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**HIGHLIGHTS**

- New effective drugs for biliary tract cancer (BTC) are emerging from genomic analyses
- Genomic-based therapies are directed toward small subsets of patients
- We found a strong correlation between overall response rate (ORR) and overall survival (OS)
- A 10%-ORR gain in second line translated into a 4.7-month benefit in OS
- This should be considered when designing new clinical trials for pretreated advanced BTC

**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**

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**List of Abbreviations**

ORR	Overall Response Rate
PFS	Progression-Free Survival
OS	Overall Survival
BTC	Biliary Tract Cancer
iCCA	Intrahepatic Cholangiocarcinoma
eCCA	Extrahepatic Cholangiocarcinoma
FGFR	Fibroblast Growth Factor Receptor
IDH	Isocitrate Dehydrogenase
HRQoL	Health-Related Quality of Life
CR	Complete Response
RECIST	Response Evaluation Criteria in Solid Tumors
CI	Confidence Interval
PS	Performance Status

**ABSTRACT**

**Background:** Overall response rate (ORR) and progression-free survival (PFS) are commonly used as endpoints for phase II trials. However, the ultimate goal is to bring survival benefit for the patients. We aimed to assess the correlation between ORR, median PFS and overall survival (OS) using aggregated data from a systematic review of second-line systemic therapies in advanced biliary tract cancer (BTC) patients.

**Methods:** Clinical trials were identified using Medline database. Studies only enrolling patients with gallbladder cancer were not included. Searches were last updated on April 2020. Eligible studies reported OS, PFS and/or ORR data for BTC patients receiving second-line systemic chemotherapy. Pearson weighted correlation was estimated between OS and ORR and between median OS and PFS.

**Results:** Seventeen studies (N= 912 patients) were selected. There was a strong correlation between median OS/ORR in the overall analysis ( $r=0.85$ ;  $P<0.0001$ ), both for trials with chemotherapy ( $r=0.90$ ;  $P=0.0152$ ) and targeted therapy ( $r=0.84$ ;  $P=0.0006$ ). In contrast, the correlation between median OS/PFS, albeit significant in the overall analysis ( $r=0.80$ ;  $P<0.0001$ ), remained significant only for targeted therapies in the sensitivity analysis ( $r=0.83$ ;  $P=0.0009$ ).

**Conclusions:** ORR seems to be a more interesting intermediate endpoint in BTC in second line for both chemotherapy and targeted therapies, while PFS may be relevant only for targeted therapy trials. Further well-designed studies for surrogacy evaluation should be performed to confirm this observation.

### **Key words**

Chemotherapy, cholangiocarcinoma, endpoint, correlation, targeted therapy

### **Lay Summary**

New effective drugs for biliary tract cancer (BTC) are emerging from genomic analyses. Genomic-based therapies are directed toward small subsets of patients.

We found a strong correlation between overall response rate (ORR) and median overall survival (OS).

This could be informative when designing new clinical trials for pretreated advanced BTC patients.

## **INTRODUCTION**

'Biliary tract cancer' (BTC) is a collective term encompassing a heterogeneous group of epithelial neoplasms(1). Although they are the second leading cause of primary liver cancer after hepatocellular carcinoma, BTCs are rare tumours in most countries (apart from endemic areas in Asia) with less than six new cases per 100,000 people each year (10,000 and 12,000 new cases/year in Europe and the United States, respectively) (2,3). They are classified into three main subtypes based on their anatomical origin, each harboring specific epidemiological, clinical, molecular, and therapeutic features: intrahepatic cholangiocarcinoma (iCCA); extrahepatic cholangiocarcinoma (eCCA), which includes perihilar cholangiocarcinoma and distal cholangiocarcinoma; and gallbladder carcinoma (1). Overall, BTCs display a poor prognosis, with a five-year overall survival (OS) rate (all stages) below 20% (2,3).

Approximately 70% of BTCs cases are diagnosed at an advanced, non-resectable stage (4). In the first-line setting, the standard chemotherapy regimen is the cisplatin plus gemcitabine doublet (CISGEM regimen) (4). Studies of this regimen have demonstrated superiority over single-agent gemcitabine (ABC-02 and BT-22

randomized studies), with overall response rates (ORR) of 19.5% (95% confidence interval [CI]: 8.8-34.9) to 26.1%, median progression-free survival (PFS) of 5.8 months (95% CI: 4.1-8.2) to 8.0 months (95% CI: 6.6-8.6), and median OS of 11.2 months (95% CI: 9.1-12.5) to 11.7 months (95% CI: 9.5-14.3) (5–7). After failure of first-line treatment, chemotherapy may be offered in the second-line setting but is associated with low ORR (8% to 12%) and short median OS (7.2 months) (8,9). The FOLFOX doublet regimen (fluorouracil/folinic acid plus oxaliplatin) recently demonstrated superiority over best supportive care alone in the ABC-06 phase III study but with limited OS (median OS gain <1 month) benefit and ORR (5%) (10), and the question of the best regimen in second-line is still open (11). Hence, there is an urgent need to develop alternate therapies with higher activity in BTC.

Recently, a better understanding of the molecular biology of BTCs and their genomic and transcriptomic segmentation has led to the emergence of new therapeutic approaches such as inhibitors targeting fibroblast growth factor receptor gene (*FGFR*) fusions (including pemigatinib (12)) and isocitrate dehydrogenase (*IDH*) gene mutations (ivosidenib (13)). Developing treatments that target rare molecular alterations in a rare condition comes with high challenges for the clinical research and practice due to the very low number of patients and the difficulty to identify them for enrollment. Hence, improving the predictability of phase II studies, *i.e.* identifying robust intermediate endpoints in phase II to predict clinical benefit and success in phase III, is an important issue in rare diseases such as BTCs.

ORR and PFS are commonly used as an endpoint for phase II trials. While ORR and PFS are relevant endpoints to use in trials assessing the level of activity of new drugs in malignant diseases, the ultimate goal is to bring benefit for the patients. OS and health-related quality of life (HRQoL), as they are patient-related, are considered as the best endpoints to capture such a benefit. Therefore, it is of interest to estimate the extent to which a gain in terms of ORR or PFS translates in a gain in OS or HRQoL.

In this work, we aimed to assess the correlation between ORR, median PFS and OS using aggregated data from published clinical trials selected by a systematic review for systemic therapies in advanced BTC patients in the second-line setting.

## **MATERIAL AND METHODS**

### ***Identification and selection of publications***

We re-used a recent systemic literature review (21th of April 2020, Medline, EMBASE, Cochrane, Medline-in-process/Pubmed) done by BresMed Health Solutions (not published) aiming at identifying studies that enrolled patients with advanced, metastatic, or surgically unresectable CCA/BTCs (iCCA, eCCA, and/or gallbladder carcinoma) for whom previous therapy had failed (see Appendix for search strategies). Studies only enrolling patients with gallbladder cancer were not included in the systematic literature review. A systematic selection of the relevant studies based on the inclusion and exclusion criteria is presented in Appendix.

Only prospective clinical trials were selected for the endpoint correlation. Assessments of ORR and PFS from retrospective studies and case reports were considered insufficiently reliable, based on a previously published research (8). Only studies evaluating systemic treatments (i.e. exclusion of locoregional therapies) were included. Phase I trials were excluded due to the specificities of patients enrolled in such trials and because their primary objective is usually the safety and not the efficacy. Studies without reported median OS value were also excluded because they were not usable for the endpoint correlation.

### ***Quality control of the study selection and data***

Several controls were carried out. First, a review of the publication was done when the study design was unclear in order to validate its inclusion or exclusion. Similarly, a review of the publication was performed when more details were requested for analyses by the statistician. Finally, all data kept for the endpoint correlation were checked in the original full-text publications to ensure their accuracy.

### ***Endpoints***

Data extraction was performed for all the clinical endpoints (ORR, PFS, OS). OS was defined as the time from treatment initiation (or randomization) to death. PFS was defined as the time from treatment initiation (or randomization) to disease progression or death. ORR was defined as the proportion of patients who achieved a complete response (CR; disappearance of all lesions) or partial response (PR; decrease of at least 30% in the

sum of the longest diameter of the target lesions) according to the Response Evaluation Criteria in Solid Tumors (RECIST).

