemcitabine and cisplatin compared with gemcitabine and cisplatin alone for patients with advanced biliary tract cancer (KEYNOTE-966): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2023;401:1853–65. https://doi.org/10.1016/S0140-6736(23)00727-4.
[27] Ioka T, Kanai M, Kobayashi S, et al. Randomized phase <scp>III</scp> study of gemcitabine, cisplatin plus S-1 versus gemcitabine, cisplatin for advanced biliary tract cancer (KHBO1401- MITSUBA). J Hepatobiliary Pancreat Sci 2023;30:102–10. https://doi.org/10.1002/jhbp.1219.
[28] **Kim ST, Kang JH,** Lee J, et al. Capecitabine plus oxaliplatin versus gemcitabine plus oxaliplatin as first-line therapy for advanced biliary tract cancers: a multicenter, open-label, randomized, phase III, noninferiority trial. Ann Oncol 2019;30:788–95. https://doi.org/10.1093/annonc/mdz058.
[29] Lee J, Park SH, Chang H-M, et al. Gemcitabine and oxaliplatin with or without erlotinib in advanced biliary-tract cancer: a multicentre, open-label, randomised, phase 3 study. Lancet Oncol 2012;13:181–8. https://doi.org/10.1016/S1470-2045(11)70301-1.
[30] Markussen A, Jensen LH, Diness LV, Larsen FO. Treatment of Patients with Advanced Biliary Tract Cancer with Either Oxaliplatin, Gemcitabine, and Capecitabine or Cisplatin and Gemcitabine—A Randomized Phase II Trial. Cancers (Basel) 2020;12:1975. https://doi.org/10.3390/cancers12071975.
[31] Vogel A, Wenzel P, Folprecht G, et al. 53MO Nal-IRI and 5-FU/LV compared to 5-FU/LV in patients with cholangio- and gallbladder carcinoma previously treated with gemcitabine-based therapies (NALIRICC – AIO-HEP-0116). Ann Oncol 2022;33:S563–4. https://doi.org/10.1016/j.annonc.2022.07.081.
[32] Yoo C, Kim K, Jeong JH, et al. Liposomal irinotecan plus fluorouracil and leucovorin versus fluorouracil and leucovorin for metastatic biliary tract cancer after progression on gemcitabine plus cisplatin (NIFTY): a multicentre, open-label, randomised, phase 2b study. Lancet Oncol 2021;22:1560–72. https://doi.org/10.1016/S1470-2045(21)00486-1.
[33] Knox J, Bazin I, Oh D, et al. O-2 Phase III study of NUC-1031 + cisplatin vs gemcitabine + cisplatin for first-line treatment of patients with advanced biliary tract cancer (NuTide:121). Ann Oncol 2023;34:S180–1. https://doi.org/10.1016/j.annonc.2023.04.017.
[34] Pape U-F, Kasper S, Meiler J, et al. Efficacy and Safety of CAP7.1 as Second-Line Treatment for Advanced Biliary Tract Cancers: Data from a Randomised Phase II Study. Cancers (Basel) 2020;12:3149. https://doi.org/10.3390/cancers12113149.

[35] Vogel A, Kasper S, Bitzer M, et al. PICCA study: panitumumab in combination with cisplatin/gemcitabine chemotherapy in KRAS wild-type patients with biliary cancer—a randomised biomarker-driven clinical phase II AIO study. Eur J Cancer 2018;92:11–9. https://doi.org/10.1016/j.ejca.2017.12.028.
[36] Demols A, Borbath I, Van den Eynde M, et al. Regorafenib after failure of gemcitabine and platinum-based chemotherapy for locally advanced/metastatic biliary tumors: REACHIN, a randomized, double-blind, phase II trial. Ann Oncol 2020;31:1169–77. https://doi.org/10.1016/j.annonc.2020.05.018.
[37] Schinzari G, Rossi E, Mambella G, et al. First-line Treatment of Advanced Biliary Ducts Carcinoma: A Randomized Phase II Study Evaluating 5-FU/LV Plus Oxaliplatin (Folfox 4) Versus 5-FU/LV (de Gramont Regimen). Anticancer Res 2017;37:5193–7. https://doi.org/10.21873/anticanres.11942.
[38] Sharma A, Dwary AD, Mohanti BK, et al. Best Supportive Care Compared With Chemotherapy for Unresectable Gall Bladder Cancer: A Randomized Controlled Study. J Clin Oncol 2010;28:4581–6. https://doi.org/10.1200/JCO.2010.29.3605.
[39] Sharma A, Kalyan Mohanti B, Pal Chaudhary S, et al. Modified gemcitabine and oxaliplatin or gemcitabine + cisplatin in unresectable gallbladder cancer: Results of a phase III randomised controlled trial. Eur J Cancer 2019;123:162–70. https://doi.org/10.1016/j.ejca.2019.10.004.
[40] Shirahama T, Muroya D, Matsueda S, et al. A randomized phase II trial of personalized peptide vaccine with low dose cyclophosphamide in biliary tract cancer. Cancer Sci 2017;108:838–45. https://doi.org/10.1111/cas.13193.
[41] Shroff RT, Guthrie KA, Scott AJ, et al. SWOG 1815: A phase III randomized trial of gemcitabine, cisplatin, and nab-paclitaxel versus gemcitabine and cisplatin in newly diagnosed, advanced biliary tract cancers. J Clin Oncol 2023;41:LBA490–LBA490. https://doi.org/10.1200/JCO.2023.41.4_suppl.LBA490.
[42] Kim RD, McDonough S, El-Khoueiry AB, et al. Randomised phase II trial (SWOG S1310) of single agent MEK inhibitor trametinib Versus 5-fluorouracil or capecitabine in refractory advanced biliary cancer. Eur J Cancer 2020;130:219–27. https://doi.org/10.1016/j.ejca.2020.01.026.
[43] Oh D-Y, Ruth He A, Qin S, et al. Durvalumab plus Gemcitabine and Cisplatin in Advanced Biliary Tract Cancer. NEJM Evid 2022;1. https://doi.org/10.1056/EVIDoa2200015.
[44] Javle MM, Oh D-Y, Ikeda M, et al. Varlitinib plus capecitabine in second-line advanced biliary tract cancer: a randomized, phase II study (TreeTopp). ESMO Open 2022;7:100314. https://doi.org/10.1016/j.esmoop.2021.100314.
[45] Ueno M, Morizane C, Furukawa M, et al. A randomized, double-blind, phase II study of oral histone deacetylase inhibitor resminostat plus S-1 versus placebo plus S-1 in biliary tract cancers previously treated with gemcitabine plus platinum-based chemotherapy. Cancer Med 2021;10:2088–99. https://doi.org/10.1002/cam4.3813.
[46] Valle JW, Vogel A, Denlinger CS, et al. Addition of ramucirumab or merestinib to standard first-line chemotherapy for locally advanced or

metastatic biliary tract cancer: a randomised, double-blind, multicentre, phase 2 study. Lancet Oncol 2021;22:1468–82. https://doi.org/10.1016/S1470-2045(21)00409-5.

