Investigational Plan & Clinical Study Protocol

Adjuvant chemotherapy with gemcitabine and cisplatin compared to standard of care after curative intent resection of cholangiocarcinoma and muscle invasive gallbladder carcinoma (ACTICCA-1 trial)

A randomized, multidisciplinary, multinational AIO/DGAV/DGVS phase III trial.

Sponsor: University Medical Center Hamburg-Eppendorf

supported by
Deutsche Krebshilfe e.V. Grant No: 110215
medac GmbH
Cancer Research UK
KWF Kanker Bestrijding The Netherlands

EudraCT Nr: 2012–005078-70

Protocol identification number: ACTICCA-1 trial

Version: 6.0 21st of June 2017

Collaborative Countries/Groups

Germany

- Arbeitsgemeinschaft Internistische Onkologie (AIO)
- Deutsche Gesellschaft für Allgemein- und Viszeralchirurgie (DGAV)
- Chirurgische Arbeitsgemeinschaft Onkologie-Viszeralchirurgie (CAO-V)
- Deutsche Gesellschaft für Verdauungs- und Stoffwechselkrankheiten (DGVS)

United Kingdom

- BILCAP study group

The Netherlands

Australia

- Australasian Gastro-Intestinal Trials Group (AGITG)

Denmark

Coordinating Facility

- University Cancer Center Hamburg (UCCH)

Principal Study Coordinator

- Henning Wege, University Medical Center Hamburg-Eppendorf

Study Coordinator

- Alexander Stein, University Medical Center Hamburg-Eppendorf

Legal Sponsor

- University Medical Center Hamburg-Eppendorf

Statistician

- Eik Vettorazzi, University Medical Center Hamburg-Eppendorf

Regulatory, Data Management, Monitoring

- CTC North GmbH & Co. KG, Hamburg

Independent Data Monitoring Committee

- Arnaud Roth, University of Geneva, Suisse
- Susanna Hegewisch-Becker, Hamburg, Gemany
- Xavier Paoletti, Institut Curie, Paris, France

International steering committee ACTICCA-1

- Dirk Arnold, Germany
- John Bridgewater, United Kingdom
- Lutz Fischer, Germany
- David Goldstein, Australia
- Thomas Gruenberger, Austria
- Lars Henrik Jensen, Denmark
- Heinz Josef Klumpen, The Netherlands
- Ansgar Lohse, Germany
- John Primrose, United Kingdom
- Jenny Shannon, Australia
- Karl Wegscheider, Germany

Steering committee translational research

- Melanie Kripp, University Medical Center, Mannheim
- Tom Lüdde, University Hospital Aachen
- Markus Möhler, University Medical Center Mainz
- Max Schmeding, University Hospital Aachen
- Alexander Stein, University Medical Center Hamburg-Eppendorf
- Henning Wege, University Medical Center Hamburg-Eppendorf

Contact: acticca@uke.de

Approval of the Protocol

University of Hamburg
University Medical Center Hamburg-Eppendorf
Medical Faculty
Office of the Dean
Martinistraße 52 · D-20246 Hamburg, Germany

Signature — Date (DD Month YYYY): 10. Jul 2017

Prof. Dr. Dr. Uwe Ulrich Gromus

Name of the Representative of the Sponsor

Signature — Date (DD Month YYYY): JUL-10-2017

PD Dr. Henning Wege

Name of Coordinating Investigator

Universitätsklinikum Hamburg-Eppendorf
Zentrum für Innere Medizin
I. Medizinische Klinik und Poliklinik
Sekretariat Prof. Dr. A. W. Lohse
Martinistraße 52 · 20246 Hamburg
Tel.: 040 / 74 10 - 5 39 10 · Fax: 040 / 74 10 - 5 85 31

Coordinating Investigator's Institution

Signature — Date (DD Month YYYY): 10. July 2017

Eik Vettorazzi

Name of Statistician

Universitätsklinikum Hamburg-Eppendorf
Zentrum für Experimentelle Medizin
Institut für Medizinische Biometrie und Epidemiologie
Martinistraße 52 · 20246 Hamburg

Statistician Institution

Investigator's Agreement

I have read the attached protocol entitled

"Adjuvant chemotherapy with gemcitabine and cisplatin compared to standard of care after curative intent resection of cholangiocarcinoma and muscle invasive gallbladder carcinoma (ACTICCA-1 Trial)."

dated 21st of June, 2017 and agree to abide by all provisions set forth therein.

I agree to comply with the International Conference on Harmonisation Tripartite Guideline on Good Clinical Practice (ICH-GCP).

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the study sponsor.

Signature

Investigator

Date (DD Month YYYY)

Investigator's Institution

Study Glossary

Abbreviation/Acronym	Definition
ADR	Adverse Drug Reaction
AE	Adverse event
ANC	Absolute neutrophil count
ALT (SGPT)	Alanine aminotransferase (serum glutamic-pyruvic transaminase)
AST (SGOT)	Aspartate aminotransferase (serum glutamic-oxaloacetic transaminase)
BIL21 Module	Questionnaire for cholangiocarcinoma and gallbladder cancer patients
BSA	Body surface area
BTC	Biliary Tract Cancer
CA 19-9	Carbohydrate antigen 19-9
CCA	Cholangiocarcinoma
CD133	Cluster of Differentiation 133
CEA	Carcinoembryonic antigen
eCRF	Electronic Case Report Form
CrP	C reactive Protein
CT	Computerized tomography
CTC	Circulating Tumor Cells
CTCAE	Common Terminology Criteria for Adverse Events
CTx	Chemotherapy
CVA	Cerebrovascular accident
CXCR4	C-X-C chemokine receptor type 4
DFS	Disease free survival
DFSR	Disease free survival rate
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EORTC QLQ INFO25	European Organization for Research and Treatment of Cancer Quality of Life Information Questionnaire
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
FDA	Food and Drug Administration (U.S. government agency)
5-FU	5-Fluorouracil
GCP	Good Clinical Practice
GCP-V	Verordnung über die Anwendung der Guten Klinischen Praxis (GCP) bei der Durchführung von klinischen Prüfungen mit Arzneimitteln zur Anwendung am Menschen
HCC	Hepatocellular carcinoma

Hif-1a	Hypoxia-inducible factor 1-alpha
ICF	Informed consent form
IDMC	Independent Data Monitoring Committee
IEC	Independent ethics committee
IMP	Investigational medicinal product
INR	International normalized ratio
ITT	Intention-to-treat
iv	intravenous
MDRD	Modification of Diet in Renal Disease
MRI	Magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NYHA	New York Heart Association
OS	Overall survival
PEF-FB-9	*Fragebogen zur Partizipativen Entscheidungsfindung*
PEF-FB-Doc	*Fragebogen zur Partizipativen Entscheidungsfindung (Arztversion)*
PSC	Primary Sclerosing Cholangitis
PTCD	Percutaneous transhepatic cholangiography
PTEN	Phosphatase and Tensin homolog
PTT	Partial thromboplastin time
QoL	Quality of life
RBC	Red blood cell count
RDE	Remote data entry
RECIST	Response Evaluation Criteria in Solid Tumors
SADR	Serious adverse drug reaction
SAE	Serious adverse event
SAR	Serious adverse reaction
SAS	Statistic software
SDM-Q-9/Doc	Shared decision making Questionnaire
SDV	Source Data Verification
SEER	Surveillance, Epidemiology, and End Results Program
SLD	Sum of the longest diameters
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TNM	Classification of malignant tumors
ULN	Upper limit of normal
VEGF	Vascular Endothelial Growth Factor
WBC	White blood cell count

Table of Contents

Table of Appendices

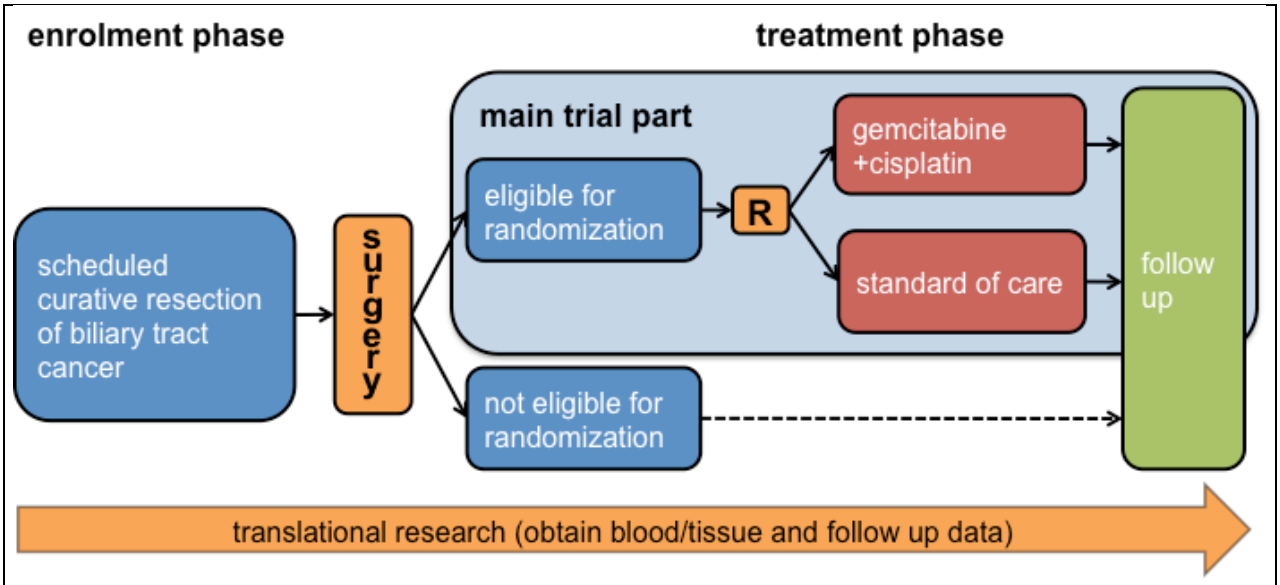
List of Tables and Figures

Tables:

Figures:

Synopsis

Title	**Adjuvant chemotherapy with gemcitabine and cisplatin compared to standard of care after curative intent resection of cholangiocarcinoma and muscle invasive gallbladder carcinoma (ACTICCA-1 trial).** **A randomized, multidisciplinary, multinational AIO/DGAV/DGVS phase III trial.**
Design	Randomized, controlled, two stage, multicenter phase III trial
Indication	Patients after curative intent resection of cholangiocarcinoma (intrahepatic, hilar or distal) or muscle invasive gallbladder carcinoma (without evidence of metastatic disease).
Sample size	781 patients to be randomized, 187 in stage 1 and 594 in stage 2
Study Duration	Duration of recruitment (stage 2): 48 months at a rate of 12 patients/ month. Follow-up from recruitment to end of trial after 388 events (defined as death or disease recurrence) have occurred (about 24 months). Expected total duration: 72 plus further 36 months follow up for overall survival (maximum of 5 years per individual patient)
Endpoints	<u>Primary endpoints:</u> • Disease free survival (DFS) <u>Secondary endpoints:</u> • Disease free survival rate at 24 months (DFSR@24) • Recurrence free survival • Overall survival (OS) • Safety and tolerability of adjuvant chemotherapy • Quality of life (QoL) • Function of biliodigestive anastomosis (in terms of surgical revision, requirement for PTCD) • Rate and severity of biliary tract infections • Patterns of disease recurrence • Locoregional control



Eligibility criteria for enrolment phase	1. Suspicion of or histologically/cytologically confirmed adenocarcinoma of biliary tract (intrahepatic, hilar or extrahepatic cholangiocarcinoma or muscle invasive gallbladder carcinoma) scheduled for radical surgical therapy 2. Written informed consent 3. No prior chemotherapy for biliary tract cancer 4. No previous malignancy within 3 years or concomitant malignancy, except: non-melanomatous skin cancer or adequately treated *in situ* cervical cancer 5. No severe or uncontrolled cardiovascular disease (congestive heart failure NYHA III or IV, unstable angina pectoris, history of myocardial infarction in the last 3 months, significant arrhythmia) 6. Absence of psychiatric disorder precluding understanding of information of trial related topics and giving informed consent 7. No serious underlying medical conditions (judged by the investigator), that could impair the ability of the patient to participate in the trial 8. Fertile women (< 1 year after last menstruation) and procreative men willing and able to use effective means of contraception (oral contraceptives, intrauterine contraceptive device, barrier method of contraception in conjunction with spermicidal jelly or surgically sterile) 9. No pregnancy or lactation
Assessments enrolment phase (for details refer to section 5.3)	**Preoperatively** • Obtaining signed written informed consent • Medical and medication history, performance status (ECOG) • Demographics • Laboratory tests: hematology and chemistry panel, tumor markers • Acquisition of blood for translational research • Quality of life assessments