### ***Statistical analysis***

Weighted means and 95% confidence intervals (CIs) were calculated for median OS, PFS and ORR according to the number of patients evaluable in the studies. If several dates of data cut-off were available, the most recent was chosen. The evaluable population for efficacy criteria was privileged. When the number of evaluable patients differed between survival and ORR analysis, a conservative approach was adopted and the lowest number was chosen. Pearson weighted correlation was estimated between median OS and ORR and between OS and median PFS.

All analyses were performed using SAS version 9.4 (SAS Institute, Cary NC) and R software version 3.6.3 (R Development Core Team, Vienna, Austria; <http://www.r-project.org>).

### ***Sensitivity analyses***

A sensitivity analysis was conducted according to the treatment administered in the trials. Correlations between median OS and ORR and OS and median PFS were estimated in the following subgroups: trials of chemotherapy alone, trials of targeted therapy alone, trials of both chemotherapy and targeted therapy.

## RESULTS

### *Studies included in the analysis and data*

Figure 1 summarizes the flowchart for selection of eligible studies. From 108 studies including patients with advanced (metastatic or unresectable) BTC who had failed previous systemic treatment, 5 were randomized trials and 103 were non-randomized trials. Among the 5 randomized trials, one was excluded because no systemic treatment was involved. Among the 103 non-randomized studies, 90 were excluded because their design did not meet eligibility criteria for our study (77 studies), median OS was not reported (10 studies), median PFS and ORR were not reported (2 studies), or because no systemic treatment was involved (1 study). Overall, 17 studies were selected for the endpoint correlation analysis: 10 assessing targeted therapy, 5 assessing chemotherapy, and 2 assessing a combination of chemotherapy and targeted therapy [Table 1].

### *Correlation between median OS and ORR*

Correlation between median OS and ORR was assessed; results are summarized in Table 2. When all the studies were included for the weighted correlation index determination, the correlation between median OS and ORR was statistically significant ( $r=0.85$ ;  $P<0.0001$ ) [Figure 2A]. This significance was maintained in the sensitivity analyses for the chemotherapy subgroup ( $r=0.90$ ;  $P=0.0152$ ) [Figure 2B] and the targeted therapy subgroup ( $r=0.84$ ;  $P=0.0006$ ) [Figure 2C].

### *Correlation between median OS and PFS*

In the overall analysis, the correlation between median OS and PFS was also statistically significant ( $r=0.80$ ;  $P<0.0001$ ) [Figure 3A]. However, in the sensitivity analyses, the correlation was significant for targeted therapy ( $r=0.83$ ;  $P=0.0009$ ) [Table 2 and Figure 3C] but not for chemotherapy [Table 2 and Figure 3B].

## DISCUSSION

We found a strong correlation (Pearson correlation coefficient: 0.85) between median OS and ORR in clinical trials assessing second-line systemic treatment in patients with BTC, either with

chemotherapy or targeted therapy. In contrast, the correlation between median OS and PFS, albeit significant in the overall analysis, remained significant only for targeted therapies in the sensitivity analysis. Based on these findings, ORR seems to be a more interesting intermediate endpoint in BTC in second line for both chemotherapy and targeted therapies, while PFS may be relevant only for targeted therapy trials. Further well-designed studies for surrogacy evaluation should be performed to confirm this observation.

In clinical trials in oncology, OS is the most robust and relevant primary endpoint so that it is frequently used in the evaluation of new therapies, particularly in phase III trials. Other endpoints such as ORR or PFS are preferred in phase II trials. However, these endpoints focus on the tumor rather than the patient and are thus considered less robust to evaluate the patient's benefit. Consequently, there is an obvious interest in assessing the association of tumor response with patient survival. The characterization of a surrogacy of alternate endpoint for OS is the highest level of demonstration for that purpose. A so-called "surrogate endpoint" predicts the primary endpoint (e.g. OS) under the conditions that it is reproducibly and reliably measurable, that the treatment has a significant effect on both the primary and surrogate endpoints, and that the effect on the surrogate endpoint captures the entire treatment effect on the primary endpoint. An example of surrogacy is 3-year disease-free survival predicting for 5-year OS in resected colorectal cancer as demonstrated by Sargent *et al.* (14). In practice, the demonstration of surrogacy should be studied within and between trials and requires to run the analysis from patient-level data. Moreover, the lack of randomized studies in this context does not allow to used Hazard Ratios. Despite the fact that a correlation is necessary but not sufficient to establish the surrogacy, when individual data and randomized trial are not available, a "correlation" approach between two judgement criteria based on aggregated data is the unique information that can be provided; despite its limitations, this approach could be informative.

In a systematic review published in 2014, Lamarca *et al.* (8) analyzed ORR and PFS as intermediate endpoints in trials published through 2013 that evaluated systemic second-line



therapies in patients with advanced BTC. Twenty-five studies (phase II and retrospective studies) were available for OS and PFS/ORR correlation. When all the studies included in the statistical analysis were included for the weighted correlation index determination, the strongest correlation was shown between median OS and PFS ( $r=0.54$ ;  $P=0.01$ ). This significance was maintained in the phase II trial subgroup ( $r=0.61$ ;  $P=0.04$ ). Correlation between median OS and ORR was significant only in the phase II trial subgroup ( $r=0.62$ ;  $P=0.03$ ), showing weaker correlation when all the studies were included ( $r=0.34$ ;  $P=0.16$ ).

Here, we used a similar approach including more recent, randomized or non-randomized studies with median OS, ORR and median PFS data, evaluating second-line or later treatment line in advanced BTC. Overall, our results, obtained from an updated analysis and focusing on data from phase II trials (we excluded retrospective studies, phase I trials or unpublished studies where the measures of response and survival are likely to be less accurate), are consistent with and confirm the findings reported by Lamarca *et al.* (8) in the phase II subgroup. We found a higher correlation coefficient and a statistically significant p-value, between ORR and median OS ( $r=0.85$ ;  $p<0.0001$ ) as well as between median PFS and OS ( $r=0.80$ ;  $p<0.0001$ ). These results are highlighted through scatter plot representations between ORR and median OS and between median PFS and ORR, showing a positive linear alignment of the points towards a positive relationship between the two variables. Interestingly, our analysis included targeted therapies that recently emerged like FGFR inhibitors and IDH inhibitors. A scatter plot with stronger dispersion both on the abscissa (median OS) and ordinate (ORR, median PFS) axes may explain why the level of correlation is better here than in previous work.

The ORR is an intermediate criterion of the efficacy of cancer therapies that allows a direct measure of their activity. It has the advantage of estimating the therapeutic contribution of a treatment for one individual patient soon after the first dose given. Above all, ORR is not influenced by subsequent treatments received or by the life expectancy of patients (*i.e.* by potential co-existing prognostic factors). Thus, the lack of control arm is less an issue when using ORR (particularly, when the comparator would be a placebo, as no response would be expected in this arm) than when using

PFS or OS. The clinical relevance of ORR is assessed through its magnitude, but also through the duration of that response and the percentage of CR. The relevance of this endpoint also depends on the clinical context (15). In the context of BTC, a tumor response can bring a direct clinical benefit for a patient if the tumor reduction can avoid or delay complications due to biliary or vascular obstruction in relation with an increase in the size of the tumor (especially with regards to the Poiseuille's law, where parietal tension is proportional to the diameter at the power 4), and thereby may account for the existing correlation between ORR and OS. The outcomes from patients receiving placebo and included in one of our sensitivity analyses are actually very low both in terms of ORR and OS. This is also observed with treatments providing limited response rates.

Our study has several limitations. First, the analyses were based on published aggregated data and not on individual data, therefore only correlations between trials were analyzed and not inter-individual correlations, so we could not establish surrogacy between the endpoints. Moreover, no randomized trials with a common anchor are available and the number of studies and the number of patients enrolled into each were low.

However, we demonstrated significant correlations between median OS and ORR/PFS, which can be of interest for designing future clinical trials and building statistical hypothesis. Hence, based on our Figures, one can infer the expected OS benefit resulting from a given ORR or PFS gain for systemic drugs used in second or later lines (for instance, a 10%-ORR gain translated into a 4.7-month benefit in OS and a 2-month PFS gain translated into a 7.4-month benefit in OS). Overall, these findings suggest the interest of tumor-related endpoints, i.e. ORR (for chemotherapy and targeted therapies) and PFS (for targeted therapies only), as intermediate endpoints to predict an OS benefit in the second-line setting for advanced BTCs. Of note, these findings may not apply to immune therapies, which were not included in our analyses and would warrant specific studies.