[47] Leone F, Marino D, Cereda S, et al. Panitumumab in combination with gemcitabine and oxaliplatin does not prolong survival in wild-type *KRAS* advanced biliary tract cancer: A randomized phase 2 trial (Vecti-BIL study). Cancer 2016;122:574–81. https://doi.org/10.1002/cncr.29778.

[48] Yang X, Zhuang L, Dai Y, et al. A prospective, multicenter, phase II trial of albumin-paclitaxel plus cisplatin versus gemcitabine plus cisplatin in first-line treatment of advanced biliary tract tumors. J Clin Oncol 2022;40:4099–4099. https://doi.org/10.1200/JCO.2022.40.16_suppl.4099.

[49] **Zheng Y, Tu X**, Zhao P, et al. A randomised phase II study of second-line XELIRI regimen versus irinotecan monotherapy in advanced biliary tract cancer patients progressed on gemcitabine and cisplatin. Br J Cancer 2018;119:291–5. https://doi.org/10.1038/s41416-018-0138-2.

Supplementary figures

Fig. S1: Assessment of publication bias. (A, C, E, G) Funnel plot including all the studies selected for the analysis for OS (A), PFS (C), DCR (E) and ORR (G). P-values were calculated using Egger's regression test to assess for funnel plot asymmetry. (B, D, F, H) P-curve analysis for OS (B), PFS (D), DCR (F) and ORR (H) showing a significant right-skewedness test with a non-significant flatness test, concluding that evidential value is present.
HR, hazard ratio.

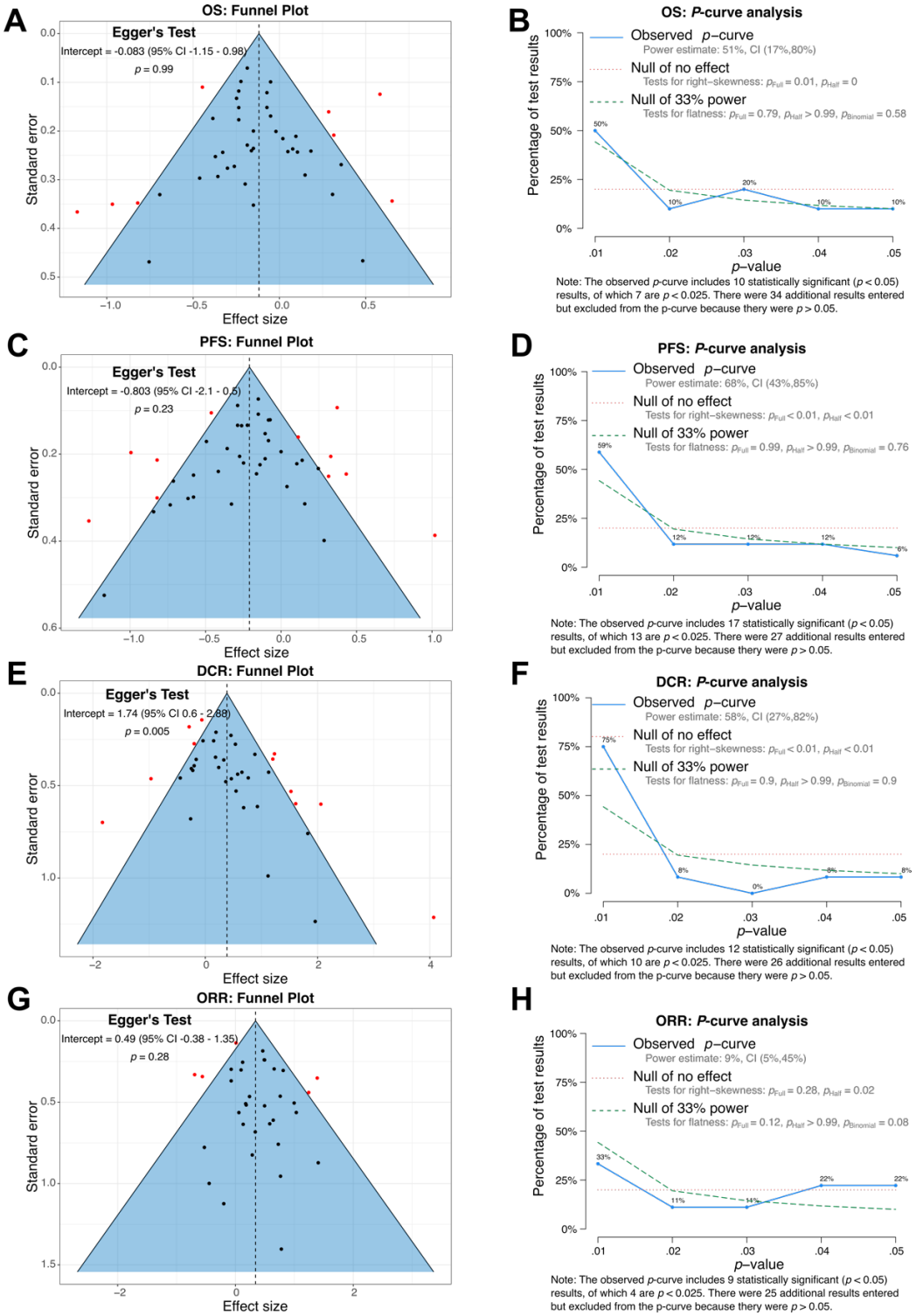


Fig. S2: Cochrane's risk of bias assessment for each trial. Each barplot depicts a domain included in the Cochrane assessment tool. The color represents the risk of bias based on the author's judgement.