	Intraoperatively • Acquisition of tissue for translational research **Postoperatively** • Acquisition of blood for translational research (during second postoperative week) • Evaluation of feasibility for treatment phase
Eligibility criteria for treatment phase (before randomization)	All enrolled patients will postoperatively be assessed for eligibility for the treatment phase. Additionally patients not previously enrolled into the trial for whatever reason (e.g. incidental finding during surgery) will be evaluated for eligibility. 1. Histologically confirmed adenocarcinoma of biliary tract (intrahepatic, hilar or extrahepatic cholangiocarcinoma or muscle invasive gallbladder carcinoma) after radical surgical therapy with macroscopically complete resection (mixed tumor entities (HCC/CCA) are excluded) (according to appendix H) 2. Macroscopically complete resection (R0/1) within 6 (-16) weeks before scheduled start of chemotherapy 3. ECOG 0-1 4. Age ≥18 years 5. Adequate hematologic function: ANC ≥1.5 x 10^9/L, platelets ≥100 x10^9/L, hemoglobin ≥9 g/dl or ≥5.59 mmol/L 6. Adequate liver function as measured by serum transaminases (AST and ALT) ≤5 x ULN and bilirubin ≤3 x ULN 7. Adequate renal function, i.e. serum creatinine ≤1.5 x ULN, glomerular filtration rate ≥ 50 ml/min 8. No active uncontrolled infection, except chronic viral hepatitis under antiviral therapy 9. No concurrent treatment with other experimental drugs or other anti-cancer therapy, treatment in a clinical trial within 30 days prior to randomization 10. Negative serum pregnancy test within 7 days of starting study treatment in pre-menopausal women and women <1 year after the onset of menopause (Note: a negative test has to be reconfirmed by a urine test, should the 7-day window be exceeded) **Criteria for initial study enrolment** 11. Written informed consent 12. No prior chemotherapy for biliary tract cancer 13. No previous malignancy within 3 years or concomitant malignancy, except: those with a 5 year overall survival rate of more than 90%, e.g. non-melanomatous skin cancer or adequately treated *in situ* cervical cancer 14. No severe or uncontrolled cardiovascular disease (congestive heart failure NYHA III or IV, unstable angina pectoris, history of myocardial infarction in the last 3 months, significant arrhythmia) 15. Absence of psychiatric disorder precluding understanding of information of trial related topics and giving informed consent 16. No serious underlying medical conditions (judged by the investigator), that could impair the ability of the patient to

	participate in the trial 17. Fertile women (< 1 year after last menstruation) and procreative men willing and able to use effective means of contraception (oral contraceptives, intrauterine contraceptive device, barrier method of contraception in conjunction with spermicidal jelly or surgically sterile) 18. No pregnancy or lactation
Treatment, Dosage and Administration	All patients eligible for the treatment phase in stage 2 will be randomized to adjuvant chemotherapy with gemcitabine and cisplatin and observation or capecitabine and observation. **Arm A: Gemcitabine/cisplatin and observation** Therapy will be administered on days 1 and 8 every 3 weeks, with cisplatin (25 mg per square meter of body-surface area) and gemcitabine (1000 mg per square meter) (Valle, Wasan et al. 2010). **Arm B: Capecitabine and observation** Therapy will be administered from day 1 to 14 every 3 weeks, with capecitabine (1250 mg per square meter of body-surface area, twice daily). **Observation** Post-resection evaluation for tumor recurrence will be conducted following current clinical standards (CT or MRI every 3 months for two years after randomization followed by 6-monthly abdominal ultrasound for further 3 years and at the discretion of the investigator thereafter) until disease recurrence (radiological signs of recurrence or histological tumor detection by cytology or biopsy) in both groups. **Duration of treatment** Adjuvant treatment will be administered for 24 weeks (8 cycles of 3 weeks) postoperatively starting 6-16 weeks after surgery. In case of progressive disease (radiological signs of recurrence), unacceptable toxicity or withdrawal of consent, treatment will be terminated.
Assessments treatment phase (for details refer to section 5.3)	**Baseline (within 4 weeks before treatment start – informed consent may be obtained before)** • Review of selection criteria, (obtaining signed written informed consent, if not previously enrolled) • Medical and medication history, physical examination, performance status (ECOG) • Demographics • Laboratory tests: hematology and chemistry panel, tumor markers • Acquisition of blood for translational research • Optional audiometry including audiogram recommended (loss of hearing according to RÖ 73, loss of hearing according to RÖ 80, Highfrequency-Audiogram loss of >20db in 4 frequencies) • Disease and quality of life assessment • Hand out and reply of EORTC INFO25, SDM-Q-9 (PEF-FB-9)

	and SDM-Q-Doc (PEF-FB-Doc) **During treatment (at start of treatment and every 3 weeks, previous to any new cycle) (may be performed up to 3 days before treatment)** • Physical examination, performance status (ECOG), assessment of toxicity, concomitant medication, issue and collect capecitabine patient diary • Laboratory tests (additional blood count on day 8 only for arm A) **Final staging (end of postoperative treatment)** When any subject discontinues dosing of all study treatment, the following assessments should be made: • Physical examination, performance status (ECOG), assessment of toxicity, concomitant medication • Laboratory tests • CA 19-9, (CEA optional) • Disease and quality of life assessment **Follow-up for disease recurrence** All subjects will be evaluated for disease recurrence every 3 to 6 months (+/-28 days), irrespective of treatment arm: • Physical examination, performance status (ECOG), assessment of toxicity • Laboratory tests: • CA 19-9, (CEA optional) • Disease and quality of life assessment • Acquisition of blood for translational research (at recurrence) **After disease recurrence every 3-6 months (+/-28 days) only for (optional: via telephone):** • Survival and disease status including further therapy **Tumor and disease assessment** Tumor assessments will be performed with contrast enhanced chest CT and CT or MRI of abdomen and determination of serum CA 19-9 every 3 months for two years after randomization followed by 6 monthly abdominal ultrasound and CA 19-9 for further 3 years in both arms. In case of clinical suspicion of recurrent disease and/or CA 19-9 elevation without tumor recurrence as diagnosed by CT/MRI scan, further examinations must be performed searching for a local recurrence or metastatic progression of the disease. Diagnosis of recurrence could either be made by radiological imaging or by positive cytology or biopsy. All radiological tumor assessments will be collected and retrospectively reviewed. **Safety**

	Safety assessments will include physical examinations with vital signs (blood pressure, heart rate, respiratory rate), performance status (ECOG), clinical laboratory profile and adverse events. All observed toxicities and side effects will be graded according to NCI CTCAE v4.03 (NCI 2009) for all patients and the degree of association of each with the procedure assessed and summarized. Treatment related serious adverse events rate (SAE), defined as SAEs considered possibly, probably or definitely related to treatment, will be determined.
Translational Research	Preoperatively and postoperatively 30ml of blood will be collected. 15 ml will be collected and immediately shipped for circulating tumor cell (CTC) analyses (only sites in Germany). 15 ml will be used for serum preparation and stored. During operation, fresh frozen tissue and formalin fixed paraffin embedded tissue from the tumor, the surrounding liver tissue and the resected/adjacent lymph nodes should be obtained and stored for microRNA and lymphangiogenic and stem cell marker analyses. At baseline and at disease recurrence 15 ml of blood will be collected and used for serum preparation and stored. Serum will be used for microRNA and lymphangiogenic and stem cell marker analyses and for further markers, which might gain importance during the course of the trial. For tissue and blood sampling working instructions refer to appendix G or the respective national lab manual.
Statistical Considerations	Based on protocol versions 2-5 187 patients were randomized to gemcitabine, cisplatin and observation vs. observation alone, which was the respective standard of care at that time-point. Meanwhile the standard of care has changed to capecitabine and observation, instead of observation alone. Thus, the trial will be amended to include the recent standard of care. To account for the adapted design the number of patients to be included in this second stage of the trial requires a separate sample size calculation. The displayed sample size calculation only covers the second stage of the trial and the required number will thus be added to the already included patients in the first stage (n=187). For the first stage and the overall trial (stage 1+2) a power analyses will be conducted based on the most recent data from the randomized trials. **Overall statistical analysis (stage 1+2) - gemcitabine/cisplatin vs. standard of care (observation +/- capecitabine)** In the first stage 187 patients have been randomized to gemcitabine/cisplatin and observation vs. observation alone. In stage 2 578 patients will be randomized to gemcitabine/cisplatin vs. capecitabine. Thus, overall 765 will be available for analysis (excluding the expected 3% loss-to-follow-up). Based on the data obtained in the observation alone arms in the current adjuvant studies and on the initial assumption of an 15% improvement of the disease free survival rate at 24 months (DFSR@24) gemcitabine and cisplatin is expected to result in a DFSR@24 of 60.2% (event rate of 39.8%), compared to 50.9%

	(event rate 49.1%) with capecitabine or observation alone, assuming the lowest expected difference (10%) between the experimental arm (gemcitabine/cisplatin) and the control arm (capecitabine or observation alone) (hazard ratio = 0.752). Taking into account the prespecified alpha of 5% and a follow up time of 48+24 months the power of the pooled analysis is 90% (compare appendix F). **Statistical analysis of stage 1 - gemcitabine/cisplatin vs. observation** In the stage 1 part 187 patients have been randomized to gemcitabine/cisplatin and observation vs. observation alone. Based on the data obtained in the observation alone arms in the current adjuvant studies and on the initial assumption of an 15% improvement of the disease free survival rate at 24 months (DFSR@24) gemcitabine and cisplatin is expected to result in a DFSR@24 of 60% (event rate of 40%), compared to 45% (event rate 55%) with observation alone (hazard ratio = 0.64). Taking into account the prespecified alpha of 5% and a follow up time of 72 months the power is expected to be 79% (compare appendix F). In addition to the above-mentioned analysis, which will be performed together with the overall and stage 2 analysis, an analysis of stage 1 will be conducted as initially planned after 154 events (defined as death or disease recurrence) have occurred (about 24 months after last patient in stage 1, approximately May 2019). This analysis will be evaluated by the IDMC for decision upon trial continuation. A statistical evaluation and decision plan will be developed beforehand. **Sample size calculation for stage 2 - gemcitabine/cisplatin vs. capecitabine** The BILCAP trial has established the new adjuvant treatment standard for biliary tract cancer with a median DFS of 24.6 months and a DFSR@24 of 50.9%. Therefore, DFSR@24 is expected to be 50.94% with adjuvant capecitabine (event rate 49.1%). The investigational treatment (adjuvant gemcitabine/cisplatin) should increase DFSR@24 by about 10% to 60.2% (event rate 39.8%) to be regarded as promising for further evaluation and of clinical relevance (hazard ratio = 0.752). The risk of falsely rejecting the null hypothesis of no difference between the experimental and the control arm was restricted to 5%. The risk of falsely rejecting the alternative hypothesis of a difference between the experimental and the control arm was set not to increase 20%, corresponding to a power of 80%. An interim analyses will be performed after 50% of events occurred (n=194) (refer to paragraph 10.1). With these restrictions, 578 evaluable study patients have to be followed for 24 months to observe 388 events (compare appendix F). With an assumed loss-to-follow-up of 3% 594 patients (297 patients per arm) have to be recruited for inclusion into the trial. Randomization will be performed according to the following criteria: <u>Stratification criteria</u>

	• intrahepatic vs. hilar/distal cholangiocarcinoma vs. gallbladder cancer • lymph node positivity vs. negativity • R0 vs. R1 resection

Flow chart (figure 1)

Study Schedule Visit	Enrolment phase			Randomized phase					
	Preop.	Intraop.	Postop	Inclusion	During treatment		End of Treatment	Follow up for all patients after random.	
Study week (W)				Baseline W -4 to 0	W0, day1 afterwards every 3 wks[15]	**Arm A only**: day 8 every 3 wks[16]		every 3/6[11] months, until recurrence	every 3/6[11] months, after recurrence[4]
Informed consent	X			(X)[10]					
Medical history, demographics	X			X					
Physical examination[1]				X	X		X	X	(X)
Vital signs[2]				X	X		X	X	(X)
Performance status (ECOG)	X			X	X		X	X	(X)
Obtain tumor tissue		X[5]		X[6]					
Audiometry optional				X[9]					
Blood draw translat. research	X		X	X				X[13]	
Laboratory determinations[3]	X			X	X	X[12]	X	X	(X)
Treatment (chemotherapy)					X	X			
Capecitabine patient diary (Arm B only)					X[17]		X[17]		
Tumor markers (CA 19-9, CEA optional)	X			X			X	X	(X)
Tumor assessment[11]				X			X	X	(X)
Quality of life assessment[8]	X			X			X	X	
EORTC INFO 25, SDM-Q-9 and SDM-Q-Doc	X[7]			X[7,10]					
Concomitant medication				X	X	X	X	X[14]	
AE monitoring				X[14]					
Survival	X								

1: including weight, height (only baseline) (baseline weight can be used for C1D1 if within 7 days of first treatment)
2: blood pressure, heart rate, respiratory rate, body temperature
3: hematology panel (hemoglobin, platelets, WBC with neutrophils, lymphocytes, monocytes), chemistry panel (sodium, potassium, calcium, serum creatinine, alkaline phosphatase, AST, ALT, total and direct bilirubin, CrP; glomerular filtration rate, (e.g.by MDRD) and coagulation (INR, aPTT, PT) at baseline and on day 1 prior every treatment cycle (coagulation not needed post baseline), serum pregnancy test in women of childbearing potential at baseline (baseline lab tests can be used for C1D1 if within 7 days of first treatment)
4: follow-up to determine survival, disease status and further therapy (e.g. by telephone)
5: intraoperative tumor tissue (fresh frozen/paraffin embedded)
6: only patients not participating in the enrolment phase, but consenting to obtain paraffin embedded tumor tissue
7: after informed consent, SDM-Q-Doc (PEF-FB-Doc) should be completed by the consenting investigator the same day
8: Quality of life assessments using EORTC QLQ-C30 and module BIL-21
9: optional audiometry including audiogram
10: informed consent may be obtained before the 4 weeks screening period; applies only for patients not previously enrolled
11: baseline scan not more than 12 weeks before randomization (preoperative imaging may be used), every 3 months (+/-28 days) for two years after randomization by CT or MRI afterwards every 6 months (+/-28 days) for further 3 years with abdominal ultrasound
12: hematology panel (hemoglobin, platelets, WBC with neutrophils)
13: at disease recurrence
14: until 28 d after last application

15: assessments may be performed up to 3 days before treatment, treatment leeway for day 1 +/- 3 days
16: day 8 only applies to arm A (gemcitabine/cisplatin), treatment leeway for day 8 -1 day/+ 2 days
17: Issue capecitabine patient diary and/or collect from previous cycle (only in arm B)

1. Introduction and Background

1.1 Epidemiology

The incidence of biliary tract cancers (BTC) varies extremely in different geographical regions, which reflects the variable distribution of local risk factors and genetic differences.
Intrahepatic cholangiocarcinomas (CCA) are most frequently observed in Northern Thailand with 96 per 100,000 male individuals, due to a more than 90% infestation with the liver fluke *Opisthorchis viverrini*. In Western countries the rate of CCA is much lower, between 0.4 and 1.0 cases are observed per 100,000. The incidence in Western countries is highest in patients older than 65 years of age. For unknown reasons, incidence and mortality rates are increasing within the last decades in most developed countries.
Extrahepatic CCA reveal only small regional differences. The incidence ranges between 0.5 and 1.1 per 100,000, with a maximum incidence between 70 and 74 years of age. A slight male predominance is found in patients with intra- and extrahepatic CCA (Seehofer, Kamphues et al. 2008, Ustundag and Bayraktar 2008, Yang and Yan 2008).
The incidence of gallbladder carcinoma is about between 2.0 per 100,000 with a median age of 67 years (Ferlay, Shin et al. 2010, Hundal and Shaffer 2014). Gallstones in particular size and duration and chronic infections represent an important risk factor.