Moreover, we previously showed that BTC patients display high heterogeneity in terms of survival, particularly depending on their performance status (PS), and that selection criteria in clinical trials (e.g. restriction to PS 0-1) may induce a selection bias toward more favorable survival (16). These

results strongly support the use of at least non-comparative randomized phase II design including a control arm to verify the calibration of the assumptions made in the experimental arm and to provide common anchor for indirect comparisons or surrogacy studies.

Overall, our works tries to offer a unifying approach for designing futures second-line trials in BTCs. The considerable heterogeneity of treatments and the small numbers of patients in most trials available for this analysis may impact the robustness of our results. Chemotherapy strongly differs from most targeted therapies, and among the latter, substantial differences are also observed between tyrosine kinase inhibitors such as regorafenib with usual poor ORR in unselected patients, or new targeted therapies such as FGR or IDH1 inhibitors that are indicated in molecularly selected cholangiocarcinoma subgroups. Moreover, we do not have data concerning immunotherapy which is emerging. Our work constitutes a first step but should be confirmed by further prospective studies to better explore whether PFS or ORR is the most tightly correlated with OS, particularly for targeted therapies.

Taken together, these data suggest that the “optimal” design for a trial of second-line chemotherapy or targeted therapy in BTC is a randomized study with, if OS is deemed not appropriate, ORR as primary endpoint for chemotherapy and ORR or PFS for targeted therapies.

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#### ***Declaration of Interest statement***

CN: honoraria/consultancy: AAA/Novartis, Amgen, AstraZeneca, Baxter, Bristol-Myers Squibb, Fresenius Kabi, Incyte Biosciences, Merck, MSD, Mylan/Viatris, Nutricia, Pierre Fabre, Roche, Sanofi, Servier. Research funding: Roche. Clinical trials: OSE Immunotherapeutics, AstraZeneca, Bristol-Myers Squibb, Fresenius Kabi, Nutricia. Support for attending congress: Merck, MSD, Mylan/Viatris, OSE Immunotherapeutics.

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DV: honoraria/consultancy: CellProthera, HalioDX, FSK, Gercor, Incyte Biosciences

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### **Appendix A**

Study selection criteria in the Primary Systematic Literature Review

## **A. Search Strategies**

### **Clinical Systematic Literature Review in CCA - 09 November 2018**

**Table 1. Databases searched**

S. No.	Database/website	Provider/Interface	Filter used for study design	Coverage	Hits
1.	Medline & EMBASE	EMBASE.com	RCT, nRCT and observational studies	No limit	6,482
2.	Cochrane	onlinelibrary.wiley.com	-	No limit	813
3.	Medline-in-process	Pubmed.com	-	No limit	156
4.	Total				7,451

### **1. Medline and Embase: Embase.com**

#### **Medline and Embase search strategy. 09<sup>th</sup> November 2018**

Sr. No.	Query	Hits
1.	'bile duct carcinoma'/exp OR 'bile duct carcinoma'/syn OR 'bile duct carcinoma' OR 'bile duct cancer' OR cholangiocarcinoma OR 'biliary tract cancer'/syn OR 'biliary tract cancer'/exp OR 'biliary tract cancer' OR 'biliary tract carcinoma'	39,381
2.	cholangiocarcinom*	17,772
3.	('bile duct':ab,ti OR 'bile tract':ab,ti OR 'biliary tract':ab,ti) AND (cancer*:ab,ti OR carcinom*:ab,ti OR malignan*:ab,ti OR neoplasm*:ab,ti OR tumor*:ab,ti OR tumour*:ab,ti)	20,132
4.	((('bile duct' OR 'bile tract' OR 'biliary tract') NEAR/2 (cancer* OR carcinom* OR malignan* OR neoplasm* OR tumor* OR tumour*)):ab,ti	7,040

5.	#1 OR #2 OR #3 OR #4	49,375
6.	'stage 3':ab,ti OR 'stage iii':ab,ti OR 'stage 3a':ab,ti OR 'stage iii':ab,ti OR 'stage 3b':ab,ti OR 'stage iiib':ab,ti OR 'stage3':ab,ti OR 'stageiii':ab,ti OR 'stage 4':ab,ti OR 'stage iv':ab,ti OR 'stage4':ab,ti OR 'stageiv':ab,ti OR metastatic OR metasta*:ab,ti OR advanced OR advanc*:ab,ti OR unresect*:ab,ti OR relap*:ab,ti OR resist*:ab,ti OR refract*:ab,ti OR ((late* NEAR/2 stag*):ab,ti) OR nonresect*:ab,ti OR ((non NEXT/1 resect*):ab,ti) OR inoperable:ab,ti OR 'locally advanced':ab,ti OR 'locally-advanced':ab,ti OR local*:ab,ti OR ((ineligible OR 'in eligible' OR unfit OR 'un fit' OR 'un-fit' OR unsuitable OR 'not amenable' OR unamenable OR inamenable OR unhealthy OR 'not healthy') NEAR/2 surgery)	4,470,185
7.	#5 AND #6	19,955
8.	('clinical trial'/exp OR 'randomized controlled trial'/exp OR 'randomization'/de OR 'single blind procedure'/de OR 'double blind procedure'/de OR 'crossover procedure'/de OR 'placebo'/de OR ((randomi?ed NEAR/2 'controlled trial*'):ab,ti) OR rct:ab,ti OR 'random allocation':ab,ti OR 'randomly allocated':ab,ti OR 'allocated randomly':ab,ti OR ((allocated NEAR/2 random):ab,ti) OR ((single NEXT/1 blind*):ab,ti) OR ((double NEXT/1 blind*):ab,ti) OR (((treble OR triple) NEAR/3 blind*):ab,ti) OR placebo*:ab,ti OR 'prospective study'/de) NOT ('case study'/de OR 'case report':ab,ti OR 'abstract report'/de OR 'letter'/de)	2,041,012
9.	'clinical study'/de OR 'case control study'/de OR 'clinical article'/de OR 'clinical trial'/de OR 'community trial'/de OR 'family study'/de OR 'intervention study'/de OR 'longitudinal study'/de OR 'major clinical study'/mj OR 'open study'/de OR 'postmarketing surveillance'/de OR 'prospective study'/de OR 'retrospective study'/de OR ('prospective study'/de NOT 'randomized controlled trial'/exp) OR 'cohort analysis'/de OR ((cohort NEAR/1 (study OR studies)):ab,ti) OR (('case control' NEAR/1 (study OR studies)):ab,ti) OR (('follow up' NEAR/1 (study OR studies)):ab,ti) OR ((observational NEAR/1 (study OR studies)):ab,ti) OR ((epidemiologic* NEAR/1 (study OR studies)):ab,ti) OR (('cross sectional' NEAR/1 (study OR studies)):ab,ti)	4,657,738
10.	#8 OR #9	5,187,553
11.	(review:it OR 'review literature as topic'/exp OR 'literature review':ti) NOT ('meta-analysis':it OR 'meta-analysis as topic'/mj OR 'systematic review':ti OR 'systematic literature review':ti OR 'meta-analysis':ab,ti OR 'meta analysis':ab,ti) OR 'case report*':ab,ti OR 'case series':ab,ti OR ('animal'/exp NOT ('animal'/exp AND 'human'/exp)) OR letter:it OR editorial:it	9,542,276
12.	#10 NOT #11	4,577,721
13.	#7 AND #12	6,482

## 2. Cochrane Library: Wiley Interscience.

### Cochrane search strategy. 09<sup>th</sup> November 2018

Sr. No.	Query	Hits
1.	MeSH descriptor: [Bile Duct Neoplasms] explode all trees	203
2.	MeSH descriptor: [Biliary Tract Neoplasms] explode all trees	356
3.	"bile duct carcinoma" or "bile duct cancer" or cholangiocarcinoma or "biliary tract carcinoma" or "biliary tract cancer"	778
4.	cholangiocarcinom*	458
5.	("bile duct" or "bile tract" or "biliary tract") and (cancer* or carcinom* or malignan* or neoplasm* or tumor* or tumour*)	1,268
6.	("bile duct" or "bile tract" or "biliary tract") near/2 (cancer* or carcinom* or malignan* or neoplasm* or tumor* or tumour*)	900
7.	#1 or #2 or #3 or #4 or #5 or #6	1,399
8.	"stage 3":ab,ti or "stage iii":ab,ti or "stage 3a":ab,ti or "stage iiiia":ab,ti or "stage 3b":ab,ti or "stage iiib":ab,ti or "stage3":ab,ti or "stageiii":ab,ti or "stage 4":ab,ti or "stage iv":ab,ti or "stage4":ab,ti or "stageiv":ab,ti or metastatic or metasta*:ab,ti or advanced or advanc*:ab,ti or unresect*:ab,ti or relap*:ab,ti or resist*:ab,ti or refract*:ab,ti or ((late* NEAR/2 stag*):ab,ti) or nonresect*:ab,ti or ((non NEXT resect*):ab,ti) or inoperable:ab,ti or "locally advanced":ab,ti or "locally-advanced":ab,ti or local*:ab,ti or ((ineligible or "in eligible" or unfit or "un fit" or "un-fit" or unsuitable or "not amenable" or unamenable or inamenable or unhealthy or "not healthy") NEAR/2 surgery)	207,943
9.	#7 AND #8	813
10.	#9 In Trials	704
11.	#9 In Cochrane Reviews	87
12.	#9 in Cochrane Protocols, Clinical Answers, Editorials and Special collections	22