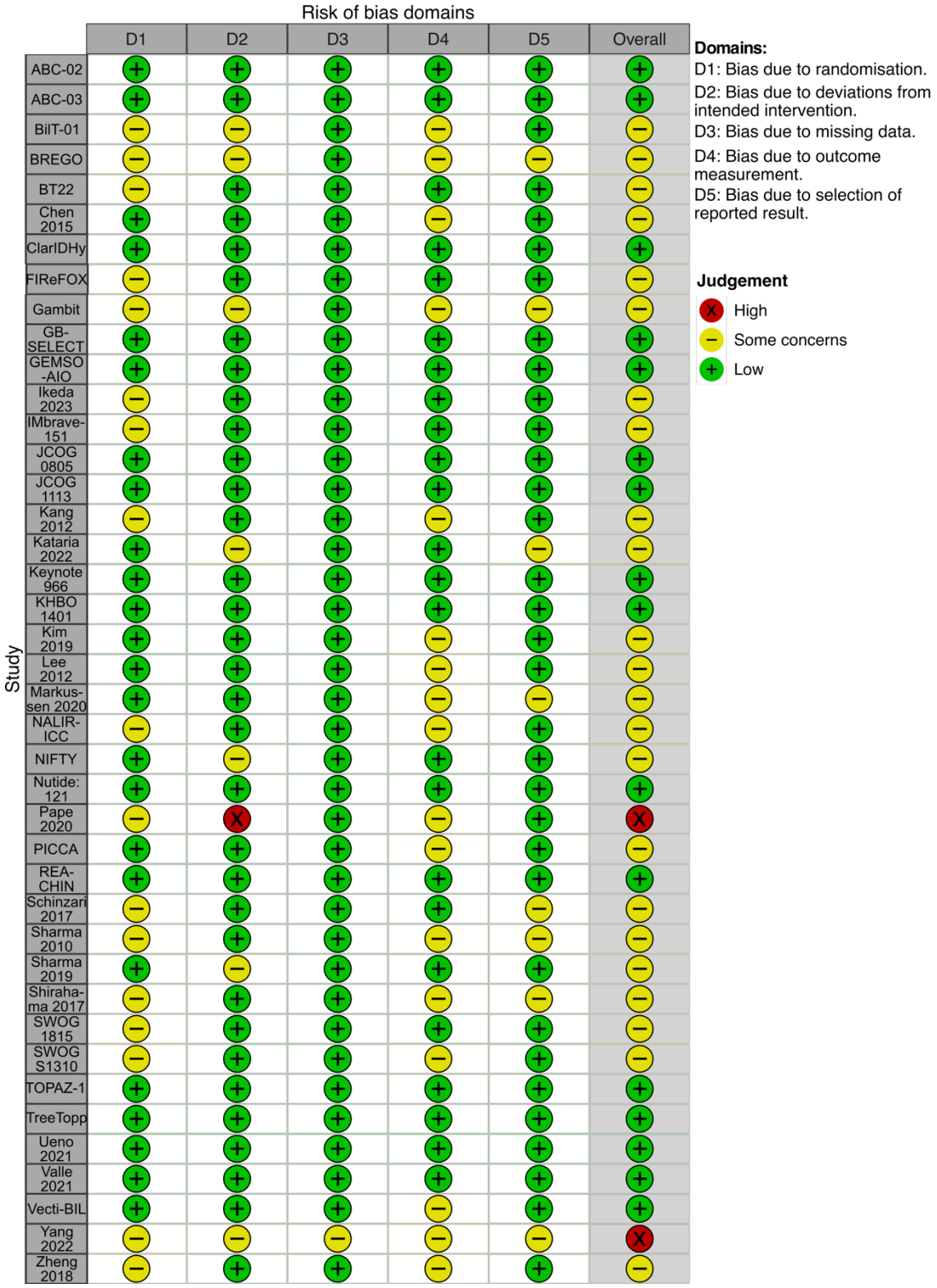


Fig. S3: Cochrane's risk of bias assessment summary. Each barplot depicts a domain included in the Cochrane assessment tool. The color represents the risk of bias based on the author's judgement.

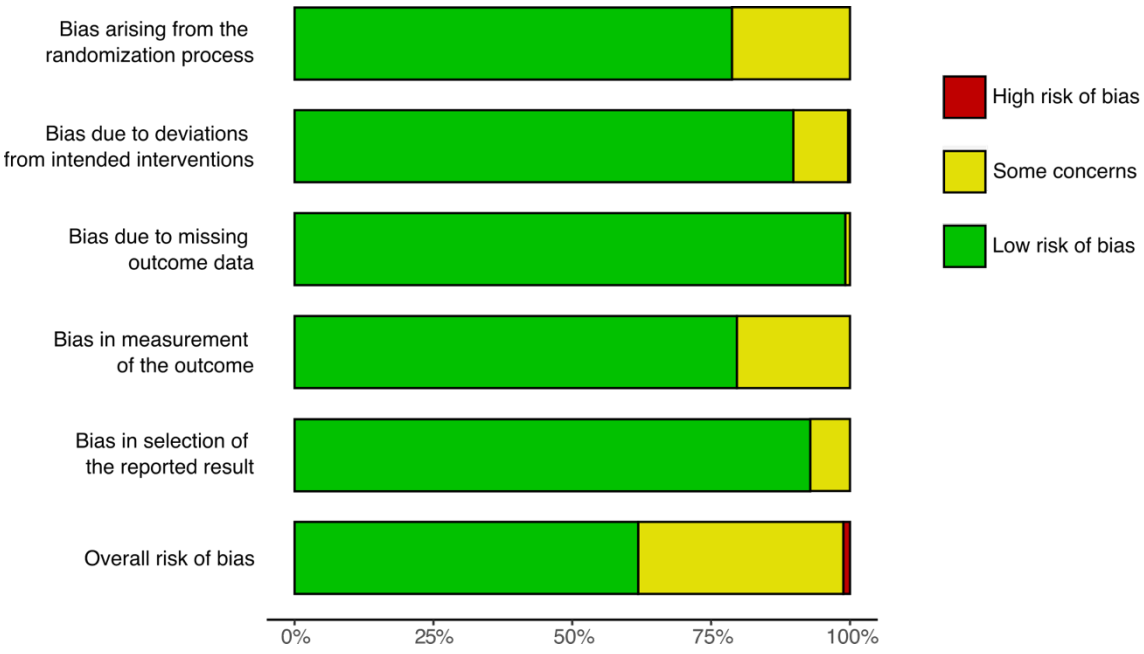


Fig. S4: Delphi quality assessment of each trial. Heatmap assessing nine different Delphi items for each trial. A blue box indicates the trial met the item and a gray box indicates it did not. The bars on the right indicate the Delphi total score.