1.2 Surgery: Results after Complete Resection of biliary tract cancer (BTC)

Up to now, complete surgical resection represents the only potentially curative treatment option for CCA and is therefore the treatment of choice if deemed surgically resectable. Unfortunately, more than 50% of patients present with unresectable disease at the time of diagnosis. The prognosis at this stage is dismal, being approximately 3 months without intervention, and 4-6 months with palliative biliary decompression. Even after curative (R0) resection, the 5-year survival rate is only 20-40%. The most relevant prognostic factors after resection are R0 status, nodal status, vascular invasion, and tumor grading (Tamandl, Herberger et al. 2008, Choi, Kim et al. 2009, Guglielmi, Ruzzenente et al. 2009, Li, Liang et al. 2009, Murakami, Uemura et al. 2010, Nuzzo, Giuliante et al. 2010, Saxena, Chua et al. 2010).
Tamandl et al. described a median disease free survival between 11.4 to 9.8 months, depending on the distance between the tumor and resection margins. In case of R1 resection, the same study observed a median disease free survival of 9.9 months. The data demonstrate that resection margins (R0 vs. R1) probably play a minor role in the prognosis of CCA following resection, as long as complete tumor clearance can be achieved with modern liver dissection techniques.
A retrospective study evaluated the results of surgical therapy for intrahepatic CCA, the incidence and the management of disease, and analyzed the change in approach during 2 different periods. The 3-year overall survival rate (OS) was 62%, whereas the 3-year disease-free survival rate was only 30%, the median survival time was 57.1 months. Patient and histologic characteristics before and after 1999 were similar, but OS was significantly better among patients operated after 1999. Following 1999, the patients were significantly more frequently node-negative, did not receive blood transfusions, and underwent adjuvant chemotherapy. The most frequent site of disease recurrence was the liver (Ercolani, Vetrone et al. 2010). Another study observed the important role of a negative node status for prognostic outcome (Choi, Kim et al. 2009). In patients with primary sclerosing cholangitis (PSC), surgery was associated with a discouraging 5-year postoperative survival of less than 10% (Ustundag and Bayraktar 2008).

In summary, despite complete resection, disease free survival rates (DFS) are low. Following complete resection, patients had disease free survival rates of 48 to 65% after one year and 23 to 35% after three years without adjuvant treatment (Takada, Amano et al. 2002, Tamandl, Herberger et al. 2008, Choi, Kim et al. 2009). Patients with a positive nodal status and/or vascular invasion at time of resection had an even higher risk of disease recurrence.
For muscle invasive gallbladder carcinoma prognosis seem to be worse than for cholangiocarcinoma (Jarnagin, Ruo et al. 2003). Following complete resection disease free survival times are about 10-12 months and overall survival rates are about 55% after 1 year and about 30% after 3 years (Takada, Amano et al. 2002, Jarnagin, Ruo et al. 2003, Duffy, Capanu et al. 2008, Mayo, Shore et al. 2010).

1.3 Treatment Modalities for biliary tract cancer

Available treatment modalities are chemotherapy, radiotherapy, chemoradiation, photodynamic treatment, and liver transplantation in localized unresectable disease for bile duct cancers.
Current approaches for systemic, unresectable BTC, either at initial diagnosis or in case of local or distant disease progression after resection, are based on systemic chemotherapy (CTx). A previous randomized trial revealed that CTx significantly improved survival and quality of life compared to best supportive care for unresectable CCA (Koeberle, Saletti et al. 2008). Several drugs were found to be active in BTC, e.g. fluorouracil (5-FU), gemcitabine, mitomycin, cisplatin, capecitabine, epirubicin, and oxaliplatin. A pooled analysis of 104 CTx studies in advanced bile duct cancers suggested that gemcitabine combined with cisplatin or oxaliplatin resulted in the best response rates, however, without significantly improving survival (Eckel and Schmid 2007). Recently, the randomized phase III ABC 02 trial revealed a median OS of 11.7 months among 204 patients treated with cisplatin and gemcitabine compared to 8.1 months among 206 patients treated with gemcitabine alone (hazard ratio 0.64; 95% confidence interval 0.52 to 0.80; p<0.001). The median progression-free survival was 8.0 months in the cisplatin/gemcitabine-group and 5.0 months in the gemcitabine only-group (p<0.001). In addition, the rate of tumor control rate (CR+PR+SD) among patients in the cisplatin/gemcitabine-group was significantly increased (81.4% vs. 71.8%; p=0.049). Adverse events were similar in the two groups, with the exception of more frequent neutropenia in the cisplatin/gemcitabine-group, although the number of neutropenia-associated infections was similar in the two groups (Valle, Wasan et al. 2010). Therefore, the combination of cisplatin and gemcitabine is currently regarded as new standard of care in metastatic or unresectable BTC.

1.4 Adjuvant Chemotherapy in biliary tract cancer

Because of high rates of disease recurrence and poor survival rates following radical surgery, postoperative treatment modalities, e.g., CTx, radiotherapy, and chemoradiation, have been considered to improve patient survival after resection of bile duct cancers (Anderson and Kim 2009).
A multicenter randomized trial evaluated the effect of adjuvant CTx with mitomycin C and 5-FU vs. surgery alone for patients with pancreato-biliary malignancies, in which a non-significant survival benefit was seen for patients with R0 resection for CCA with a DFS at 5 years of 15.8% vs. 32.4% and an OS at 5 years of 28.3% to 41.0% in favor of the adjuvant treatment (Takada, Amano et al. 2002).
A recent single-institutional retrospective evaluation found that gemcitabine-based adjuvant CTx after curative intent surgery significantly improved patient survival (Murakami, Uemura et al. 2010).

The Retrospective analysis of the Surveillance, Epidemiology, and End Results (SEER) database showed a significant benefit for adjuvant radiation therapy (Shinohara, Mitra et al. 2008). Combined chemoradiation with 5-FU and mitomycin in 34 patients seemed to be beneficial compared to historical survival data (Hughes, Frassica et al. 2007). Current retrospective analyses or guidelines (NCCN version 2/2012) recommend in the absence of randomized data consideration of radio(chemo)therapy in case of positive margin and/or positive lymph nodes, particularly in extra hepatic tumors (Horgan 2011).
The gallbladder carcinoma subgroup of a randomized trial evaluating 5-FU and mitomycin compared to observation alone showed a significant increase of 8.7% in the 5 year DFS rate in favor of the adjuvant chemotherapy (Takada, Amano et al. 2002). Additionally, adjuvant 5-FU based chemoradiation has been used as adjuvant treatment after complete or margin positive resection (Duffy, Capanu et al. 2008, Gold, Miller et al. 2009, Mayo, Shore et al. 2010, Wang, Lemieux et al. 2011).
Recently, the results of two randomized trials were presented evaluating the role of either gemcitabine and oxaliplatin (PRODIGE 12) or capecitabine (BILCAP) compared to observation alone. The PRODIGE 12 trial showed a numerical, but non-significant recurrence free survival (RFS) benefit for gemcitabine and oxaliplatin compared to observation alone (30.4 months vs. 22 months, HR 0.83, 95% CI: 0.58-1.19, p=0.31) in 196 patients (primary endpoint) (Edeline, Bonnetain et al. 2017). The treatment was well tolerated, showing no unexpected safety signals. Quality of life was not negatively affected by chemotherapy.
The most recent results of the BILCAP trial in 447 patients showed a significantly improved RFS in favor of capecitabine (17.6 months vs. 24.6 months, HR 0.76, 95% CI: 0.58-0.99, p=0.039). Furthermore, the primary endpoint (OS) was clinically relevant, although non-significantly improved from 36.4 months to 51.1 months in the intent to treat population (HR 0.81, 95% CI: 0.63-1.04, p=0.097) (Primrose, Fox et al. 2017). In a sensitivity analysis, adjusting for further prognostic factors (nodal status, disease grade and gender) this benefit became significant (HR 0.70, 95% CI: 0.55-0.91, p=0.007). The treatment was well tolerated without unexpected adverse events or a detriment in quality of life.
Subgroup analyses revealed a non-significant trend for poorer outcome in patients with hilar tumors and R1 resection, which may be related with each other.

1.5 Rationale for the Clinical Trial

Survival after curative intent surgery in BTC remains poor due to high rates of disease recurrence. Data from recent randomized clinical trials have shown the activity of a gemcitabine and platinum based regimen and the survival benefit for capecitabine both compared to observation alone. Based on the activity shown for both regimen gemcitabine/oxaliplatin and capecitabine the comparative efficacy needs to be established. In the palliative setting gemcitabine and cisplatin is the current standard of care showing a clinically relevant efficacy and good tolerability compared to gemcitabine alone (Valle, Wasan et al. 2010). Gemcitabine and cisplatin has a relevantly higher dose of gemcitabine 18 applications of 1000mg/m2 vs. 12 and may thus be of increased efficacy compared to the gemcitabine/oxaliplatin regimen applied in the PRODIGE 12 trial. Therefore, the ACTICCA trial will be amended to compare the highly active and established standard regimen in the metastatic setting (gemcitabine and cisplatin) to the newly established standard regimen in the adjuvant setting capecitabine, aiming for superiority of the combination regimen vs. the oral monotherapy.

In regard of inclusion criteria for adjuvant trials in pancreatic cancer (e.g. ESPAC IV) with a comparable surgical approach and postoperative recovery time inclusion of patients within a maximum interval of 16 weeks between surgery and start of chemotherapy was chosen.
The chosen stratification factors are based on currently available data. Intra- and extrahepatic CCA and gallbladder cancers (GBC) are usually regarded as different entities of biliary tract cancers, although there is a lack of comparative retrospective data for both, as the majority of analyses evaluates either intra- or extrahepatic CCA or GBC. Subgroup-analyses of the recent adjuvant trials showed no significant interaction of tumour location and effect of adjuvant chemotherapy. Therefore, all different locations will be included in the ACTICCA trial. However, stratification was chosen to exclude influence of localization.
Although lymphadenectomy was only recently added to standard surgical approach lymph node status seems to be the most important pathological factor, as demonstrated in several analyses (Choi, Kim et al. 2009, Murakami, Uemura et al. 2010, Saxena, Chua et al. 2010, Horgan 2011). Recent large retrospective analyses in 449 patients with intrahepatic CCA, of whom 248 received lymph node dissection demonstrated a significant difference in OS of 30 vs. 24 months (N0 vs N1) (de Jong, Nathan et al. 2011). Similarly lymph node positivity is a strong prognostic factor in gallbladder carcinoma and was thus chosen as a stratification factor for the gallbladder carcinoma cohort (Mayo, Shore et al. 2010, Wang, Lemieux et al. 2011, Goetze and Paolucci 2012).
Furthermore, several analyses have shown R0 resection rates of 56-80% depending on localization of tumor and a prognostic value of R0 resection (Su, Tsay et al. 1996, Jarnagin, Fong et al. 2001, Guglielmi, Ruzzenente et al. 2009, de Jong, Nathan et al. 2011). Based on the recent subgroup analyses of the adjuvant trials resection status seem to be of relevance, although not significantly interfering with treatment effect. Thus resection status was included as stratification factor.

1.6 Rationale for the translational part

Data on prognostic factors for BTC are rare. Moreover, if adjuvant chemotherapy will become a standard of care in the future predictive markers might gain particular importance. Within the current trial tumor tissue and serum (both stored locally) will be collected together with the clinical data. Beside the clinical case report form an allocation database will be established gathering the data of the available patient samples at each study site to enable translational research.

1.7 Rationale for the investigation of the information content of the informed consent and the shared decision-making process

Relating to new media providing a fast and easy access to information and an enhancing patient autonomy patients´ competence concerning the consequences of their disease is growing. Nevertheless, the information and education by the physician is not replaced but becomes even more important. In the doctor-patient relationship the physician plays a central role as consultant who not only provides information but also involves patients in the decision-making process (shared decision making). Although medical tasks consist mainly of giving information and consulting patients, physicians are neither trained nor supervised.

Surveys among oncological patients and physicians on the subject of „shared decision making", show the differences between physicians´ and patients´ perspective concerning aims of treatment and involvement in decision-making processes.
Therefore, quantity and quality of information patients have gained after the explanatory talk and the involvement of patients in the decision-making process will be investigated (Kriston, Scholl et al. 2010, Scholl, Kriston et al. 2012, Scholl, Kriston et al. 2012). This could provide more clarity about the need of physician training.