## 3. Medline In-process: PubMed.com.

### Medline In-process search strategy. 09<sup>th</sup> November 2018

Sr. No.	Query	Hits
1.	Bile Duct Neoplasms[MeSH Terms]	16,747
2.	Biliary Tract Neoplasms[MeSH Terms]	26,505
3.	"bile duct carcinoma" OR "bile duct cancer" OR cholangiocarcinoma OR "biliary tract carcinoma" OR "biliary tract cancer"	15,023
4.	cholangiocarcinom*	12,782
5.	("bile duct" OR "bile tract" OR "biliary tract") AND (cancer* OR carcinom* OR malignan* OR neoplasm* OR tumor* OR tumour*)	31,055

6.	#1 OR #2 OR #3 OR #4 OR #5	41,446
7.	"stage 3"[tiab] OR "stage iii"[tiab] OR "stage 3a"[tiab] OR "stage iiiia"[tiab] OR "stage 3b"[tiab] OR "stage iiib"[tiab] OR "stage3"[tiab] OR "stageiii"[tiab] OR "stage 4"[tiab] OR "stage iv"[tiab] OR "stage4"[tiab] OR "stageiv"[tiab] OR metastatic OR metasta*[tiab] OR advanced OR advanc*[tiab] OR unresect*[tiab] OR relap*[tiab] OR resist*[tiab] OR refract*[tiab] OR ((late* AND stag*)[tiab]) OR nonresect*[tiab] OR ((non AND resect*)[tiab]) OR inoperable[tiab] OR "locally advanced"[tiab] OR "locally-advanced"[tiab] OR local*[tiab] OR ((ineligible OR "in eligible" OR unfit OR "un fit" OR "un-fit" OR unsuitable OR "not amenable" OR unamenable OR inamenable OR unhealthy OR "not healthy") AND surgery)	4,018,592
8.	#6 AND #7	14,717
9.	(publisher[sb] NOT pubstatusnihms NOT pubstatuspmcsd NOT pmcbook) OR (pubstatusaheadofprint)	449,212
10.	#8 AND #9	156

### Clinical Systematic Literature Review in rrCCA – 21 april 2020

**Table 2: Databases searched**

S. No.	Database/website	Provider/Interface	Filter used for study design	Coverage	Hits
5.	Medline & EMBASE	EMBASE.com	RCT, nRCT and observational studies	No limit	1,940
6.	Cochrane	onlinelibrary.wiley.com	-	No limit	278
7.	Medline-in-process	Pubmed.com	-	No limit	164
8.	Total				2,382

### 1. Medline and Embase: Embase.com

#### Medline and Embase search strategy. 21 April 2020

Sr. No.	Query	Hits
14.	'bile duct carcinoma'/exp OR 'bile duct carcinoma'/syn OR 'bile duct carcinoma' OR 'bile duct cancer' OR cholangiocarcinoma OR 'biliary tract cancer'/syn OR 'biliary tract cancer'/exp OR 'biliary tract cancer' OR 'biliary tract carcinoma'	45,053
15.	cholangiocarcinom*	20,930
16.	('bile duct':ab,ti OR 'bile tract':ab,ti OR 'biliary tract':ab,ti) AND (cancer*:ab,ti OR carcinom*:ab,ti OR malignan*:ab,ti OR neoplasm*:ab,ti OR tumor*:ab,ti OR tumour*:ab,ti)	22,282

17.	((('bile duct' OR 'bile tract' OR 'biliary tract') NEAR/2 (cancer* OR carcinom* OR malignan* OR neoplasm* OR tumor* OR tumour*)):ab,ti	7,968
18.	#1 OR #2 OR #3 OR #4	55,822
19.	'stage 3':ab,ti OR 'stage iii':ab,ti OR 'stage 3a':ab,ti OR 'stage iiiA':ab,ti OR 'stage 3b':ab,ti OR 'stage iiib':ab,ti OR 'stage3':ab,ti OR 'stageiii':ab,ti OR 'stage 4':ab,ti OR 'stage iv':ab,ti OR 'stage4':ab,ti OR 'stageiv':ab,ti OR metastatic OR metasta*:ab,ti OR advanced OR advanc*:ab,ti OR unresect*:ab,ti OR relap*:ab,ti OR resist*:ab,ti OR refract*:ab,ti OR ((late* NEAR/2 stag*):ab,ti) OR nonresect*:ab,ti OR ((non NEXT/1 resect*):ab,ti) OR inoperable:ab,ti OR 'locally advanced':ab,ti OR 'locally-advanced':ab,ti OR local*:ab,ti OR ((ineligible OR 'in eligible' OR unfit OR 'un fit' OR 'un-fit' OR unsuitable OR 'not amenable' OR unamenable OR inamenable OR unhealthy OR 'not healthy') NEAR/2 surgery)	5,015,317
20.	#5 AND #6	22,986
21.	('clinical trial'/exp OR 'randomized controlled trial'/exp OR 'randomization'/de OR 'single blind procedure'/de OR 'double blind procedure'/de OR 'crossover procedure'/de OR 'placebo'/de OR ((randomi?ed NEAR/2 'controlled trial*'):ab,ti) OR rct:ab,ti OR 'random allocation':ab,ti OR 'randomly allocated':ab,ti OR 'allocated randomly':ab,ti OR ((allocated NEAR/2 random):ab,ti) OR ((single NEXT/1 blind*):ab,ti) OR ((double NEXT/1 blind*):ab,ti) OR (((treble OR triple) NEAR/3 blind*):ab,ti) OR placebo*:ab,ti OR 'prospective study'/de) NOT ('case study'/de OR 'case report':ab,ti OR 'abstract report'/de OR 'letter'/de)	2,297,734
22.	'clinical study'/de OR 'case control study'/de OR 'clinical article'/de OR 'clinical trial'/de OR 'community trial'/de OR 'family study'/de OR 'intervention study'/de OR 'longitudinal study'/de OR 'major clinical study'/mj OR 'open study'/de OR 'postmarketing surveillance'/de OR 'prospective study'/de OR 'retrospective study'/de OR ('prospective study'/de NOT 'randomized controlled trial'/exp) OR 'cohort analysis'/de OR ((cohort NEAR/1 (study OR studies)):ab,ti) OR (('case control' NEAR/1 (study OR studies)):ab,ti) OR (('follow up' NEAR/1 (study OR studies)):ab,ti) OR ((observational NEAR/1 (study OR studies)):ab,ti) OR ((epidemiologic* NEAR/1 (study OR studies)):ab,ti) OR (('cross sectional' NEAR/1 (study OR studies)):ab,ti)	5,397,357
23.	#8 OR #9	6,011,022
24.	(review:it OR 'review literature as topic'/exp OR 'literature review':ti) NOT ('meta-analysis':it OR 'meta-analysis as topic'/mj OR 'systematic review':ti OR 'systematic literature review':ti OR 'meta-analysis':ab,ti OR 'meta analysis':ab,ti) OR 'case report*':ab,ti OR 'case series':ab,ti OR ('animal'/exp NOT ('animal'/exp AND 'human'/exp)) OR letter:it OR editorial:it	10,162,518