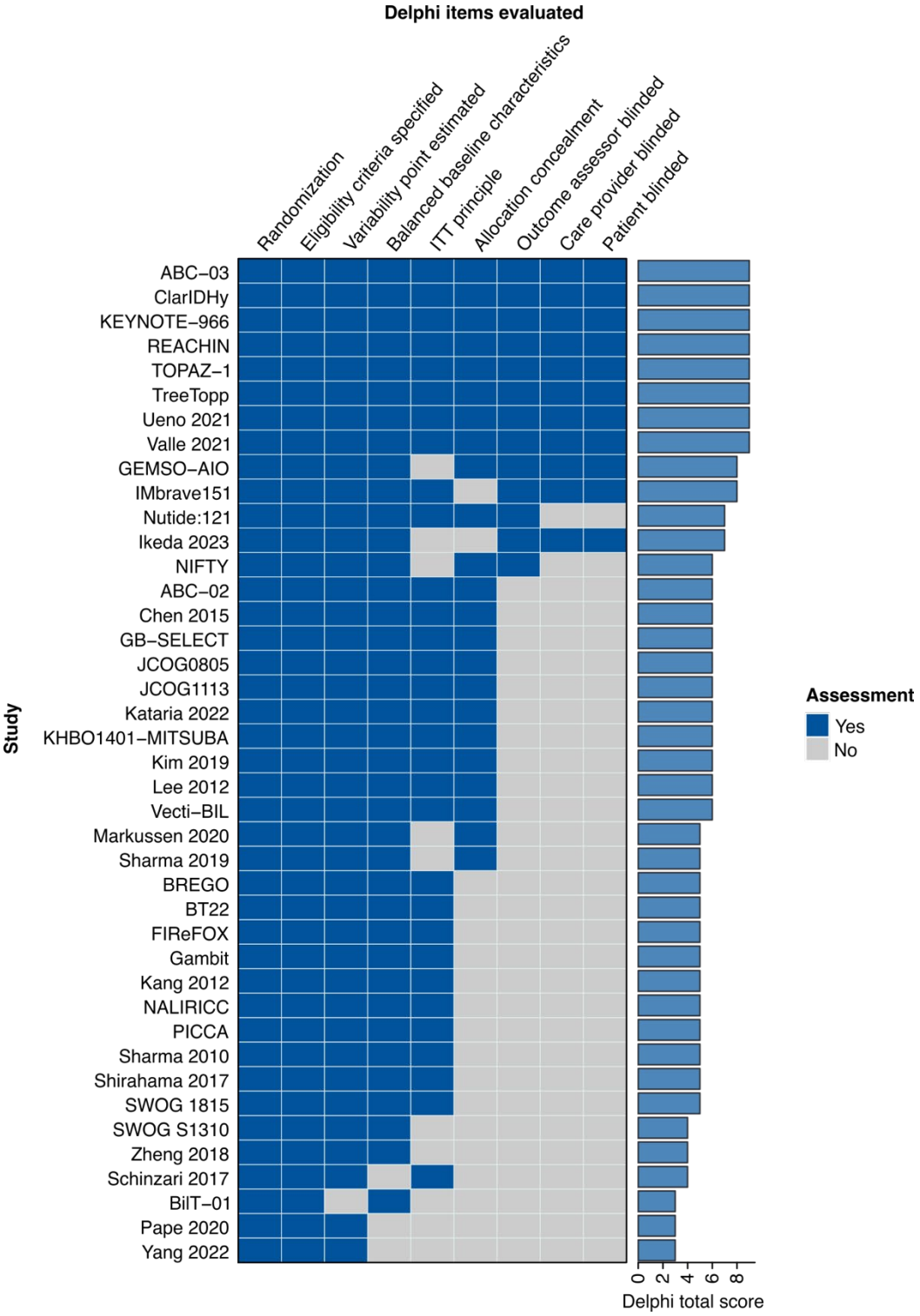


Fig. S5: Bubble plots showing the trial-level correlation for ORR and OS across different subgroups. Every bubble represents a trial, the colour represents the treatment type and the size is proportional to the number of patients included in the trial. The odds ratios are presented in the logarithmic scale. The red lines show the 95% prediction interval for a weight (i.e sample size) of 200. The correlation was estimated by using a linear regression model weighed by trial size. The variation of the weighted treatment effects explained by the model was measured with the coefficient of determination (R^2).
CI, confidence interval; ORR, objective response rate; OS, overall survival; STE, surrogate threshold effect.