2. Study Objective

The primary objective of this study is to evaluate the efficacy of gemcitabine and cisplatin compared with standard of care (observation alone in stage 1 and capecitabine and observation in stage 2) in patients with BTC after complete resection in terms of DFS. Secondary objectives are safety and tolerability of the treatment as well as RFS and OS, quality of life, function of biliodigestive anastomoses, and evaluation of the quantity and quality of information patients have gained after the informed consent as well as of the involvement of patients in the decision-making process (shared decision making).

3. Study Design

This is a multicenter, prospective, randomized, controlled phase III trial designed to assess the clinical performance of gemcitabine with cisplatin and observation vs. standard of care (observation alone in stage 1 and capecitabine and observation in stage 2) in patients after curative intent resection of BTC.

3.1 Primary Endpoint

The primary endpoint is:

- Disease free survival (DFS)

3.2 Secondary Endpoints

The secondary endpoints will include:

- Disease free survival rate at 24 months (DFSR@24)
- Recurrence free survival (RFS)
- Overall survival (OS)
- Safety and tolerability of adjuvant chemotherapy
- Quality of life (QoL)
- Function of biliodigestive anastomosis (in terms of surgical revision, requirement for PTCD)
- Rate and severity of biliary tract infections
- Patterns of disease recurrence
- Locoregional control

4. Study Population

4.1 Number of Patients

781 patients (187 in stage 1 and 594 in stage 2) will be randomized in the treatment phase of the study. Study enrolment will be continued until the 594th patient is randomized in stage 2. Patients withdrawn from the trial will not be replaced.

4.2 Selection criteria

The study contains two phases (enrolment and treatment phase) with different selection criteria. Patients will be enrolled into the trial according to the selection criteria in section 4.2.1, resected and afterwards evaluated for eligibility for the treatment phase according to selection criteria in section 4.2.2. Patients not previously enrolled into the trial for whatever reason (e.g. incidental finding during surgery) can still be evaluated for eligibility and included in the treatment phase.

4.2.1 Eligibility criteria for enrolment phase

1. Suspicion of or histologically/cytologically confirmed adenocarcinoma of biliary tract (intrahepatic, hilar or extrahepatic cholangiocarcinoma, or muscle invasive gallbladder carcinoma) scheduled for radical surgical therapy
2. Written informed consent
3. No prior chemotherapy for biliary tract cancer
4. No previous malignancy within 3 years or concomitant malignancy, except those with a 5 year overall survival rate of more than 90%, e.g. non-melanomatous skin cancer or adequately treated *in situ* cervical cancer
5. No severe or uncontrolled cardiovascular disease (congestive heart failure NYHA III or IV, unstable angina pectoris, history of myocardial infarction in the last 3 months, significant arrhythmia)
6. Absence of psychiatric disorder precluding understanding of information of trial related topics and giving informed consent
7. No serious underlying medical conditions (judged by the investigator), that could impair the ability of the patient to participate in the trial
8. Fertile women (< 1 year after last menstruation) and procreative men willing and able to use effective means of contraception (oral contraceptives, intrauterine contraceptive device, barrier method of contraception in conjunction with spermicidal jelly or surgically sterile)
9. No pregnancy or lactation

4.2.2 Eligibility criteria for treatment phase (before randomization)

All enrolled patients will postoperatively be assessed for eligibility for the treatment phase. Additionally patients not previously enrolled into the trial for whatever reason (e.g. incidental finding during surgery) will be evaluated for eligibility.

1. Histologically confirmed adenocarcinoma of biliary tract (intrahepatic, hilar or extrahepatic cholangiocarcinoma or muscle invasive gallbladder carcinoma) after radical surgical therapy with macroscopically complete resection (mixed tumor entities (HCC/CCA) are excluded) (according to appendix H)
2. Macroscopically complete resection (R0/1) within 6 (-16) weeks before scheduled start of chemotherapy
3. ECOG 0-1
4. Age ≥18 years

5. Adequate hematologic function: ANC ≥1.5 x 10^9/L, platelets ≥100 x10^9/L, hemoglobin ≥9 g/dl or ≥5.59 mmol/L
6. Adequate liver function as measured by serum transaminases (AST and ALT) ≤5 x ULN and bilirubin ≤3 x ULN
7. Adequate renal function, i.e. serum creatinine ≤1.5 x ULN, glomerular filtration rate ≥ 50 ml/min (determination of GFR according to local institutional standards, e.g. MDRD, (Appendix E))
8. No active uncontrolled infection, except chronic viral hepatitis under antiviral therapy
9. No concurrent treatment with other experimental drugs or other anti-cancer therapy, treatment in a clinical trial within 30 days prior to randomization
10. Negative serum pregnancy test within 7 days of starting study treatment in pre-menopausal women and women <1 year after the onset of menopause (Note: a negative test has to be reconfirmed by a urine test, should the 7-day window be exceeded)

Criteria for initial study enrolment (refer to section 4.2.1)

11. Written informed consent
12. No prior chemotherapy for biliary tract cancer
13. No previous malignancy within 3 years or concomitant malignancy, except: non-melanomatous skin cancer or adequately treated in situ cervical cancer
14. No severe or uncontrolled cardiovascular disease (congestive heart failure NYHA III or IV, unstable angina pectoris, history of myocardial infarction in the last 3 months, significant arrhythmia)
15. Absence of psychiatric disorder precluding understanding of information of trial related topics and giving informed consent
16. No serious underlying medical conditions (judged by the investigator), that could impair the ability of the patient to participate in the trial
17. Fertile women (< 1 year after last menstruation) and procreative men willing and able to use effective means of contraception (oral contraceptives, intrauterine contraceptive device, barrier method of contraception in conjunction with spermicidal jelly or surgically sterile)
18. No pregnancy or lactation

5. Study Procedures and Methodology

5.1 Overall Study Schedule Overview

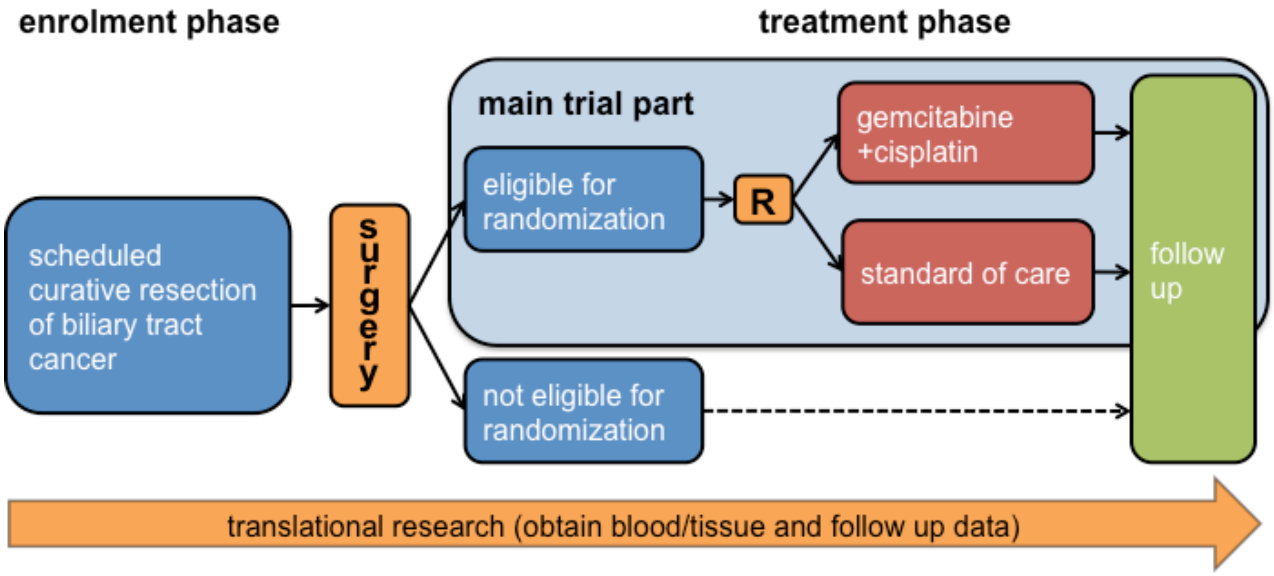


Figure 2: Overall study schedule overview

5.2 Treatment Phase Overview (stage 2)

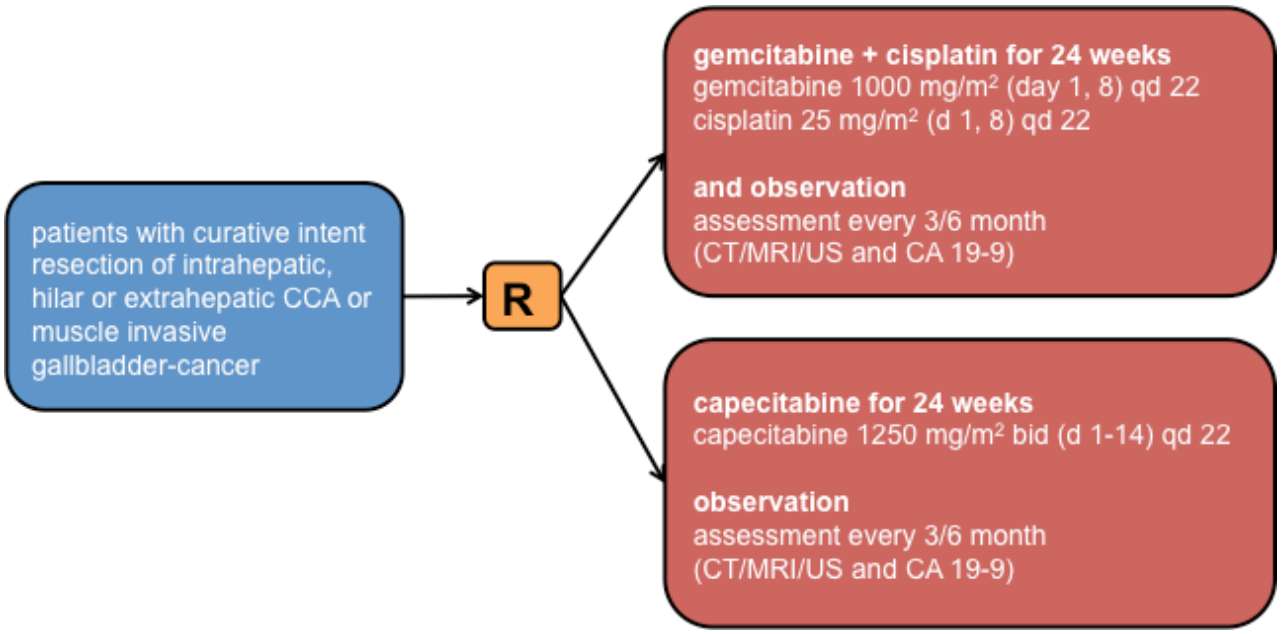


Figure 3: Treatment phase overview in stage 2

5.2.1 Treatment in stage 2

Adjuvant chemotherapy with capecitabine is the current standard of care for BTC. The experimental treatment with gemcitabine and cisplatin will be supplied by medac GmbH in some countries (e.g. Germany), and defined as investigational medicinal products (IMP).

Adjuvant chemotherapy should start as soon as possible after the date of definitive surgery (within a minimum of 6 and a maximum of 16 weeks of that date) and ideally within 1 week of randomisation.

5.2.1.1 Arm A (gemcitabine plus cisplatin and observation)

Patients assigned to gemcitabine and cisplatin will receive every three weeks on days 1 and 8 (treatment leeway for day 1 +/- 3 days, day 8 -1 day/+ 2 days):

- *Cisplatin* 25 mg/m^2 i.v. (over 1h)
- *Gemcitabine* 1000 mg/m^2 i.v (over 30min.)

for 24 weeks (8 cycles).

Follow up every 3 months after baseline irrespective of treatment visits via CT or MRI for two years followed by 6 monthly abdominal ultrasound for further 3 years, together with clinical evaluation, and determination of CA 19-9.

5.2.1.2 Arm B (capecitabine and observation)

Patients assigned to capecitabine will receive every three weeks from day 1 to 14:

- *Capecitabine* 1250 mg/m^2 twice daily orally

for 24 weeks (8 cycles).

Follow up every 3 months after baseline irrespective of treatment visits via CT or MRI for two years followed by 6 monthly abdominal ultrasound for further 3 years, together with clinical evaluation, and determination of CA 19-9.

5.2.2 Treatment duration

Treatment will be administered every three weeks until progression, intolerable toxicity, or for a maximum of 8 cycles (24 weeks). In case of recurrent disease, unacceptable toxicity, or withdrawal of consent, treatment will be terminated.

5.2.3 Study medication

The relevant information on the drug characteristics, storage, application, mode of action and adverse reactions is included in the Summary of Product Characteristics (SmPC, “Fachinformation“) for the used drugs. The study medication will be supplied by medac GmbH in some countries (e.g. Germany) in vials of 1500 and 200mg for gemcitabine and 50mg for cisplatin and delivered to the local pharmacy for preparation and administration. Standard calculations for body surface area (BSA) based on height and actual body weight will be applied. Capecitabine as standard of care for BTC will not be supplied by the sponsor.

5.2.3.1 Capecitabine

Capecitabine is available from various pharmaceutical companies. Capecitabine should be ordered and administered as per local standard of care. Suggested dose modifications are displayed in paragraph 6.2.2. A dosage of capecitabine at the standard dose of 1250 mg/m^2 given orally twice a day on day 1 to 14 of a 3 weekly cycle for a total of 24 weeks

(8 cycles). Capecitabine tablets should be administered morning and evening and swallowed with water within 30 minutes after a meal.