25.	#10 NOT #11	5,306,466
26.	#7 AND #12	8,106
27.	#13 AND [1-10-2018]/sd	1,940

## 2. Cochrane Library: Wiley Interscience.

### Cochrane search strategy. 21 April 2020

Sr. No.	Query	Hits
13.	MeSH descriptor: [Bile Duct Neoplasms] explode all trees	218
14.	MeSH descriptor: [Biliary Tract Neoplasms] explode all trees	415
15.	"bile duct carcinoma" or "bile duct cancer" or cholangiocarcinoma or "biliary tract carcinoma" or "biliary tract cancer"	1,176
16.	cholangiocarcinom*	662
17.	("bile duct" or "bile tract" or "biliary tract") and (cancer* or carcinom* or malignan* or neoplasm* or tumor* or tumour*)	1,760
18.	("bile duct" or "bile tract" or "biliary tract") near/2 (cancer* or carcinom* or malignan* or neoplasm* or tumor* or tumour*)	1,246
19.	#1 or #2 or #3 or #4 or #5 or #6	1,992
20.	"stage 3":ab,ti or "stage iii":ab,ti or "stage 3a":ab,ti or "stage iiiia":ab,ti or "stage 3b":ab,ti or "stage iiib":ab,ti or "stage3":ab,ti or "stageiii":ab,ti or "stage 4":ab,ti or "stage iv":ab,ti or "stage4":ab,ti or "stageiv":ab,ti or metastatic or metasta*:ab,ti or advanced or advanc*:ab,ti or unresect*:ab,ti or relap*:ab,ti or resist*:ab,ti or refract*:ab,ti or ((late* NEAR/2 stag*):ab,ti) or nonresect*:ab,ti or ((non NEXT resect*):ab,ti) or inoperable:ab,ti or "locally advanced":ab,ti or "locally-advanced":ab,ti or local*:ab,ti or ((ineligible or "in eligible" or unfit or "un fit" or "un-fit" or unsuitable or "not amenable" or unamenable or inamenable or unhealthy or "not healthy") NEAR/2 surgery)	252,813
21.	#7 AND #8	1,147
22.	#9 with Publication Year from 2018 to 2020, in Trials	255
23.	#9 with Cochrane Library publication date from Jan 2018 to Dec 2020, in Cochrane Reviews	18
24.	#9 with Cochrane Library publication date from Jan 2018 to Dec 2020, in Cochrane Protocols, Clinical Answers, Editorials and Special collections	5

## 3. Medline In-process: PubMed.com.

### Medline In-process search strategy. 21 April 2020

Sr. No.	Query	Hits
11.	Bile Duct Neoplasms[MeSH Terms]	17,868

12.	Biliary Tract Neoplasms[MeSH Terms]	28,163
13.	"bile duct carcinoma" OR "bile duct cancer" OR cholangiocarcinoma OR "biliary tract carcinoma" OR "biliary tract cancer"	17,024
14.	cholangiocarcinom*	14,629
15.	("bile duct" OR "bile tract" OR "biliary tract") AND (cancer* OR carcinom* OR malignan* OR neoplasm* OR tumor* OR tumour*)	33,323
16.	#1 OR #2 OR #3 OR #4 OR #5	44,730
17.	"stage 3"[tiab] OR "stage iii"[tiab] OR "stage 3a"[tiab] OR "stage iiiia"[tiab] OR "stage 3b"[tiab] OR "stage iiib"[tiab] OR "stage3"[tiab] OR "stageiii"[tiab] OR "stage 4"[tiab] OR "stage iv"[tiab] OR "stage4"[tiab] OR "stageiv"[tiab] OR metastatic OR metasta*[tiab] OR advanced OR advanc*[tiab] OR unresect*[tiab] OR relap*[tiab] OR resist*[tiab] OR refract*[tiab] OR ((late* AND stag*)[tiab]) OR nonresect*[tiab] OR ((non AND resect*)[tiab]) OR inoperable[tiab] OR "locally advanced"[tiab] OR "locally-advanced"[tiab] OR local*[tiab] OR ((ineligible OR "in eligible" OR unfit OR "un fit" OR "un-fit" OR unsuitable OR "not amenable" OR unamenable OR inamenable OR unhealthy OR "not healthy") AND surgery)	4,431,668
18.	#6 AND #7	16,182
19.	(publisher[sb] NOT pubstatusnihms NOT pubstatuspmcsd NOT pmcbook) OR (pubstatusaheadofprint)	319,067
20.	#8 AND #9	164

## B. Primary systematic literature review of clinical studies

Potentially relevant publications were reviewed to collate a final set of studies which formed the main body of the clinical evidence. To determine which studies were eligible for review, explicit inclusion and exclusion criteria were applied to the literature search results (see Table 3).

Table 3: Inclusion and exclusion criteria for the systematic literature review

Category	Inclusion criteria <sup>a</sup>	Exclusion criteria
Population	<ul style="list-style-type: none"> <li>Adults (<math>\geq 18</math> years) with advanced, metastatic, or surgically unresectable FGFR2+ CCA for whom at least one treatment has failed</li> <li>Adults (<math>\geq 18</math> years) with advanced, metastatic, or surgically unresectable CCA for whom at least one treatment has failed</li> </ul>	<ul style="list-style-type: none"> <li>Publications reporting on patient populations in the following categories: <ul style="list-style-type: none"> <li>Children</li> <li>Patients without metastatic and advanced stage</li> <li>Treatment-naïve patients</li> </ul> </li> <li>Resectable CCA</li> </ul>
Line of therapy	Second or later lines of therapy**	First-line therapy

Interventions	<ul style="list-style-type: none"> <li>• All pharmacological interventions</li> </ul>	<ul style="list-style-type: none"> <li>• Non-pharmacological interventions</li> <li>• Surgical procedures</li> <li>• Adjuvant/neoadjuvant treatment</li> <li>• Stents</li> <li>• Chemoradiotherapy/radiotherapy</li> <li>• Photodynamic therapy</li> </ul>
Comparators	<ul style="list-style-type: none"> <li>• Placebo</li> <li>• Best supportive care (author defined)</li> <li>• Any other pharmacological intervention</li> <li>• No comparator limit for single-arm trials</li> </ul>	None
Outcomes (tentative, not exhaustive)	<ul style="list-style-type: none"> <li>• Response rate</li> <li>• Overall survival</li> <li>• Progression-free survival</li> <li>• Time to treatment discontinuation</li> <li>• Duration of response</li> <li>• Mortality</li> <li>• Health-related quality of life</li> <li>• Incidence of adverse events</li> <li>• Study/treatment discontinuation</li> <li>• Relationship between intermediate outcomes (progression-free survival, response rate) and overall survival</li> <li>• Disease control rate</li> <li>• Stable disease</li> <li>• Time on treatment</li> <li>• Time to response</li> <li>• Overall response rate</li> <li>• Quality of life/patient-reported outcome</li> </ul>	None
Study type	<ul style="list-style-type: none"> <li>• Randomized controlled trials</li> <li>• Non-randomized controlled trials, including single-arm and observational studies, e.g. retrospective studies</li> <li>• Systematic reviews<sup>c</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Preclinical studies</li> <li>• Comments, letters, editorials</li> <li>• Case reports, case series</li> <li>• Pharmacokinetic and economic studies</li> </ul>
Time limit	<ul style="list-style-type: none"> <li>• Original SLR: data inception to 9 November 2018</li> <li>• SLR Update: 1 October 2018 to 21 April 2020</li> </ul>	<ul style="list-style-type: none"> <li>• No limits</li> </ul>
Language	Only English language articles/conference abstracts	Non-English language articles/conference abstracts

**Key:** CCA, cholangiocarcinoma; FGFR2+, fibroblast growth factor receptor-2.

**Note:**<sup>a</sup>, the SLR was not limited by sample size. A study was also included if it reported data for one patient and met review criteria.<sup>b</sup>, if disease stage, FGFR2 status or treatment line were not clear at the primary screening stage, the study was included, and a decision was taken at the secondary screening stage after reviewing the full text. Studies with multiple lines of therapy were also included.<sup>c</sup>, systematic reviews of randomized controlled trials, non-randomized controlled trials, single-arm, and observational studies were utilized only for bibliography searches.

**\*\***, citations assessing patients receiving multiple lines of therapy were included at primary screening.

### **Study selection**

All retrieved studies were assessed against the eligibility criteria.

Primary (Level 1) screening was performed by two independent BresMed reviewers who reviewed each reference (title and abstract) identified in the literature search, applied basic study selection criteria (population, intervention, study design) and made decisions on whether to include or exclude the study reference at that stage. Any uncertainty regarding the inclusion of studies was checked by a senior BresMed reviewer, independent of the initial reviewers.