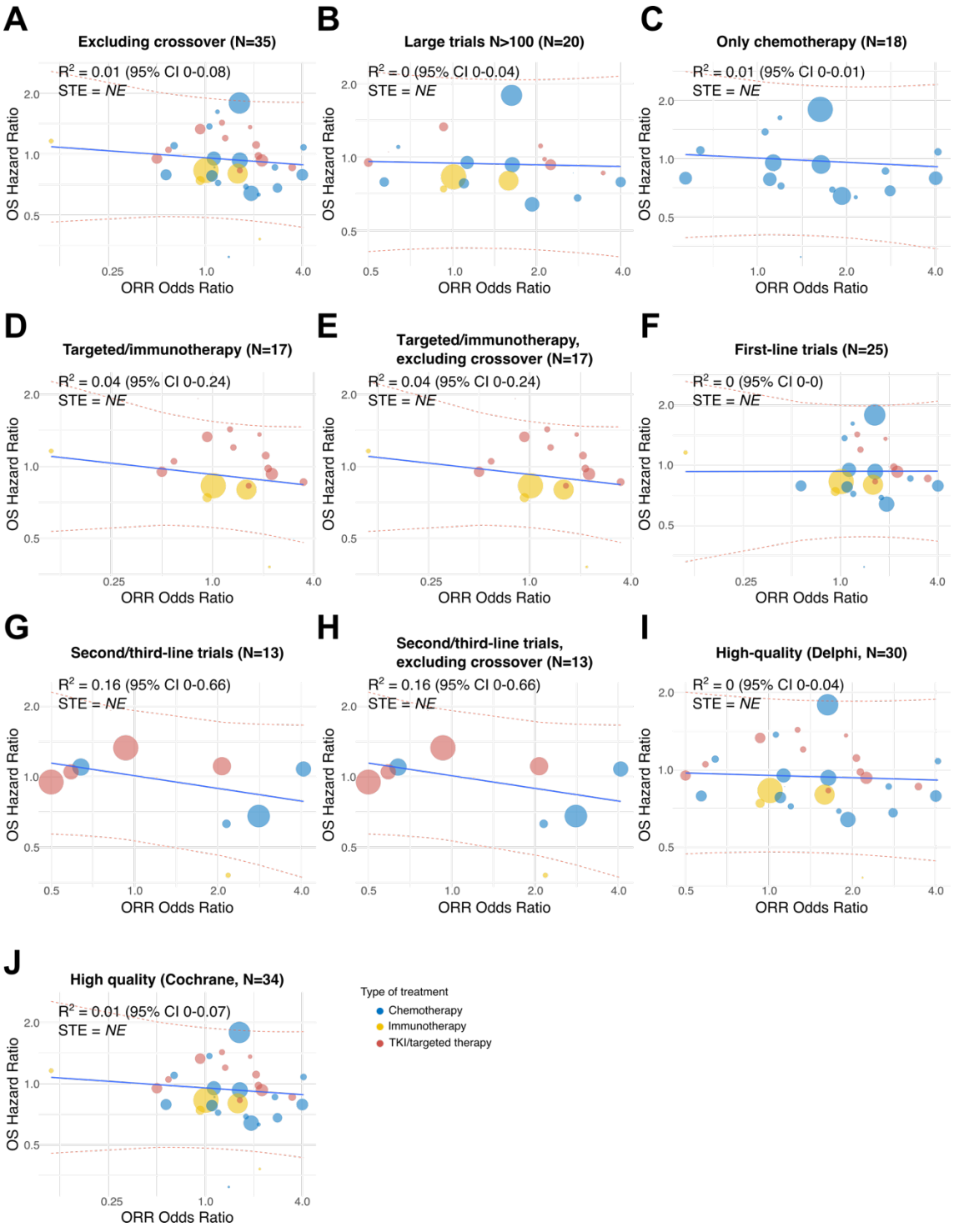


Fig. S6: Bubble plots showing the trial-level correlation for DCR and OS across different subgroups. Every bubble represents a trial, the colour represents the treatment type and the size is proportional to the number of patients included in the trial. The odds ratios are presented in the logarithmic scale. The red lines show the 95% prediction interval for a weight (i.e sample size) of 200. The correlation was estimated by using a linear regression model weighed by trial size. The variation of the weighted treatment effects explained by the model was measured with the coefficient of determination (R^2).
CI, confidence interval; DCR, disease control rate; OS, overall survival; STE, surrogate threshold effect.