Adverse reactions of capecitabine include diarrhea and dehydration, hand-foot syndrome, nausea/vomiting, myelosuppression, particularly anemia, and increase of liver enzymes or bilirubine. Please refer to the SmPC ("Fachinformation") for further details on capecitabine, including side effects.

5.2.3.2 Cisplatin

Cisplatin is available from various pharmaceutical companies. A dosage of 25 mg/m^2 is applied on day 1 and 8 of each three-week cycle together with gemcitabine according to routine procedures of the respective institution, with adequate pre- and posthydration. The following schedule is recommended: cisplatin in 1000ml 0.9% saline with KCl 20mmol and $MgSO_4$ 8mmol during the one hour cisplatin infusion followed by 500ml 0.9% saline over 30 minutes prior to the gemcitabine.

Adverse effects of cisplatin include myelosuppression (mostly moderate), severe nausea/vomiting, nephrotoxicity, neurotoxicity, ototoxicity. Please refer to the SmPC ("Fachinformation") for further details on cisplatin, including side effects.

5.2.3.3 Gemcitabine

Gemcitabine is registered for the use in a variety of epithelial cancers, also in combination with other drugs. A dosage of Gemcitabine 1000 mg/m² is applied i.v. on day 1 and 8 of each three-week cycle according to routine procedures of the respective institution. The following schedule is recommended: gemcitabine in 250 - 500ml 0.9% saline.

Adverse reactions of gemcitabine include myelosuppression, nausea/vomiting, diarrhea, obstipation, increase of liver enzymes, flu-like symptoms, dyspnea, edema, skin reactions. Please refer to the SmPC ("Fachinformation") for further details on gemcitabine, including side effects.

5.2.4 Criteria for deferring subsequent courses for gemcitabine and cisplatin

Initiation of subsequent treatment cycles will be dependent upon the full blood count taken prior to treatment and on the assessment of renal function. Treatment will be deferred for toxicity by one week only (note this does not apply to biliary tract obstruction). If a second deferral is required, the treatment week in question is omitted and the patient will move on to the next treatment point (not necessarily next cycle).

For example: A patient has received cycle 3 day 1 (C3D1) of treatment and is due cycle 3 day 8 (C3D8):

Gemcitabine & Cisplatin

No deferral	C3D1	C3D8	C3D15	C4D1	
Treatment given	✓	✓	×	✓	
1-week deferral	C3D1	C3D8	C3D8	C3D15	C4D1
Treatment given	✓	×	✓	×	✓
			ie cycle 3D8 is given 1 week late		
2-week deferral	C3D1	C3D8	C3D8	C3D15/C4D1	
Treatment given	✓	×	×	✓*	
		ie cycle 3D8 is omitted altogether and *next cycle starts			

Table 1 Treatment deferral

5.2.5 Concomitant medication

5.2.5.1 Antiemetics

Gemcitabine/cisplatin

For prevention of nausea and vomiting, the 5-hydroxytryptamine-3 (5-HT3) receptor antagonists and dexamethasone are recommended for cisplatin-based CTx. In case of insufficient double prophylaxis, secondary escalation with aprepitant might be considered. For delayed nausea and vomiting, the use of oral dexamethasone is recommended; metoclopramide, alizapride, prochlorperazine may be used at the discretion of the prescribing physician. (See table 2 for an optional schedule.)
Subjects should have a supply of antiemetics available at home should delayed nausea and vomiting occur.

Pre chemo on day 1	8 mg dexamethasone iv plus 5HT3 iv (e.g. 0.25mg Palonosetron or 1 mg Granisetron or 4 mg Ondansetron)
Day 2	4-8 mg dexamethasone PO
Day 3	4-8 mg dexamethasone PO
Days 1-5	Domperidone ≥10 mg tid PRN Metoclopromide 10 mg tid PO

Table 2. Schedule of optional dosage of antiemetics

The above antiemetic schedules are optional; alternatively anti-emetics should be given according to local practice with reference to the information above.

Capecitabine

Anti-emetics will be given to patients in the capecitabine arm if required. Generally, capecitabine is not highly emetogenic and does not require routine anti-emetic dosage.

5.2.5.2 Antibiotics

Antibiotics which are potentially nephrotoxic or ototoxic should not be given during treatment with cisplatin.

5.2.5.3 Anticoagulants

The use of full dose anticoagulants is allowed as long as the INR or PTT is within therapeutic limits (according to the medical standards in the institution) and the patient has been on a stable dose for anticoagulants for at least two weeks at the time of registration. During treatment close monitoring of INR for oral anticoagulants is recommended.

5.2.5.4 Anti-epileptic Substances

Cisplatin may diminish the effect of anti-epileptic substances (phenobarbital, primidone, phenytoin and succinimides) and may increase the frequency of seizures.

5.2.5.5 Growth factors

Hematopoietic growth factors (i.e., G-CSF) may be used according to institutional guidelines to treat febrile neutropenia, but should not be used as primary or secondary prophylaxis. Growth factors must be discontinued at least 48 hours prior to initiation of the next treatment of chemotherapy.

5.2.5.6 Others

For capecitabine the concomitant use of **sorivudine and analogues** is prohibited due to interactions with the dihydropyrimidin-dehydrogenase. Current data in gastric cancer indicate a potential worse survival with the concomitant use of **protone-pump inhibitors**, which should be avoided if possible. For details of contraindications, Investigators should refer to the respective SmPC.

5.3 Assessments and Guidelines for Visits

5.3.1 Assessments for the enrolment phase

Preoperatively

- Obtaining signed written informed consent,
- Medical history including previous cancer history and cancer treatment.
- Demographics
- Performance Status (ECOG) (Appendix B)
- Laboratory test: hematology panel (hemoglobin, platelets, WBC and WBC differential with neutrophils, lymphocytes, monocytes) chemistry panel (sodium, potassium, calcium, creatinine, total and direct bilirubin, alkaline phosphatase, ALT, AST, CrP, INR, aPTT, PT) and CA 19-9, CEA (optional)
- Blood draw for translational research: 30 ml of blood (15 ml shipped immediately for CTC analyses only for Germany, 15 ml stored for further analyses) (Appendix G)
- Quality of life assessment using the EORTC QLQ-C30 and the module BIL21 (Appendix D)
- EORTC INFO 25, SDM-Q-9 (PEF-FB-9) and SDM-Q-Doc (PEF-FB-Doc) (Should be handed out to the patient and should be completed by the consenting investigator the same day.)

Intraoperatively

- Fresh frozen tissue and formalin fixed paraffin embedded tissue from the tumor, the surrounding liver tissue and the resected/adjacent lymph nodes will be obtained and stored locally

Postoperatively

- Blood draw for translational research: 30 ml of blood (15 ml shipped immediately for CTC analyses only for Germany, 15 ml stored for further analyses) (Appendix G)
- Evaluation of feasibility for treatment phase

5.3.2 Baseline assessments for the treatment phase (postoperatively)

All enrolled patients will postoperatively be assessed for eligibility for the treatment phase. Previously not enrolled patients with curative intent resection of BTC will be reviewed for study eligibility. After checking suitability to enter the study, previously not enrolled patients who agree to participate must sign the informed consent form before undergoing any study related procedures or treatment.
Consenting patients will have the following screening/baseline assessments performed prior to the first treatment.

Within four weeks of the first treatment:

- Review of eligibility criteria and obtaining signed written informed consent, if not previously enrolled (may be performed before the 4 weeks pre-treatment interval)
- Relevant medical history including previous cancer history and cancer treatment, any additional relevant medication taken one year prior to study start will also be recorded
- Demographics
- Obtain surgical and pathological report (in case of incidental gallbladder cancer prior to oncological resection, initial stage and residual tumour at resection should be recorded)
- Physical examination including weight, height and vital signs (blood pressure, heart rate, respiratory rate, body temperature)
- Laboratory test: hematology panel (hemoglobin, platelets, WBC and WBC differential with neutrophils, lymphocytes, monocytes) chemistry panel (sodium, potassium, calcium, creatinine, total and direct bilirubin, alkaline phosphatase, ALT, AST, CrP, INR, aPTT, PT) (These can be used as Cycle 1 Day 1 laboratory tests as long as within 7 days of Cycle 1 Day 1).
- Determination of glomerular filtration rate, e.g by MDRD (Appendix E)
- CA 19-9, CEA (optional)
- Performance Status (ECOG) (Appendix B)
- Serum pregnancy test (for women of child bearing potential)
- Quality of life assessment using the EORTC QLQ-C30 and the module BIL21 (Appendix D)
- Optional audiometry including audiogram (loss of hearing according to RÖ 73, loss of hearing according to RÖ 80, High frequency-Audiogram loss of >20db in 4 frequencies)
- Documentation of disease status by contrast enhanced abdominal MRI or CT and chest CT. Preoperative imaging can be used if performed within 12 weeks prior to randomization.

- Obtain paraffin embedded tumor tissue (only patients not previously enrolled, but consenting to obtain paraffin embedded tumor tissue).
- Blood draw for translational research at baseline: 15ml of blood used for serum preparation and stored for further analyses (Appendix G)
- EORTC INFO 25, SDM-Q-9 (PEF-FB-9) and SDM-Q-Doc (PEF-FB-Doc) (Should be handed out to the patient and should be completed by the consenting investigator the same day.)

The investigator will confirm the patient's eligibility after all baseline scans and laboratory results have been reviewed.

5.3.3 Randomization

After inclusion in the treatment phase patients will be randomized to arm A or B stratified according to the following criteria:

- intrahepatic vs. hilar/extrahepatic CCA vs. gallbladder cancer
- lymph node positivity vs. negativity
- resection status R0 vs. R1

5.3.4 Assessments during Treatment

5.3.4.1 Assessment at start of treatment and every 3 weeks, previous to any new cycle (day 1) *(may be performed up to 3 days before treatment)* and on day 8 of every cycle (day 8 only in arm A)

The following assessments will be made previous to any new cycle in arm A

- Physical examination including weight, vital signs, performance status (ECOG) (only day 1), assessment of toxicity, concomitant medication and adverse events (day 1 and 8 in arm A and day 1 only in arm B)
- Laboratory Tests
    - On day 1 hemoglobin, platelets, WBC, neutrophils, sodium, potassium, calcium, creatinine, total bilirubin, alkaline phosphatase, ALT, AST, CrP
    - On day 8 only hematology panel (hemoglobin, platelets, WBC, neutrophils) (only in arm A)
- Issue Capecitabine Patient Diary Arm B only (and collect diary from previous cycle)

5.3.4.2 Final staging (end of postoperative treatment)

The following assessments will be made if patient discontinues treatment due to progression (e.g. lack of therapeutic efficacy), severe toxicity disabling further treatment continuation or severe adverse events related to the treatment.

- Physical examination including weight, vital signs, performance status (ECOG), assessment of toxicity, concomitant medication and adverse events
- Laboratory Tests: hemoglobin, platelets, WBC, neutrophils, sodium, potassium, calcium, creatinine, total bilirubin, alkaline phosphatase, ALT, AST, CrP
- CA 19-9, CEA (optional)
- Disease assessment (CT or MRI-scan of chest and abdomen)
- Quality of life assessment using the EORTC QLQ-C30 and the module BIL21 (Appendix D

5.3.5 Follow-up for disease recurrence

All subjects will be followed every 3 months (+/-28 days) for two years and afterwards 6 monthly for further 3 years after randomization (and at the discretion of the investigator thereafter)
Evaluation for disease recurrence will be performed by clinical visitation including

- Physical examination including weight, vital signs, performance status (ECOG), assessment of toxicity, concomitant medication and adverse events
- Laboratory Tests: hemoglobin, platelets, WBC, neutrophils, sodium, potassium, calcium, creatinine, total bilirubin, alkaline phosphatase, ALT, AST, CrP
- Quality of life assessment using the EORTC QLQ-C30 and the module BIL21 (Appendix D
- CA 19-9, CEA (optional)
- Disease assessment (CT or MRI-scan of chest and abdomen for two years, afterwards abdominal ultrasound) according to RECIST v1.1
- Blood draw for translational research at disease recurrence: 15ml of blood used for serum preparation and stored for further analyses (Appendix G)

5.3.6 Follow-up after disease recurrence (+/-28 days)

After disease recurrence only for (optional: via telephone):

- Survival
- Disease status
- Further Therapy

5.3.7 Follow-up for patients enrolled into the trial but not randomized

All subjects enrolled into the trial but not randomized (e.g. due to prolonged postoperative interval) should be evaluated postoperatively for

- Surgical and pathological report of the resection of the biliary tract cancer and every 3 months (+/-28 days) for two years and afterwards 6 monthly (+/-28 days) for further 3 years after surgery (optional: via telephone) for
- Use of adjuvant treatment
- Disease status (recurrence)
- Further Therapy
- Survival

5.4 Study Duration

Study duration in stage 2 is planned as follows:

Recruitment period	48 months
Follow up for primary endpoint	24 months
Follow up for overall survival	36 months

5.5 Study Termination

Criteria for study termination will be defined in the Independent Data Monitoring Committee (IDMC) charta.

5.5.1 Patient Withdrawal

Patients may be withdrawn from therapy based on the following reasons:

- Post-consent determination of ineligibility based on safety criteria
- Lack of therapeutic efficacy, as evidenced by progression
- Treatment related toxicity according to dose modification criteria (section 6)
- Physician's judgment following an adverse event
- Termination by the sponsor, or a regulatory authority
- Patients that require radiation therapy for local palliative purposes
- Any other reason for withdrawal that the study physician or patient indicates is in the overall best interest of the patient

After withdrawal of therapy, follow-up has to be continued up to the end of trial.