For secondary (Level 2) screening of potentially relevant articles, the full articles were obtained. These were independently reviewed by two BresMed reviewers against each eligibility criterion. Any uncertainty regarding the inclusion of studies was again checked and judged by a senior BresMed reviewer independent of the initial reviewers.

Electronic searches were conducted using English language keywords. All potential studies either had abstracts available in English, or the abstract was unavailable and thus a positive exclusion was not possible. For the full publication, if the language was not English the publication was excluded based on language.

The SLR identified few published SLRs that were conducted in CCA or BTC patients receiving multiple lines of therapy. The published SLRs were used for bibliographic purposes; all studies relevant to the review objective have been included in the current SLR.

### **REFERENCES**

1. Rizvi S, Khan SA, Hallemeier CL, Kelley RK, Gores GJ. Cholangiocarcinoma - evolving concepts and therapeutic strategies. *Nat Rev Clin Oncol*. 2018 Feb;15(2):95–111.
2. Lepage C, Capocaccia R, Hackl M, Lemmens V, Molina E, Pierannunzio D, et al. Survival in patients with primary liver cancer, gallbladder and extrahepatic biliary tract cancer and pancreatic cancer in Europe 1999-2007: Results of EURO-CARE-5. *Eur J Cancer*. 2015 Oct;51(15):2169–78.
3. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin*. 2019 Jan;69(1):7–34.
4. Valle JW, Borbath I, Khan SA, Huguet F, Gruenberger T, Arnold D, et al. Biliary cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2016 Sep;27(suppl 5):v28–37.
5. Valle JW, Furuse J, Jitlal M, Beare S, Mizuno N, Wasan H, et al. Cisplatin and gemcitabine for advanced biliary tract cancer: a meta-analysis of two randomised trials. *Ann Oncol*. 2014 Feb;25(2):391–8.
6. Okusaka T, Nakachi K, Fukutomi A, Mizuno N, Ohkawa S, Funakoshi 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 Aug 10;103(4):469–74.
7. Valle J, Wasan H, Palmer DH, Cunningham D, Anthoney A, Maraveyas A, et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. *N Engl J Med*. 2010 Apr 8;362(14):1273–81.
8. Lamarca A, Hubner RA, David Ryder W, Valle JW. Second-line chemotherapy in advanced biliary cancer: a systematic review. *Ann Oncol*. 2014 Dec;25(12):2328–38.

9. Brieau B, Dahan L, De Rycke Y, Boussaha T, Vasseur P, Tougeron D, et al. Second-line chemotherapy for advanced biliary tract cancer after failure of the gemcitabine-platinum combination: A large multicenter study by the Association des Gastro-Entérologues Oncologues. *Cancer*. 2015 Sep 15;121(18):3290–7.
10. Lamarca A, Palmer DH, Wasan HS, Ross PJ, Ma YT, Arora 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*. 2021 May;22(5):690–701.
11. Neuzillet C, Casadei-Gardini A, Brieau B, Vivaldi C, Brandi G, Tougeron D, et al. Fluropyrimidine single agent or doublet chemotherapy as second line treatment in advanced biliary tract cancer. *Int J Cancer*. 2020 Dec 1;147(11):3177–88.
12. Abou-Alfa GK, Sahai V, Hollebecque A, Vaccaro G, Melisi D, Al-Rajabi R, et al. Pemigatinib for previously treated, locally advanced or metastatic cholangiocarcinoma: a multicentre, open-label, phase 2 study. *Lancet Oncol*. 2020;21(5):671–84.
13. Abou-Alfa GK, Macarulla T, Javle MM, Kelley RK, Lubner SJ, Adeva J, et al. Ivosidenib in IDH1-mutant, chemotherapy-refractory cholangiocarcinoma (ClarIDHy): a multicentre, randomised, double-blind, placebo-controlled, phase 3 study. *Lancet Oncol*. 2020;21(6):796–807.
14. Sargent D, Shi Q, Yothers G, Van Cutsem E, Cassidy J, Saltz L, et al. Two or three year disease-free survival (DFS) as a primary end-point in stage III adjuvant colon cancer trials with fluoropyrimidines with or without oxaliplatin or irinotecan: data from 12,676 patients from MOSAIC, X-ACT, PETACC-3, C-06, C-07 and C89803. *Eur J Cancer*. 2011 May;47(7):990–6.
15. Food and Drug Administration, Oncology Center of Excellence, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). *Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. Guidance for Industry*. 2018.
16. Neuzillet C, Casadei Gardini A, Brieau B, Vivaldi C, Smolenschi C, Brandi G, et al. Prediction of survival with second-line therapy in biliary tract cancer: Actualisation of the AGEO CT2BIL cohort and European multicentre validations. *Eur J Cancer*. 2019 Apr;111:94–106.
17. Demols A, Borbath I, Van Den Eynde M, Houbiers G, Peeters M, Maréchal R, et al. Regorafenib after failure of gemcitabine and platinum-based chemotherapy for locally advanced (nonresectable) and metastatic biliary tumors: A randomized double-blinded placebo-controlled phase II trial. *JCO*. 2019 Jan 29;37(4\_suppl):345–345.
18. Sun W, Patel A, Normolle D, Patel K, Ohr J, Lee JJ, et al. A phase 2 trial of regorafenib as a single agent in patients with chemotherapy-refractory, advanced, and metastatic biliary tract adenocarcinoma. *Cancer*. 2019 Mar 15;125(6):902–9.
19. Kim RD, Poklepovic AS, Nixon AB, Kim DW, Soares HP, Kim J, et al. Multi institutional phase II trial of single agent regorafenib in refractory advanced biliary cancers. *JCO*. 2018 May 20;36(15\_suppl):4082–4082.
20. Goyal L, Zheng H, Yurgelun MB, Abrams TA, Allen JN, Cleary JM, et al. A phase 2 and biomarker study of cabozantinib in patients with advanced cholangiocarcinoma. *Cancer*. 2017 01;123(11):1979–88.
21. Neuzillet C, Seitz J, Fartoux L, Malka D, Lledo G, Tijeras-Raballand A, et al. Second Line Therapy with Sunitinib As Single Agent in Patients with Advanced Intrahepatic Cholangiocarcinoma (Update on Sun-Ck Phase II Trial). *Annals of Oncology*. 2014 Sep 1;25:iv244.
22. Buzzoni R, Pusceddu S, Bajetta E, De Braud F, Platania M, Iannacone C, et al. Activity and safety of RAD001 (everolimus) in patients affected by biliary tract cancer progressing after prior chemotherapy: a phase II ITMO study. *Ann Oncol*. 2014 Aug;25(8):1597–603.

23. Javle M, Lowery M, Shroff RT, Weiss KH, Springfield C, Borad MJ, et al. Phase II Study of BGJ398 in Patients With FGFR-Altered Advanced Cholangiocarcinoma. *J Clin Oncol*. 2018 Jan 20;36(3):276–82.
24. Verlingue L, Malka D, Allorant A, Massard C, Ferté C, Lacroix L, et al. Precision medicine for patients with advanced biliary tract cancers: An effective strategy within the prospective MOSCATO-01 trial. *Eur J Cancer*. 2017;87:122–30.
25. Zheng Y, Tu X, Zhao P, Jiang W, Liu L, Tong Z, 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(3):291–5.
26. Suzuki E, Ikeda M, Okusaka T, Nakamori S, Ohkawa S, Nagakawa T, et al. A multicenter phase II study of S-1 for gemcitabine-refractory biliary tract cancer. *Cancer Chemother Pharmacol*. 2013 May;71(5):1141–6.
27. Chakrabarti S, Zemla TJ, Ahn DH, Ou FS, Fruth B, Borad MJ, et al. Phase II Trial of Trifluridine/Tipiracil in Patients with Advanced, Refractory Biliary Tract Carcinoma. *Oncologist*. 2020;25(5):380-e763.
28. Lim KH, Han SW, Oh DY, Im SA, Kim TY, Bang YJ. Outcome of infusional 5-fluorouracil, doxorubicin, and mitomycin-C (iFAM) chemotherapy and analysis of prognostic factors in patients with refractory advanced biliary tract cancer. *Oncology*. 2012;83(2):57–66.
29. Larsen FO, Markussen A, Diness LV, Nielsen D. Efficacy and Safety of Capecitabine, Irinotecan, Gemcitabine, and Bevacizumab as Second-Line Treatment in Advanced Biliary Tract Cancer: A Phase II Study. *Oncology*. 2018;94(1):19–24.
30. Kim R, Chiorean EG, Amin M, Rocha-Lima CMS, Gandhi J, Harris WP, et al. Phase 2 study of combination SPI-1620 with docetaxel as second-line advanced biliary tract cancer treatment. *Br J Cancer*. 2017 Jul 11;117(2):189–94.