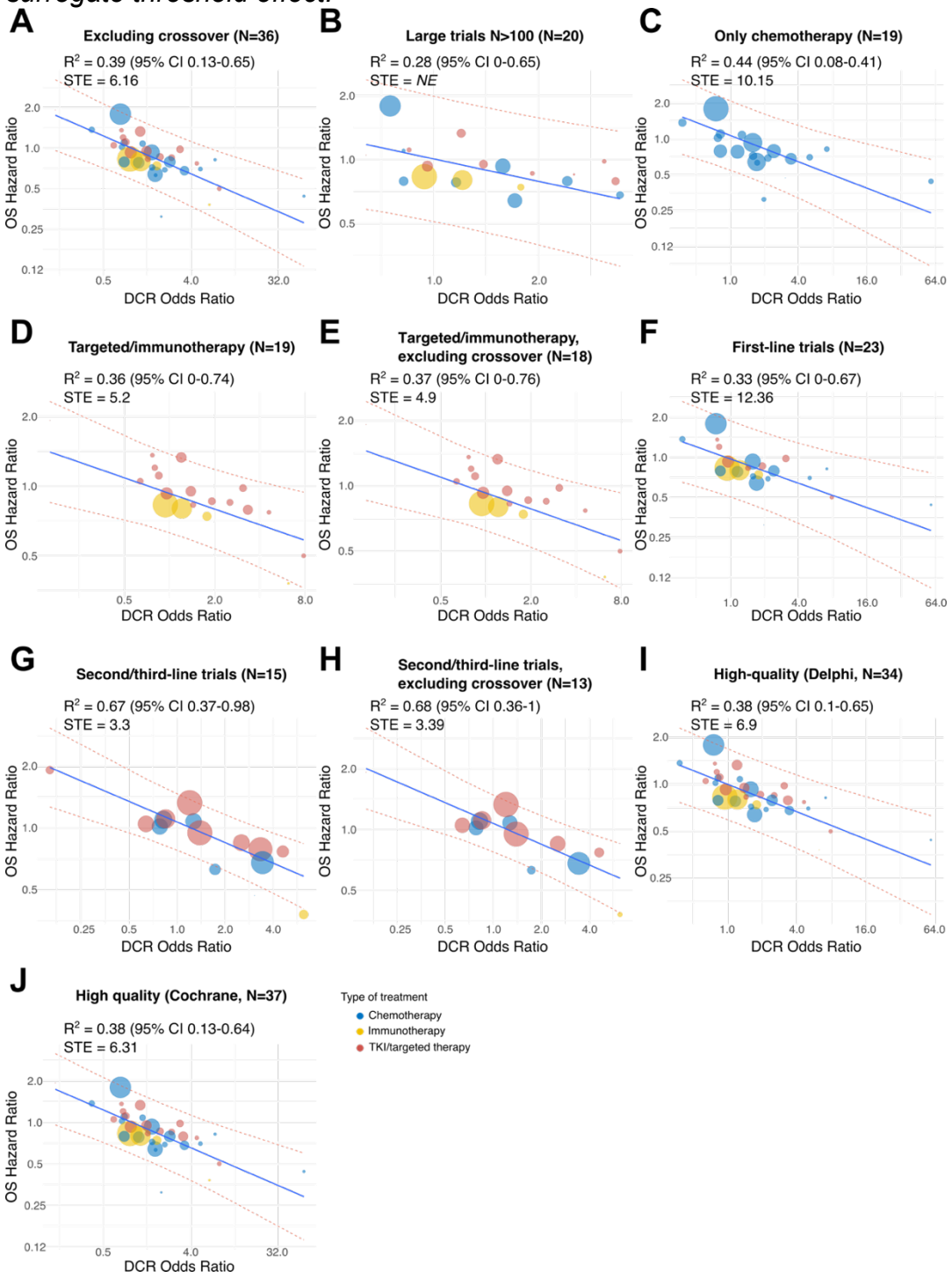


Fig. S7: Sensitivity analysis for PFS based on disease location and stage. Every bubble represents a trial, the colour represents the treatment type and the size is proportional to the number of patients for each category included in the trial. The hazard ratios are presented in the logarithmic scale. The red lines show the 95% prediction interval for a weight (i.e sample size) of 200. The correlation was estimated by using a linear regression model weighed by category size. The variation of the weighted treatment effects explained by the model was measured with the coefficient of determination (R^2).
CI, confidence interval; OS, overall survival; PFS, progression-free survival; STE, surrogate threshold effect.

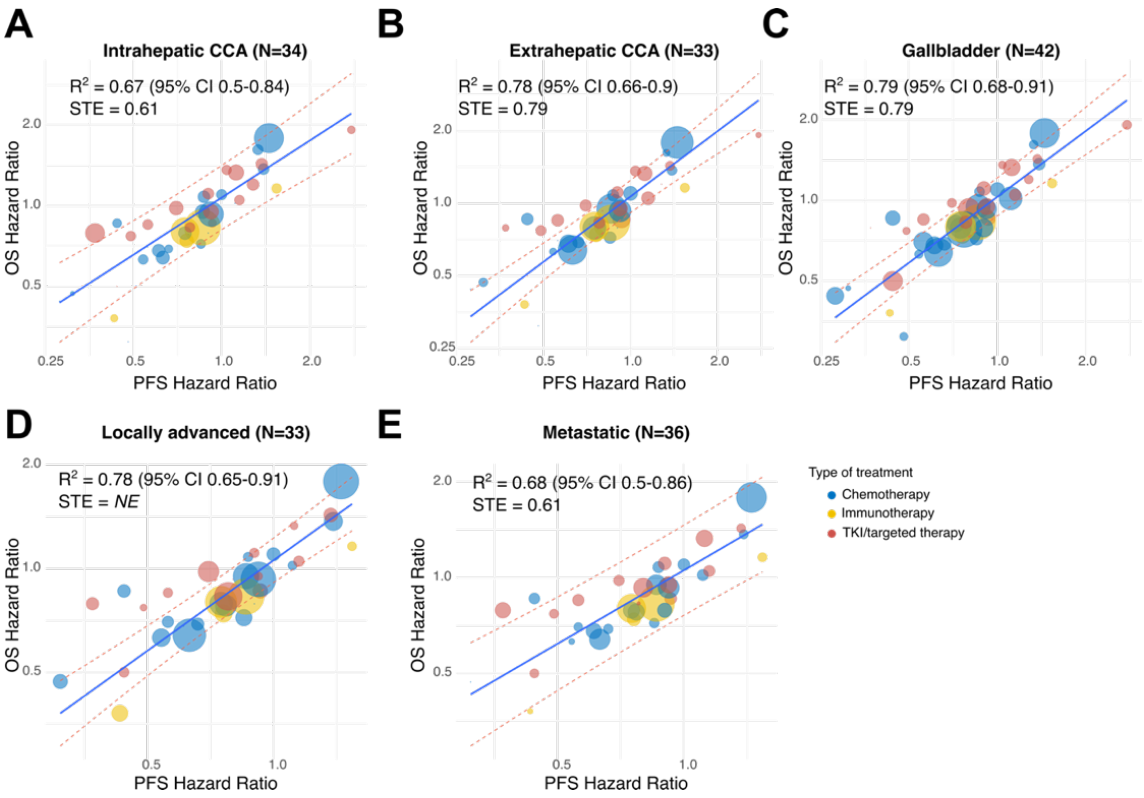


Fig. S8: Sensitivity analysis for ORR based on disease location and stage. Every bubble represents a trial, the colour represents the treatment type and the size is proportional to the number of patients for each category included in the trial. The hazard ratios are presented in the logarithmic scale. The red lines show the 95% prediction interval for a weight (i.e sample size) of 200. The correlation was estimated by using a linear regression model weighed by category size. The variation of the weighted treatment effects explained by the model was measured with the coefficient of determination (R^2).
CI, confidence interval; OS, overall survival; ORR, objective response rate; STE, surrogate threshold effect.