The trial participation of a patient terminates at the regular end of trial or on her/his own wish. If a patient withdraws the consent to study participation, the follow-up ends at the day the patient determines. Patients who voluntarily withdraw consent or who are withdrawn by the study physician for any reason after receiving therapy will be followed-up for at least 7 days. The purpose of this follow-up is to capture all adverse events and document any serious, procedure related adverse events.
All patients will be followed by clinical visitations or telephone contact post withdrawal for assessment of overall survival.
If a patient dies prior to the last scheduled study visit, the date and cause of death will be recorded.

5.5.2 Study Completion

The overall trial (stage 1 + 2) will be analysed for primary endpoint (DFS) when 388 events in stage 2 (recurrence or death) have been observed. Follow up for survival will be performed for up to 5 years per individual patient.

6. Dose Modifications

6.1 General Remarks

Toxicity will be graded according to NCI CTCAE, version 4.03 (Appendix C). Treatment modifications described below are applied according to this severity grading. Toxicities of severity grade 1 only will not lead to any dose reduction or cycle delay. The same holds for adverse reactions without any potential of serious or life-threatening complications according to the judgment of the physician (e.g. alopecia).
Presumably, severe overlapping toxicity between chemotherapies will not occur. Thus, in case of toxicity requiring treatment modification, this alteration should reflect the causal relationship of the respective drug(s). For example, if the toxicity is unequivocally caused by only one drug, a dosage modification of the other drugs is not required.
If more than one different type of toxicity occurs concurrently, the most severe grade will determine the modification.
If toxicity or patient wish requires a cycle delay of more than 3 weeks the patient is taken off protocol treatment.
In case of acute allergic reactions of grade 3 or 4, the respective agent should be discontinued permanently; in case of grade 1 or 2, it is up to the physician to continue treatment without dose modification, if this is in the best interest of the patient.
Each dose modification or treatment delay has to be documented in the CRF, including the respective reason.

6.2 Guidelines for Dose Modifications

All adverse events will be graded according to NCI CTCAE v4.03.

6.2.1 Suggested Action for Dose Modification for Gemcitabine and Cisplatin

Patients developing toxicity with gemcitabine and cisplatin will be managed according to table 3 or for renal and haematological toxicity as mentioned below.
If a grade 3 or 4 toxicity occurs after a dose reduction the patient is taken off treatment.

Adverse Event	Grade	Dose modification
Renal	GFR < 45 ml/min	Withhold cisplatin (see further details below)
Oedema	1-2	Consider appropriate diuretics
	Grade >2	Dipstick urine test for protein followed by full 24-hour urinary protein estimation if result ≥+ Delay until recovery to baseline (with use of appropriate diuretics). Then reduce gemcitabine to 75%. If no improvement discontinue treatment.
Lethargy	Grade >2	Reduce gemcitabine to 75%. If no improvement discontinue treatment.
Nausea/vomiting	Grade >2	Ensure optimal use of antiemetics (according to local policy) Delay until recovery to baseline, then: Omit cisplatin first. If no improvement reduce gemcitabine to 75%. If no improvement discontinue treatment.
Peripheral neuropathy	Grade 1-2	Delay cisplatin until recovery to baseline, then continue at full dose. If no recovery, treat as for grade 3-4. Continue with gemcitabine (full dose).
	Grade >2	Omit cisplatin from further treatment. Continue with gemcitabine (full dose).
Ototoxicity/Tinnitus		No dose modification required if full recovery between cycles. Omit cisplatin if no recovery between cycles. Continue gemcitabine (full dose).
Pulmonary toxicity	Grade >1	Discontinue treatment Supportive therapy (high dose steroids) should be initiated immediately
Other related significant organ toxicities (except alopecia and haematological)	Grade ≥2	Delay/interrupt chemotherapy until resolution to grade ≤1
	Grade ≥3	Delay/interrupt chemotherapy until resolution to grade ≤1 Reduce all further doses of cisplatin and gemcitabine to 75%
	Grade ≥3 2nd occurrence	Discontinue treatment

Table 3. Dose modifications for gemcitabine and cisplatin induced toxicity

Renal Toxicity

Cisplatin dosage will depend on the renal function (GFR). Repeat the creatinine clearance assessment ensuring the patient is adequately hydrated prior to this test and further cisplatin administration in line with local institutional standard practice. Proceed with cisplatin if the repeated reading is ≥45ml/min, otherwise cisplatin is to be omitted until recovery of renal function. If cisplatin has to be omitted, continue with gemcitabine. If a sudden increase in creatinine occurs, hemolytic uraemic syndrome should be ruled out.

Hematological toxicity

Gemcitabine will be dose-reduced if hematological toxicity occurs. The dose to be administered will depend on the full blood count result on the day of treatment.

WBC ($x10^9$/L)		**ANC ($x10^9$/L)**		**Platelets (x1000/mm3)**	**Gemcitabine Dose**	**Cisplatin Dose**
≥ 2	**And /or**	≥1	**And /or**	≥100	Full	Full
1-1.9		0.5-0.9		50-99	75% dose	Full
<1		<0.5		<50	Delay*	Delay

Table 4. Hematological toxicity dose modifications for gemcitabine and cisplatin

* If delay is > 3 weeks for hematological toxicity, the patient will be withdrawn from treatment

Note: The dose of gemcitabine will be re-escalated to full dose upon recovery of hematological toxicity despite a previous dose reduction in order to maintain the dose-intensity of therapy.

6.2.2 Suggested Action for Dose Modification for Capecitabine

Dose reductions, treatment delays and discontinuation of treatment can be considered at the clinician's discretion, with reference to the SmPC and the guidelines below.

For those toxicities considered by the investigator to be unlikely to become serious or life threatening and which do not result in a delay or interruption of therapy (e.g., alopecia, altered taste, etc) OR for any grade 1 toxicities, treatment will be continued at the original dosage, as determined at baseline, day 1.

If any grade 2, 3 or 4 toxicity occurs: there will be selective dose reduction depending on the following criteria:

Anaemia
All grades: no dose reduction, to be treated as clinically indicated.

Hand-Foot Syndrome
For grades 2, 3 or 4: dose reduction to be carried out according to table 5.

Diarrhoea, Nausea, Vomiting
For grade 2/3 diarrhoea, nausea, vomiting: (for grade 4 see table 5)

- Stop capecitabine and treat symptomatically (recommended use of Imodium [Loperamide] for diarrhoea).
- Restart at 100% of original dose if considered adequately controlled within 2 days of initiation of treatment.
- If control takes longer, then the dose should be modified according to table 5

(NOTE: diarrhoea of > 2 days requires medical evaluation, including relevant diagnostic procedures, alternative treatment and possible investigation of DPD deficiency).

If the adverse event recurs despite prophylaxis then dose modifications should also be made according to table 5**.**

Liver Function

a) **Drug-related Hyperbilirubinaemia**
For drug related **grade 2/3/4** elevations in bilirubin:

- Administration of capecitabine should be immediately interrupted until the hyperbilirubinaemia resolves or decreases in intensity or grade

Dose modifications should be managed according to Table 5

b) Liver Function Abnormalities Present at Baseline
Due to the commonly observed disruption to liver function, particularly intrahepatic cholestasis, associated with major hepatectomy, the trial inclusion criteria allow patients to enter the study with baseline liver function (total bilirubin or ALT/AST) equivalent to a Grade 2 adverse event (CTCAE v4.03).

For those patients for whom liver function on entry into the study (i.e. at baseline) is equivalent to a grade 2 adverse event, treatment should begin at standard dose and liver function should be monitored weekly. If liver function deteriorates to grade 3, dose delays and reductions should be managed as per table 5 and the SPC (i.e. Interrupt treatment until resolved to grade 0 - 1, then continue at 75% of original dose).

All other toxicities
For all other grade 2, 3 or 4 toxicities, capecitabine dosage should be reduced as indicated in Table 5.

	GRADE 2*	**GRADE 3**	**GRADE 4**
1st appearance	Interrupt treatment until resolved to grade 0- 1, then continue capecitabine at original dose, with prophylaxis where possible	Interrupt treatment until resolved to grade 0- 1, then continue at 75% of original dose with prophylaxis where possible	Discontinue treatment, unless investigator considers it to be in the best interest of the patient to continue at 50% of the original dose, once toxicity has resolved to grade 0-1.

2nd appearance	Interrupt treatment until resolved to grade 0- 1, then continue at 75% of original dose	Interrupt treatment until resolved to grade 0- 1, then continue at 50% of original dose	Discontinue treatment
3rd appearance	Interrupt treatment until resolved to grade 0-1, then continue at 50% of original dose	Discontinue treatment	
4th appearance	Discontinue treatment		

Table 5 Dose modifications for capecitabine induced toxicity

Adverse events are to be graded according to the NCI-CTCAE grading system Version 4.03.

* If a patient experiences recurrent grade 2 toxicity at the end (last 4 days) of the 2 week treatment period, which resolves to grade 0-1 within the scheduled treatment-free rest period, the investigator can decide to continue at the same dose.

NOTE: For any event/toxicity that was apparent at baseline, the dose modifications will apply according to a corresponding shift in toxicity grading, if the investigator feels it is appropriate.

Once the dose of capecitabine has been reduced, it should not be increased at a later stage for any reason.

6.2.3 Toxicity at the Start of the Following Cycle

Patients must meet the following criteria before each new cycle:

- Recovery from any treatment-related grade 3/4 non-hematological toxicity (except alopecia) to baseline or ≤grade 1
- No ongoing requirement for anti-diarrheic treatment
- No treatment delay of more than 3 weeks

Patients not meeting the above criteria on the date scheduled for the new cycle must suspend treatment with the anticancer drugs cisplatin and gemcitabine or capecitabine until they meet the above criteria.

Dose adjustments are at the investigator's discretion insofar as they must take account of the patient's clinical situation and the suspected causal relationship between the toxicities and administration of the anticancer drugs. If the above criteria necessitate postponement for more than 3 weeks, the patient should be withdrawn from the study.

7. Criteria of Evaluation

7.1 Disease Free Survival

Time from randomization to date of first observed disease recurrence (either local or distant) or death from any cause. Second malignancy will not be counted as events in the DFS analysis.
In order to determine disease recurrence tumor assessments (contrast enhanced chest CT and CT or MRI of abdomen, and determination of serum CA 19-9) will be performed every 3 months for two years and afterwards every 6 months for further 3 years by

abdominal ultrasound and CA 19-9. In case of clinical suspicion of recurrent disease and/or CA 19-9 elevation without tumor recurrence as diagnosed by CT/MRI scan, further examinations must be performed searching for a local recurrence or metastatic progression of the disease. Diagnosis of recurrence could either be made by radiological imaging or by positive cytology or biopsy. All radiological tumor assessments will be collected and retrospectively reviewed for pattern of recurrence and locoregional control.

7.2 Recurrence Free Survival

Recurrence free survival is defined as time from randomization to date of first observed disease recurrence (either local or distant) or disease related death.

7.3 Overall Survival

Overall survival will be determined as time from randomization to date of death.

7.4 Safety Endpoints

Safety assessments will include physical examinations including vital signs (blood pressure, heart rate, respiratory rate), performance status (ECOG), clinical laboratory profile, concomitant medication and adverse events.
All observed toxicities and side effects will be graded according to NCI CTCAE v4.03 (NCI 2009) for all patients and the degree of association of each with the procedure assessed and summarized.
Treatment related serious adverse events rate (SAE), defined as SAEs considered possibly, probably or definitely related to treatment, will be determined.

7.5 Quality of life (QoL)

Quality of life will be assessed using the EORTC QLQ C30 questionnaire and the module BIL21 at baseline and every 3 months for two years and afterwards every 6 months for further 3 years during follow up.

7.6 Function of Biliodigestive Anastomosis (in terms of surgical revision, requirement of PTCD), and Rate and Severity of biliary tract infections

Function of biliodigestive anastomosis (in terms of surgical revision, requirement of PTCD) will be assessed during the follow up visits. Severity of biliary tract infections will be classified according to NCI CTCAE v4.03.

7.7 Pattern of Disease Recurrence and Locoregional Control

Pattern of recurrence will be classified according to distant vs. local recurrence. Local control will be defined as rate of locoregional failures (local recurrence or locoregional lymph node metastases). Both endpoints will be evaluated in regard of pathological stage according to TNM version 7 at resection. Pathological assessments should be according to TNM including evaluation of margin status (R0 for >1mm distance to resection margin), T stage and careful evaluation of lymph nodes (including locoregional lymph nodes and lymph nodes in the hilar fat in case of extrahepatic CCA). Surgical resection should include lymphadenectomy, as currently recommended.

7.8 Investigation of the information content of the informed consent and the shared decision-making process

Evaluation of the level of information will be performed with the EORTC QLQ INFO25, which is a valid self-reported instrument consisting of 25 questions.
Evaluation of the involvement of patients in the decision-making process will be performed with an additional questionnaire consisting of 9 questions. This questionnaire

is available in two versions the PEF-Q-9 (SDM-Q-9) investigates the decision-making process from the patient´s perspective und the PEF-Q-Doc (SDM-Q-Doc) from the physician´s perspective.

8. Translational research

8.1 Translational research projects

Translational research will be performed to evaluate the prognostic and predictive impact of different blood and tissue markers in biliary tract cancer with particular regard of adjuvant chemotherapy with gemcitabine and cisplatin. Three different projects are already planned for the German part of the ACTICCA trial. Further markers, which might gain importance during the course of the trial, will be analysed.