Table 1: Studies included in the endpoint correlation analysis.

Study number	Meshid	Trial	Phase	Drugs	ORR – Evaluable patients (n)	ORR (n %)	ORR (n %)	CR (n %)	P (n %)	SD (%)	PD (n %)	DCR (%)	OS – Evaluable patients (n)	Median OS (months)	Median PFS (months)
<b>Targeted therapies</b>															
2	8325	Demois 2019 (17)	2R	Regorafenib	33	0	0	0	0	70	30	70	33	5.3	3
14	8418	Sun 2019 (18)	2	Regorafenib	34	5	14.7	0	14.7	55.9	23.2	70.6	34	7.3	3.6
15	8458	Kim 2018 (19)	2	Regorafenib	32	2	6.3	0	6.3	NR	NR	62.5	32	9.9	3.7
6	540	Goyal 2017 (20)	2	Cabozantinib	19	0	0	0	0	26.3	63.2	26.3	19	5.2	1.8
7	657	Neuzillet 2015 (21)	2	Sunitinib	51	7	13.7	0	13.7	70.6	NR	84.3	53	9.6	3.7
9	1239	Buzzoni 2014 (22)	2	Everolimus	38	2	5.3	2.6	2.6	42.1	55.3	47.2	39	7.7	3.2

3	91 82	Abou- Alfa 2020 (13)	3	Ivosidenib	124	3	2. 4	0	2. 4	51	3 3	53 .2	124	10.8	2.7
8	90 5	Javle 2018 (23)	2	Infigratinib (BGJ398)	71	2 2	3 1	0	2 5. 4	57 .7	1 1. 3	83 .6	71	12.5	6.8
12	70 19	Abou- Alfa 2020 (12)	2	Pemigatinib (INCB054828) ( <i>FGFR2</i> rearrangement)	107	3 8	3 5. 5	2. 8	3 2. 7	46 .7	1 5	82 .2	107	21.1	6.9
				Pemigatinib (INCB054828) (other <i>FGFR2</i> alterations)	20	0	0	0	0	40	3 5	40	20	6.7	2.1
				Pemigatinib (INCB054828) (no <i>FGFR2</i> alteration)	18	0	0	0	0	22 .2	6 1. 1	22 .2	18	4.0	1.7
16	18	Verlingue 2017 (24)	2	Various targeted therapies (matched patients)	18	6	3 3. 3	5. 5	2 7. 7	55 .5	1 1. 1	88 .7	18	17	5.2
<b>Chemotherapy</b>															
1	95 7	Zheng 2018 (25)	2R	Irinotecan + capecitabine	30	4	1 3. 3	6. 7	6. 7	50	3 6. 7	63 .3	30	10.1	3.7
				Irinotecan	30	2	6. 7	0	6. 7	43 .3	5 0	50	30	7.3	2.4
10	19 24	Suzuki 2013 (26)	2	S-1	26	2 7	7. 7	0	7. 7	65 .4	2 6. 9	73 .1	26	7.5	2.5
13	74 98	Chakraba rti 2019 (27)	2	Trifluridine-tipiracil (TAS-102)	27	0	0	0	0	48 .1	3 7	48 .1	27	6.1	3.8
17	23 32	Lim 2012 (28)	2	iFAM	48	2	4. 2	0	4. 8	18 .7	N R	22 .9	50	5.6	2.2
4	78 03	Lamarca 2021 (10)	3	Active symptom control + mFOLFOX	80	4	5	1. 2 5	3. 7 5	28 .7 5	3 7. 5	33 .7 5	81	6.2	4
<b>Chemotherapy and targeted therapy</b>															
11	19 88	Larsen 2018 (29)	2	Capecitabine. irinotecan. gemcitabine and bevacizumab	48	2	4. 2	0	4. 2	58 .3	3 7. 5	62 .5	48	6.4	3.6
5	51	Kim 2017 (30)	2	SPI-1620 (analogue of endothelin-) + docetaxel	29	3	1 0. 3	0	1 0. 3	37 .9	N R	48 .3	29	4.9	2.6

CR, complete response. DCR, disease control rate (CR+PR+SD). NR, not reported. ORR, overall response rate (CR+PR). OS, overall survival. PD, progressive disease. PFS, progression-free survival. PR, partial response. SD, stable disease. iFAM, 5-fluorouracil, doxorubicin, and mitomycin-C. mFOLFOX, modified FOLFOX, 5-fluorouracil, folinic acid, and oxaliplatin.

**Table 2.** OS, Overall survival; PFS, Progression Free Survival; ORR, overall response rate; CI, confidence interval

Treatment type	Studies (arms) with	Patient s	Weighted mean			Coefficient of weighted correlation p-value	
			OS (months )	PFS (months )	ORR (%) (95%CI)	OS and PFS	OS and ORR

	data available		(95%CI)	(95%CI)	)		
Overall	17 (20)	883	9.86 (7.51 - 12.21)	3.89 (3.10 - 4.68)	11.78 (5.83 - 17.73)	0.80 <0.0001	0.85 <0.0001
Chemotherapy	5 (6)	241	6.83 (5.25-8.42)	3.22 (2.32-4.12)	5.81 (1.82-9.80)	0.13 0.8141	0.90 0.0152
Targeted therapy	10 (12)	565	11.71 (8.25-15.16)	4.26 (3.01-5.51)	15.04 (5.57-24.52)	0.83 0.0009	0.84 0.0006
Both	2 (2)	77	5.82 (0-15.24)	3.22 (0-9.38)	6.49 (0-44.53)	1	1

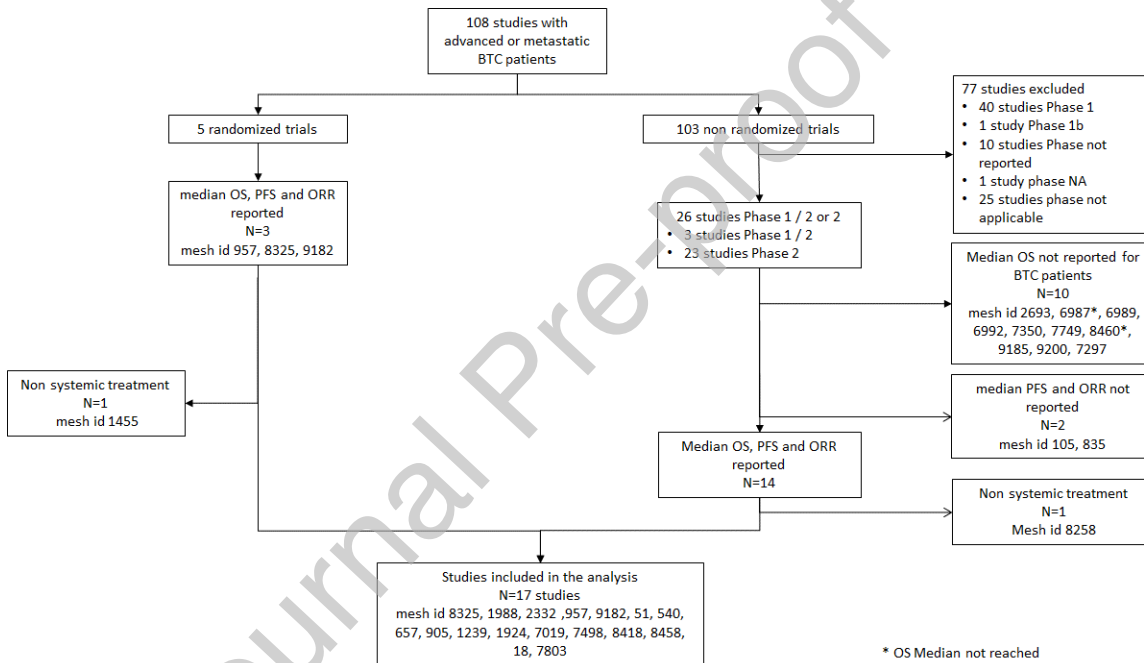
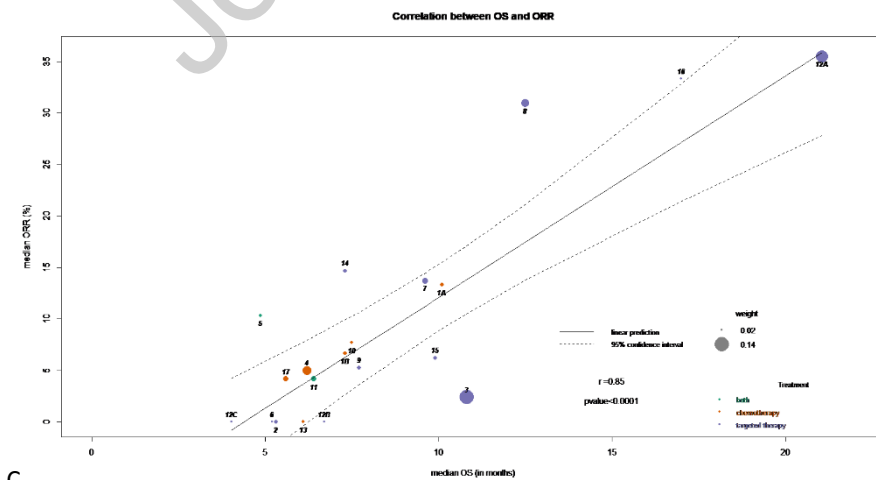