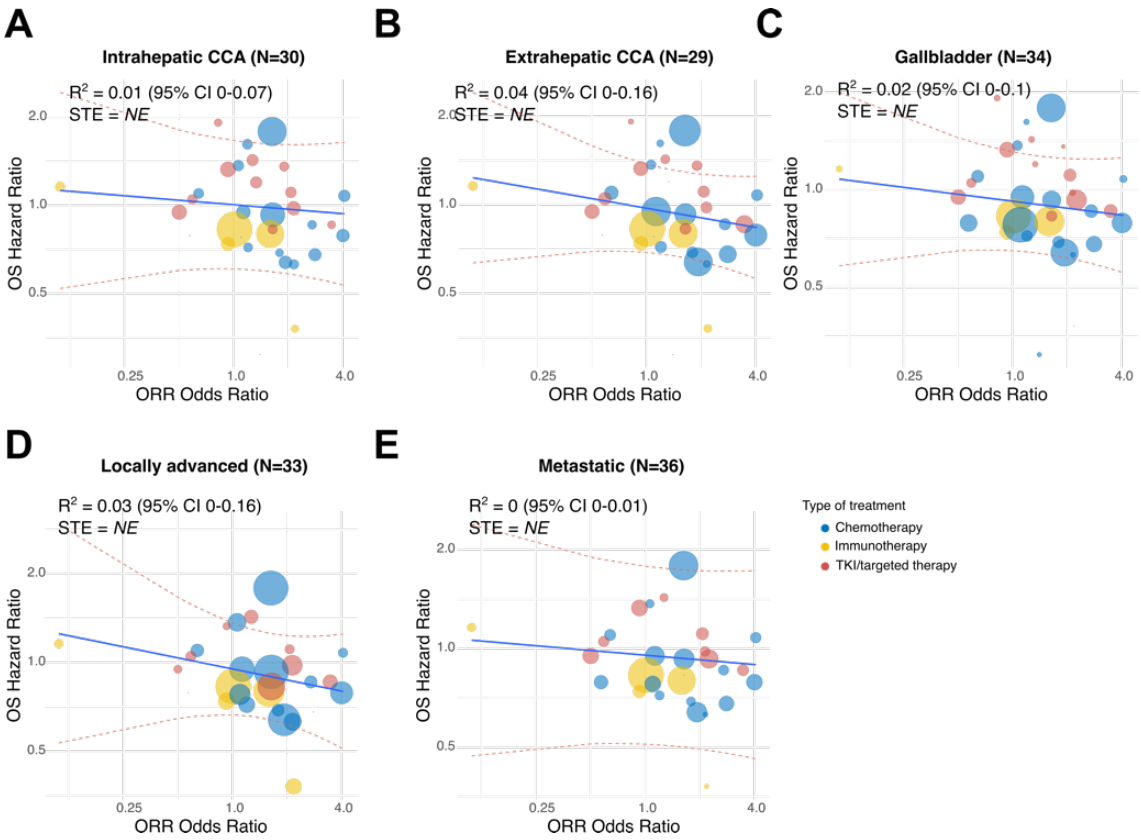


Fig. S9: Sensitivity analysis for DCR based on disease location and stage. Every bubble represents a trial, the colour represents the treatment type and the size is proportional to the number of patients for each category included in the trial. The hazard ratios are presented in the logarithmic scale. The red lines show the 95% prediction interval for a weight (i.e sample size) of 200. The correlation was estimated by using a linear regression model weighed by category size. The variation of the weighted treatment effects explained by the model was measured with the coefficient of determination (R^2).
CI, confidence interval; OS, overall survival; DCR, disease control rate; STE, surrogate threshold effect.

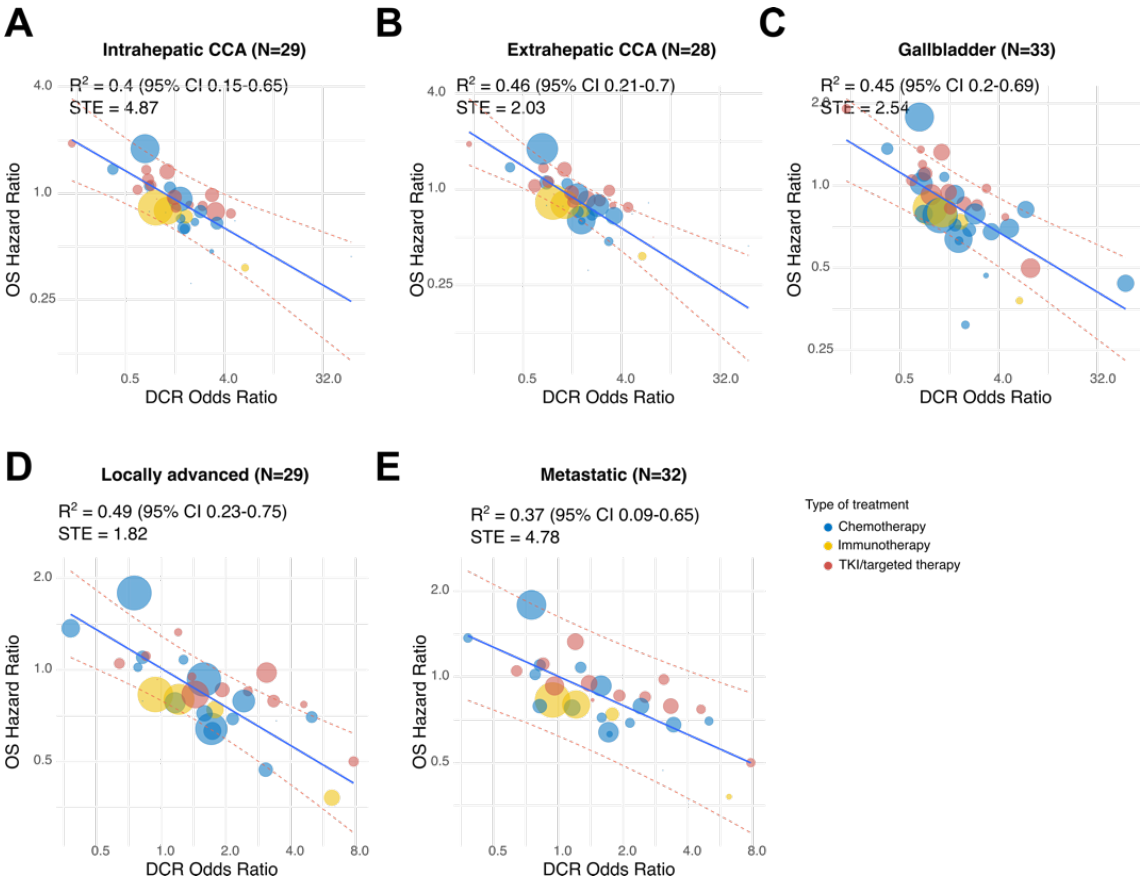


Fig. S10: Leave-one-out cross validation for the correlation analysis of PFS and OS. (A) The red dots are the predicted HR for OS, the black dots show the reported HR for OS and the black lines represent the 95% intervals of HR for OS. (B) Histogram showing the distribution of the R^2 values for each of the models generated after excluding a single trial.
HR, hazard ratio; OS, overall survival.