The evaluation of lymphangiogenic and stem cell-like markers (CD133, CXCR4, Hif-1a, PTEN, VEGF-C, VEGF-D and VEGFR3) will be performed by the research group of Markus Moehler et al. in Mainz. The analyses of circulating tumour cells (CTC) including molecular characterization will be performed by the research group of Henning Wege et al. in Hamburg. The research group by Tom Luedde and Max Schmeding in Aachen will perform microRNA profiling.

8.2 Sampling time points and materials

Preoperatively and postoperatively 30ml of blood will be collected. 15 ml will be collected and immediately shipped for circulating tumor cell (CTC) analyses (only sites in Germany). 15 ml will be used for serum preparation and stored.

During operation, fresh frozen tissue and formalin fixed paraffin embedded tissue from the tumor, the surrounding liver tissue and the resected/adjacent lymph nodes should be obtained and stored for microRNA and lymphangiogenic and stem cell marker analyses.

At baseline and at disease recurrence 15ml of blood will be collected and used for serum preparation and stored.

Serum will be used for microRNA and lymphangiogenic and stem cell marker analyses and for further markers, which might gain importance during the course of the trial.

For tissue and blood sampling working instructions refer to appendix G or the respective national lab manual. Additional translational research working instruction will be supplied to the sites.

8.3 Data management translational research

An allocation database will be established besides and separate from the clinical database (eCRF) gathering the data of the available patient samples at each study site to enable translational research. The allocation database will collect the identification forms send to the central translational unit based at the University Medical Center Hamburg-Eppendorf. Clinical data of all patients entering the translational part will be entered into the eCRF.

8.4 Usage of translational data

The translational data obtained by the respective research groups will be analysed and published in conjunction and under participation of the coordinating investigator and study coordinator. Further analyses or research proposals will be discussed within the translational steering committee to decide upon feasibility in terms of availability of serum and tissue, coverage by the current patient informed consent and access to clinical data.

9. Assessment of Adverse Events

9.1 Independent Data Monitoring Committee (IDMC)

An independent data monitoring committee will follow the progress of the clinical trial, evaluate the safety and primary efficacy parameters and will propose changes, ending or continuing of the trial to the sponsor. A separate IDMC charta will be developed and submitted to competent authority and EC. The planned interim analysis will be performed by the IDMC with the data collected and prepared by the CRO (CTC North GmbH & Co. KG). For the first interim analysis a log-rank test should be performed. In case p is < 0.0137 (or equivalently the log-rank test statistic > 2.464) trial could be terminated.

9.2 Definitions

An Adverse Event (AE) is defined as any untoward medical occurrence or experience in a subject or clinical investigation subject. This can include any unfavorable and unintended signs (such as rash or enlarged liver), or symptoms (such as nausea or chest pain), a significant abnormal laboratory finding (including blood tests, x-rays or scans) or a disease.
Disease progression itself is not considered an adverse event. However, signs and symptoms of disease progression may be recorded as adverse events or serious adverse events. This is in the decision of the investigator in accordance with legal requirements. Death due to progressive disease during the study should be reported on the applicable study termination case report form with ‘death’ as reason for study termination and ‘disease progression’ as reason for death.
Worsening of a pre-existing medical condition (e.g. diabetes, migraine headaches, gout) should be considered an adverse event if there is either an increase in severity, frequency, or an association with significantly worse outcomes.
Interventions for pre-treatment conditions (e.g. elective cosmetic surgery) or medical procedures that were planned before study enrolment are not considered adverse events.

The investigator is responsible for reviewing laboratory test results and determining whether an abnormal value in an individual study subject represents a change from values before the study.
An Adverse Drug Reaction (ADR) is defined as any response to a medical product, that is noxious and unintended, related to any dose (ICH-GCP).
Response to a medical product (used in the above definition) means that a causal relationship between the medical product and the adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out.
An Unexpected Adverse Drug Reaction is any adverse reaction for which the nature or severity is not consistent with the applicable product information (e.g. Summary of product characteristics) (ICH-GCP).
A Serious Adverse Event (SAE) is defined as any undesirable experience occurring to a subject, whether or not considered related to the protocol treatment. A Serious Adverse Event (SAE) which is considered related to the protocol treatment is defined as a Serious Adverse Drug Reaction (SADR).
Adverse events and adverse drug reactions which are considered as serious are those which result in:

- death
- a life threatening event (i.e. the subject was at immediate risk of death at the time the reaction was observed)

- hospitalization or prolongation of hospitalization
- persistent or significant disability/incapacity
- a congenital anomaly/birth defect
- a medically significant condition, defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above

A hospitalization meeting the regulatory definition for “serious” is any inpatient hospital admission that includes a minimum of an overnight stay in a health care facility. Any adverse event that does not meet one of the definitions of serious (e.g. emergency room visit, outpatient surgery, or requires urgent investigation) may be considered by the investigator to meet the “other significant medical hazard” criterion for classification as a serious adverse event. Examples include allergic bronchospasm, convulsions, and blood dyscrasia.
Hospitalization for the performing of protocol-required procedures for elective procedures that have been booked in advance of enrolment, or administration of study treatment is not classified as an SAE.
SUSAR: Suspected Unexpected Serious Adverse Reactions (the reference documents to assess expectedness are the summary of product characteristics).

9.3 Reporting Procedure for All Adverse Events

The investigator is responsible for ensuring that as defined all adverse events observed by the investigator or reported by subjects are properly captured in the subjects’ medical records and the eCRF. Adverse events will be collected for those subjects who have provided informed consent and entered the study and will be recorded throughout the study period in both arms, beginning after the randomization until 28 days after the last administration of treatment.
Events CTC grade 1 and 2 should only be regarded as AE, if judged as “clinically relevant” by the investigator or if interfering with treatment administration.
Only events CTC grade 3 and 4 are to be regarded as AE. Laboratory values being CTC grade 3 or 4 should only be recorded if judged as “clinically relevant” by the investigator or if interfering with treatment administration.
Additionally all adverse events related to study medication (= adverse drug reactions) must be recorded through the follow-up visits, which occur within 18 months after last study drug administration.
The investigator must **unhesitatingly** (within 24 hours) report all serious adverse events on a separate SAE report form to the CTC North GmbH & Co. KG using the appropriate SAE Form in the eCRF. The following adverse event attributes must be assigned by the investigator: adverse event diagnosis or syndrome(s) (if known, signs or symptoms if not known), event description (with detail appropriate to the event), dates of onset and resolution, severity, assessment of relatedness to study treatment, and action taken. The investigator may be asked to provide follow-up information, discharge summaries, and extracts from medical records or CRFs and for serious adverse events on the serious adverse event report form.
The sponsor will medically review all SAEs. The sponsor is responsible for ensuring that all reporting requirements to all concerned investigators, to the IEC, and to Regulatory Authorities are fulfilled. In accordance with the legal requirements (Directives 2005/28/EC and 2001/20/EC, GCP-V and the German Drug Law) all Adverse Drug Reactions that are both serious and unexpected are subject to expedited reporting. Data Safety Update

Reports will be sent to the IEC and the competent authority (e.g. Bundesoberbehörde (BfArM).

9.3.1 Assessment of Causality of Adverse Events

An adverse event will not be considered possibly related to study treatment if it:

- may be judged to be due to extraneous causes such as disease or environment or toxic factors
- may be judged to be due to the subject's clinical state or other therapy being administered
- is not biologically plausible that the event is related to study medication
- does not reappear or worsen when study treatment is re-administered
- does not follow a temporal sequence from administration of study treatment

An adverse event will be considered possibly related to study treatment if it:

- follows a temporal sequence from administration of study treatment
- is a known response to the investigational product based on clinical or preclinical data
- could not be explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other therapy administered to the subject
- disappears or decreases upon cessation or reduction of dose of study treatment
- reappears or worsens when study treatment is re-administered

Medically significant according to CTCAE Version 4.03 Grad 3 or 4 i.e. serious adverse events will be followed until resolved or considered stable.
It will be left to the investigator's clinical judgment to determine whether an adverse event is related and of sufficient severity to require the subject's removal from treatment or from the study. A subject may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable adverse event. If either of these situations arises, the subject should be strongly encouraged to undergo a safety follow-up assessment and be under medical supervision until symptoms are resolved.

9.3.2 Assessment of Severity of Adverse Events

The severity of adverse events will be graded according to the CTCAE Version 4.03. When an adverse event cannot be graded by CTCAE Version 4.03, the following severity grades are to be used:

1 = mild
2 = moderate
3 = severe

10. Data Analysis and Statistical Considerations

10.1 Sample Size and Power Calculation

Based on protocol versions 2-5 187 patients were randomized to gemcitabine, cisplatin and observation to observation alone, which was the respective standard of care to this time-point. Meanwhile the standard of care has changed to capecitabine and observation, instead of observation alone. Thus, the trial will be amended to include the recent standard of care. To account for the adapted design the number of patients to be included

in this second stage of the trial requires a separate sample size calculation. The displayed sample size calculation only covers the second stage of the trial and the required number will thus be added to the already included patients in the first stage (n=187). For the first stage and the overall trial (stage 1+2) a power analyses will be conducted based on the most recent data from the randomized trials.

Overall statistical analysis (stage 1+2) - gemcitabine/cisplatin vs. standard of care (observation +/- capecitabine)

In the first stage 187 patients have been randomized to gemcitabine/cisplatin and observation vs. observation alone. In stage 2 578 patients will be randomized to gemcitabine/cisplatin vs. capecitabine. Thus, overall 765 will be available for analysis (excluding the expected 3% loss-to-follow-up). Based on the data obtained in the observation alone arms in the current adjuvant studies and on the initial assumption of an 15% improvement of the disease free survival rate at 24 months (DFSR@24) gemcitabine and cisplatin is expected to result in a DFSR@24 of 60.2% (event rate of 39.8%), compared to 50.9% (event rate 49.1%) with capecitabine or observation alone, assuming the lowest expected difference (10%) between the experimental arm (gemcitabine/cisplatin) and the control arm (capecitabine or observation alone) (hazard ratio = 0.752). Taking into account the prespecified alpha of 5% and a follow up time of 48+24 months the power of the pooled analysis is 90% (compare appendix F).

Statistical analysis of stage 1 - gemcitabine/cisplatin vs. observation

In the stage 1 part 187 patients have been randomized to gemcitabine/cisplatin and observation vs. observation alone. Based on the data obtained in the observation alone arms in the current adjuvant studies and on the initial assumption of an 15% improvement of the disease free survival rate at 24 months (DFSR@24) gemcitabine and cisplatin is expected to result in a DFSR@24 of 60% (event rate of 40%), compared to 45% (event rate 55%) with observation alone (hazard ratio = 0.64). Taking into account the prespecified alpha of 5% and a follow up time of 72 months the power is expected to be 79% (compare appendix F).

Sample size calculation for stage 2 - gemcitabine/cisplatin vs. capecitabine

The BILCAP trial has established the new adjuvant treatment standard for biliary tract cancer with a median DFS of 24.6 months and a DFSR@24 of 50.9%.

Therefore, DFSR@24 is expected to be 50.94% with adjuvant capecitabine (event rate 49.1%). The investigational treatment (adjuvant gemcitabine and cisplatin) should increase DFSR@24 by about 10% to 60.2% (event rate 39.8%) to be regarded as promising for further evaluation and of clinical relevance (hazard ratio = 0.752).

The risk of falsely rejecting the null hypothesis of no difference between the experimental and the control arm was restricted to 5%. The risk of falsely rejecting the alternative hypothesis of a difference between the experimental and the control arm was set not to increase 20%, corresponding to a power of 80%. An interim analyses will be performed after 50% of events occurred (n=194). The interim analyses will be conducted regarding superiority (compare appendix F). In addition a futility stop will be implemented at the same point in time. Thus, based on the Freidlin, Korn, Gray, approach the possibility of

reaching the target HR of 0.75 will be determined (unlikely in case of a lower 95% CI of 0.7514 or larger for the HR corresponding to an observed HR of 0.98 at this point) (Freidlin, Korn et al. 2010). The results of the interim analyses will be submitted to the IDMC for determination of trial continuation.

With these restrictions, 578 evaluable study patients have to be followed for 24 months to observe 388 events (compare appendix F). With an assumed loss-to-follow-up of 3% 594 patients (297patients per arm) have to be recruited for inclusion into the trial.

Randomization will be performed according to the following criteria:

Stratification criteria

- intrahepatic vs. hilar/distal cholangiocarcinoma vs. gallbladder cancer
- lymph node positivity vs. negativity
- R0 vs. R1 resection

10.2 Populations for Analysis

All patients receiving at least one dose of study treatment will be evaluable for safety and included in the safety population.

The Intention-to-treat (ITT) population will include all patients in the study (signed ICF and confirmation of eligibility). All patients will be grouped according to their randomization regardless of treatment received.

In addition to the above-mentioned analysis, which will be performed together with the overall and stage 2 analysis, an analysis of stage 1 will be conducted as initially planned after 154 events (defined as death or disease recurrence) have occurred (about 24 months after last patient in stage 1, about May 2019). This analysis will be evaluated by the IDMC for decision upon trial continuation. A statistical evaluation and decision plan will be developed beforehand.
Furthermore, a per protocol population will be analysed, defined as patients receiving at least 2 cycles (6 weeks) of treatment and/or observation according to their randomization.

10.3 Patient Demographics/Other Baseline Characteristics

The following demographic and baseline characteristics will be summarized descriptively by treatment group:

- Gender and age
- ECOG performance status
- Tumor marker (CA 19-9 and optional CEA)
- Disease status
- Other characteristics (e.g liver chemistry)

Medical history will be summarized by primary body system organ class and preferred term.

10.4 Treatments (study treatments)

The number and dose of treatment cycles will be summarized by treatment group.