Figure 1: Flowchart of studies included in the analyses



C



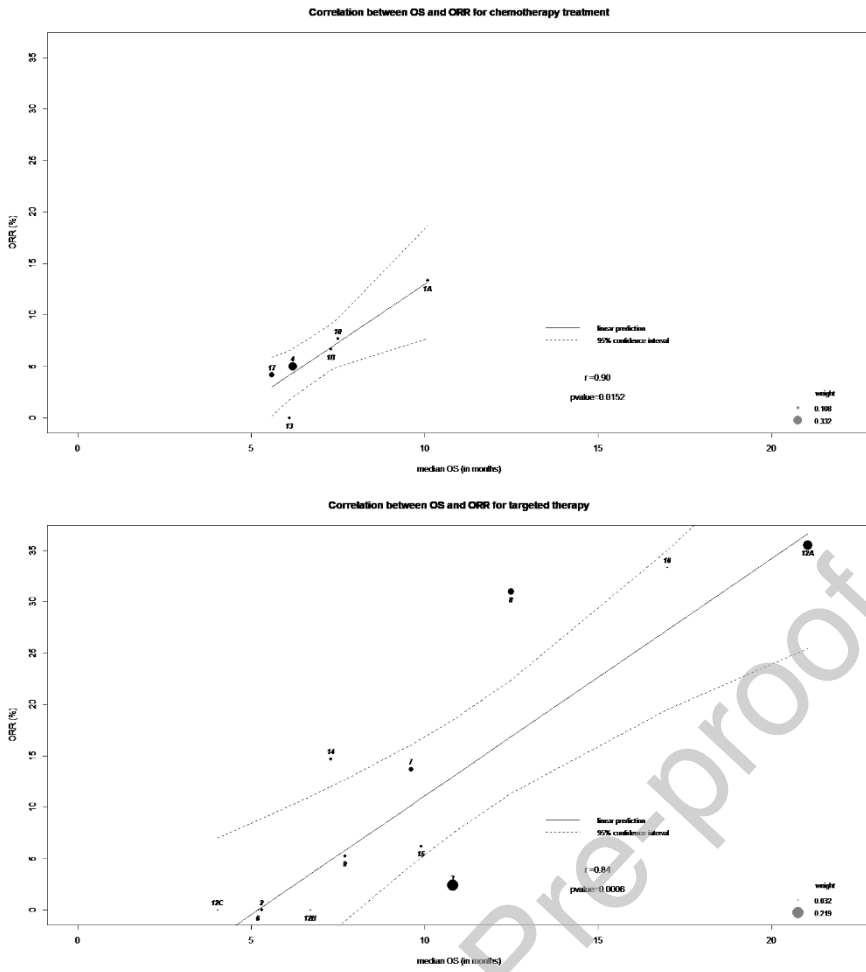
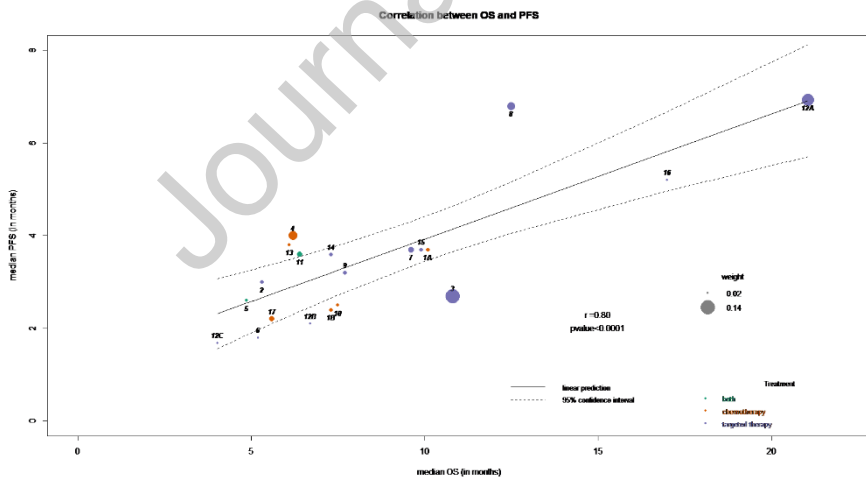


Figure 2: Correlation between OS and ORR; 2A: overall analysis; 2B: sensitivity analysis in the chemotherapy group; 2C: sensitivity analysis in the targeted therapy group



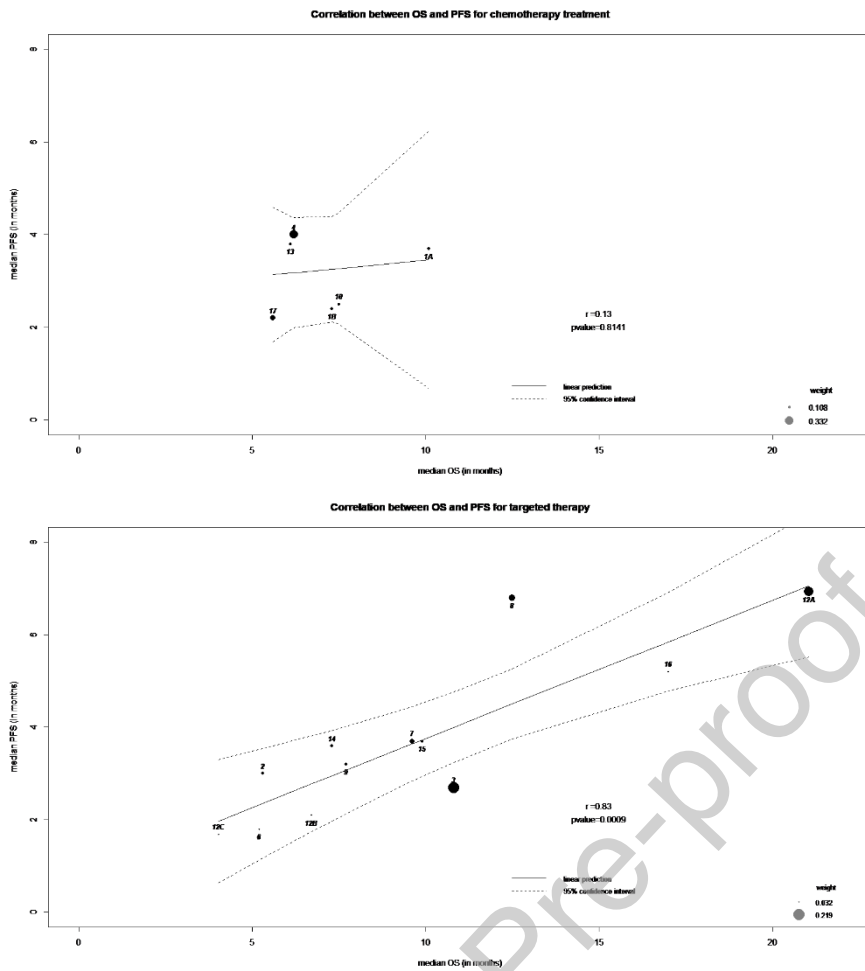


Figure 3: Correlation between OS and PFS; 3A: overall analysis; 3B: sensitivity analysis in the chemotherapy group; 3C: sensitivity analysis in the targeted therapy group