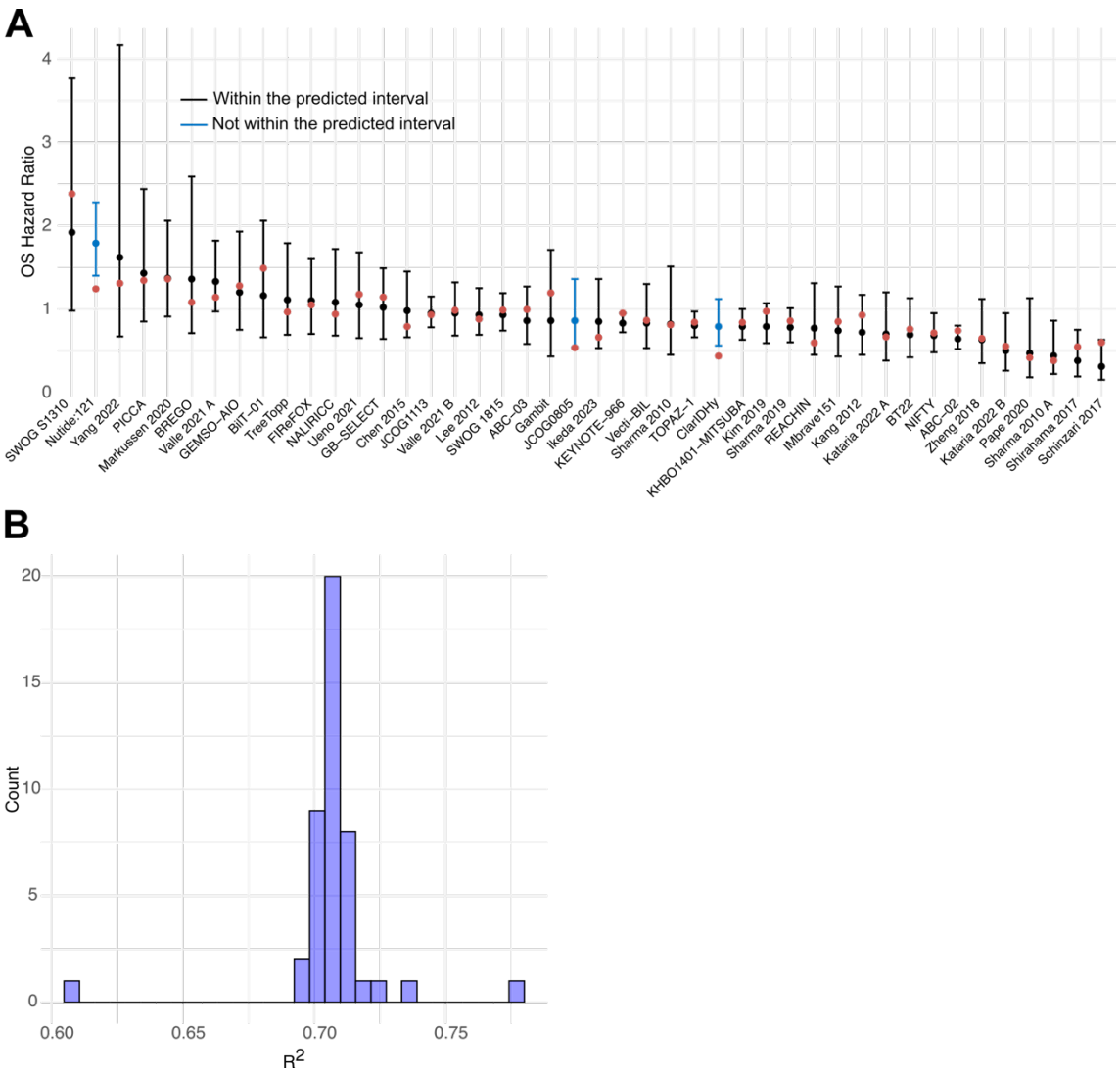
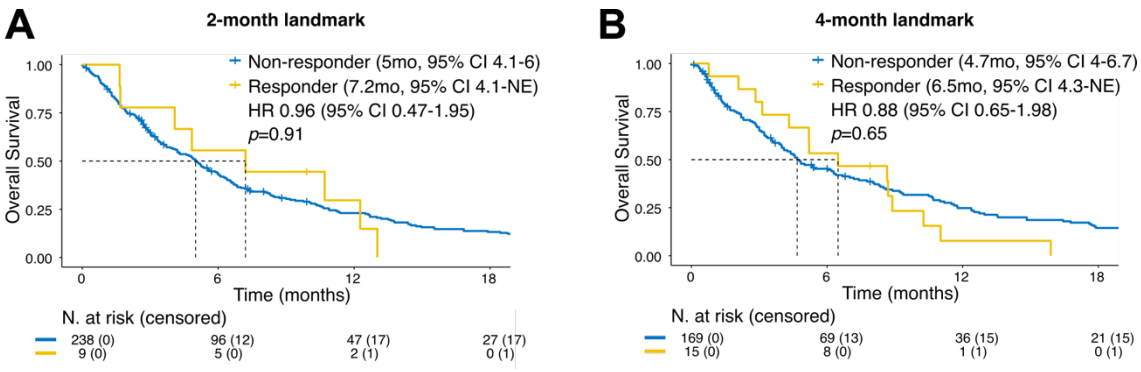


Fig. S11: Impact of response on survival in patients treated with second-line chemotherapy. Kaplan-Meier estimates of overall survival between responders and nonresponders (Condition 2) who were alive and had achieved response at 2 months (A) and 4 months (B). The hazard ratios (HR) were estimated by applying a Cox regression model and the p-values obtained from the Cox regression model.



PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	8-9
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	11-12
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	12
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	14-15
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	14
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Table S1
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	14
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	15
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	15
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	15
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	15
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	15
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	14-15
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	16
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	16
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	16
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	16
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	16
Reporting bias	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	15

Section and Topic	Item #	Checklist item	Location where item is reported
assessment			
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	15
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	18
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	18
Study characteristics	17	Cite each included study and present its characteristics.	Table 2, Table S3
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Fig.S2-4
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Fig. 2
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	18-19
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	18-19
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	18.19, Fig. 2-3, Fig. S5-6
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	18.19, Fig. 2, Fig. S5-9
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	18-19, Fig. 1
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Fig. 2
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	21-23
	23b	Discuss any limitations of the evidence included in the review.	24
	23c	Discuss any limitations of the review processes used.	24
	23d	Discuss implications of the results for practice, policy, and future research.	23-25
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	14
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	14
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	14

Section and Topic	Item #	Checklist item	Location where item is reported
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	6
Competing interests	26	Declare any competing interests of review authors.	4-6
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Supp Mat

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71.