10.5 Efficacy Analysis

10.5.1 Primary Efficacy Endpoint

The primary efficacy endpoint will be the disease free survival (DFS) in the overall ITT, ITT 1 and ITT 2 population.

All ITT populations will be analyzed using the two-sided two-sample log-rank test. Treatment effects will be estimated using Cox proportional hazards regression and will be reported with a 95% confidence interval. In stage 2 one interim analysis after 194 events is prespecified and the final analysis will be performed when 388 events have occurred, following a group-sequential plan according to O'Brien and Fleming (see appendix F). The significance bound and power at the interim analyses can be found in appendix F.

An analysis of stage 1 will be conducted as initially planned 24 months after the inclusion of the last patient into stage 1 (May 2019). This analysis will be evaluated by the IDMC for decision upon trial continuation. A statistical evaluation and decision plan will be developed beforehand.

10.5.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints will be the following variables:

- Disease free survival at 24 months (DFSR@24)
- Recurrence free survival
- Overall survival (OS)
- Toxicity (Safety assessments will include physical examinations (blood pressure, heart rate, respiratory rate), vital signs, clinical laboratory profile and monitoring of adverse events, according to NCI CTCAE v4.03)
- Quality of life (QoL) using the EORTC QLQ-C30 and the module BIL21
- Function of biliodigestive anastomosis (in terms of surgical revision, requirement for PTCD)
- Patterns of disease recurrence
- Locoregional control

For the time-to-event variables DFS, RFS and OS, the Kaplan-Meier method will be used to estimate the event free survival in an analogous manner to the primary endpoint OS will be analysed using the log-rank test. Cox's proportional hazard model will be used to adjust for the influences of the strata for DFS, RFS and OS.

Toxicity, quality of life and function of biliodigestive anastomosis (in terms of surgical revision, requirement for PTCD) will be documented in a descriptive way. Continuous variables will be compared using t-test and categorical variables using a Chi-square test. Patterns of disease recurrence and local control will be documented in a descriptive way and compared between treatment groups and pathological variables (margin and lymph node status) and localization. Multivariate analyses will be performed.

All secondary efficacy analyses, excluding toxicity, which will be based on the safety population, will be based on the ITT population and the corresponding statistical testing results will be interpreted in an exploratory sense.

10.5.3 Safety analyses (toxicity)

Data from all subjects who receive one or more doses of study treatment will be incorporated into the safety analyses. Study treatment exposure will be summarized. Adverse events, vital sign measurements, ECOG performance status, clinical laboratory information, and concomitant medications will be tabulated and summarized by group. All toxicities will be summarized by relative and absolute frequency, severity grade based on the CTCAE Version 4.03. Serious adverse events (SAE) will be listed separately. Safety information obtained during the Follow-up period during each segment will be incorporated into these analyses. Graphical displays will be provided where useful in the interpretation of results.

11. Data management

11.1 Randomization Procedure

Randomization to study treatment should occur within seven days after eligibility criteria have been met. Upon confirmation of eligibility, study subjects will be randomized by the eCRF to arm A (adjuvant chemotherapy and observation) or B (observation alone) in 1:1 ratio, according to the above mentioned stratification factors.

11.2 Patient identification list

All randomized patients have to be documented in a confidential patient identification list. This list contains the patient specific numbers (patient- and randomization-number) together with date of birth and the full name of the patient. Patient related data will be just transmitted in pseudonymized form. The identification list will stay at each center.

11.3 Data capture

All data will be entered directly at the center by the site staff with remote data entry (RDE). A study-management software will be used for data capture and query management. Automatic edit checks will validate data directly during entry into the study database. Data will be evaluated for consistency, accuracy and completeness regularly. After completion of data capture data base will be closed and the data will be transferred into the statistic software.

12. Quality assurance

12.1 Standardization

Criteria for assessing efficacy and safety endpoints will be standardized by using NCI-CTCAE Version 4.03 for safety issues and RECIST Version 1.1 for efficacy parameters (to determine disease recurrence). Every center has to reveal their laboratory norm values and their validation through certification.

12.2 Data access

All source data have to be in the patients file under the responsibility of the investigator. Documentation in the eCRF must correspond to source data in the patient file. For this trial source data are defined as:

- medical and demographical data
- results of laboratory and imaging data
- selection criteria
- signed informed consent form (original)

12.3 Monitoring/ Source Data Verification (SDV)

The monitoring will be conducted according to local requirements.

For Germany monitoring will be performed by the CTC North GmbH & Co. KG, Hamburg. The study monitor will review the eCRF data for completeness and accuracy during the monitoring visits (source data verification / SDV). The study monitor will point out any discrepancies between source data and the data captured in the eCRF. The monitor will issue electronic queries to site staff to initiate discrepancy resolution. Discrepancies which require eCRF data corrections have to be re-solved by authorized site personnel by answering these monitoring queries.
Source data verification will be performed for 20 % of the core data and 15% of all other data. The frequency of on-site visits will depend on the number of recruited patients. The monitor must be given access to subject medical records and other study-related records needed to verify the entries on the eCRF. The investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing case report forms, are resolved. The investigator has to ensure that all data required according to this protocol will be entered promptly in the eCRF.

Quality control of data will be done by reviewing the data entered into the trial software for consistency, accuracy and completeness. During on-site visits the correct transmission of data into the eCRF (source data verification) as well as informed consent forms, selection criteria, efficacy and safety parameters will be reviewed. The complete scale of the monitoring will be defined by the trial specific monitoring plan.

12.4 Audits and Inspections

To ensure quality of data, study integrity, and compliance with the protocol and the various applicable regulations and guidelines, the sponsor may conduct site visits to institutions participating to protocols.
The investigator, by accepting to participate to this protocol, agrees to co-operate fully with any quality assurance visit undertaken by third parties, including representatives from the sponsor, national and/or foreign regulatory authorities or company supplying the product under investigation, as well as to allow direct access to documentation pertaining to the clinical trial (including CRFs, source documents, hospital subject charts and other study files) to these authorized individuals.
The investigator must inform the sponsor immediately in case a regulatory authority inspection will be scheduled.

13. Regulatory and Legal Obligations

13.1 General provisions/Declaration of Helsinki

This study is conducted in agreement with the ICH Harmonized Tripartite Guideline on Good Clinical Practice, valid since 17.01.1997, the Declaration of Helsinki (in its current version)) and the respective national laws in its current version). The Principle Investigator has more than two years of experience in the conduction of clinical drug trials.

13.2 Patient Protection

The responsible investigator will ensure that this study is conducted in agreement with either the Declaration of Helsinki (in its current version) or the laws and regulations in its current version.
The protocol has been written, and the study will be conducted according to the ICH Harmonized Tripartite Guideline for Good Clinical Practice (reference: http://www.ifpma.org/pdfifpma/e6.pdf). The protocol will be approved by Independent Ethics Committees.

13.3 Competent Authority

Prior to the start of the trial an application for authorization by the competent Higher Federal Authority is submitted by the sponsor including a copy of the protocol and other information and documents required by the competent national Higher Federal Authority. A copy of the written approval must be available before the start of recruitment of subjects into the study. All changes of the study protocol or other study document classified “substantial” as well as adverse events will be announced to the CA (according to the appropriate Directives and national legal requirements). Once a year or whenever it is questioned the CA will get information about all SAR and about the security of the affected subjects, according to the appropriate Directives and national legal requirements. Recommendations and tips of the CA will be taken up into the study protocol. The sponsor will inform the CA about the course of the investigation in security aspects according to the appropriate Directives and national legal requirements and also about the end and the results of the investigation.

13.4 Independent Ethics Committee

Prior to the start of the trial an application for the favorable opinion for Germany is submitted by CTC North GmbH & Co. KG on behalf of the sponsor to the central independent, interdisciplinary ethics committee responsible under federal law for the principle investigator and to the local ethics committees responsible for the other participating institutions including a copy of the protocol, proposed informed consent form and other information and documents required by the ethics committees for their opinion. A copy of the written favorable opinion of the protocol and informed consent form must be available before the start of recruitment of subjects into the study. All changes of the study protocol or other study document classified “substantial” as well as adverse events, will be announced to the Independent Ethics Committee (IEC), according to the local requirements, e.g. for Germany §13, (2) und (3) GCP-V. Once a year or whenever it is questioned the IEC will get information about all SAR and about the security of the affected subjects, (e.g. according to §13. (6) GCP-V). Recommendations and tips of the IEC will be taken up into the study protocol. The sponsor will inform the IEC about the course of the Investigation in security aspects (e.g. according §13 GCP-V, (1) till (6)) and also about the end and the results of the investigation (e.g. according to §13 GCP-V, (8) and (9)).
The investigator cannot influence the decisions of the IEC. A list of the IEC members will be ordered.

13.5 Amendments

The appendices, attached to this protocol and referred to in the protocol, form an integral part of the protocol. No changes or amendments to this protocol may be made by the Investigator. The sponsor must submit and obtain favorable opinion/approval from the IEC and competent Higher Federal Authority for all subsequent protocol amendments.

For changes to the informed consent form favorable opinion from the IEC might be necessary.

13.6 Study Reports

Within one year after the end of the trial a clinical trial report will be written and provided to the IEC and competent Higher Federal Authority independent of the completion or a premature closure of the trial.

13.7 Informed Consent

The informed consent form will be submitted together with the study protocol to the independent ethics committees (IEC) for review and approval. If requested, modifications must be incorporated. A copy of the written approval of the IEC must be available before starting the trial and dispensing any trial medication to trial subjects. The informed consent form must not be altered by the investigator except for contact data of the investigators. Changes to the informed consent form also have to be approved by the IEC. The revised form will be sent to all sites to replace the preceding version.
Before a subject's participation in the clinical study, the investigator must obtain written informed consent from the subject (an appropriately trained person designated by the investigator is permitted in UK sites). All subjects will be informed of the aims of the study, the possible adverse events, the anticipated benefits, the procedures and possible hazards to which he/she will be exposed, and the mechanism of treatment allocation the subjects also will be informed about alternative treatments. Subjects will be informed of their insurance protection and the obligations which are linked to insurance. They will be informed as to the strict confidentiality of their subject data, but that their medical records may be reviewed for trial purposes by authorized individuals other than their treating physician. It will be emphasized that the participation is voluntary and that the subject is allowed to refuse further participation in the protocol whenever he/she wants. This will not prejudice the subject's subsequent care. The informed consent procedure must conform to the ICH guidelines on Good Clinical Practice.
The informed consent consists of three parts: consent to the diagnostic and therapeutic procedures of the trial, consent to the collection and storage of biological material, and consent to the processing and storage of data. The latter one includes consent to inspections where records may be reviewed by authorized individuals (other than their treating physician) of the sponsor or surveillance authorities / ethics committees. If the subject does not consent to the collection, processing and storage of his data, inclusion in the study is not possible and the subject's refusal should be documented in the medical notes. The subject must be informed about the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or any study treatment are administered. The collection and storage of biological material in this clinical trial is optional; consent to this part of the trial is not necessary for the participation in this clinical trial.
The investigator is also responsible for asking the subject if the subject agrees to have his/her primary care physician informed of the subject's participation in the clinical study. If the subject agrees to such notification, the investigator shall inform the subject's primary care physician of the subject's participation in the clinical study.
If a potential subject is illiterate or visually impaired, the investigator must provide an impartial witness to read the informed consent form to the subject and must allow for questions. Thereafter, both the subject and the witness must sign the informed consent form to attest that informed consent was freely given and understood.

Adequate explanations of the aims, methods, anticipated benefits, and potential hazards of the study, the mechanism of treatment allocation must be given. The subject will have enough time to decide to participate in the study or not.
The acquisition of informed consent and the subject's agreement or refusal of his/her notification of the primary care physician must be documented in the subject's medical records, and the informed consent form must be signed and personally dated by the subject and by the investigator. One signed original of the informed consent form must be retained in accordance with institutional policy and another original must be provided to the subject. Treatment cannot start before the subject has signed the informed consent, meets all inclusion and no exclusion criteria and is registered.
With signing the informed consent form the investigator confirms that an individual clarification conversation has taken place and that the subject has signed the informed consent form.

13.8 Subject Confidentiality

The investigator must ensure that the subject's confidentiality is maintained. On the case report forms, subjects should be identified by their subject study number and only on the SAE report form additionally the age.
In compliance with ICH-GCP Guidelines, it is required that the investigator and institution permit authorized representatives of the sponsor, and of regulatory agencies direct access to review the subject's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The investigator is obligated to inform and obtain the consent of the subject to permit named representatives to have access to his/her study-related records without violating the confidentiality of the subject. The investigator must keep a list for the identification of the subjects (including name, birthday, gender, date of informed consent, date of randomization / registration).

13.9 Study Documentation and Archive

The investigator must maintain a list of appropriately qualified persons to whom he/she has delegated study duties, including all those authorized to make entries and/or corrections on case report forms.
Source documents are original documents, data, and records from which the subject's case report form data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.
The investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation, suitable for inspection at any time by representatives from the study sponsor and/or applicable regulatory authorities. Elements include:

- Subject files containing completed case report forms, informed consent forms, and subject identification list.
- Study files containing the protocol with all amendments, the summary of product characteristics, copies of pre-study documentation, and all correspondence to and from the IEC.
- If kept, proof of receipt, Investigational Product Accountability Record, Return of Investigational Product for Destruction, Final Investigational Product Reconciliation Statement, and all drug-related correspondence.

In addition, all original source documents supporting entries in the case report forms must be maintained and be readily available.
All study documents and source documents must be kept for at least 10 years from submission of the final study report. Should the investigator wish to assign the study records to another party or move them to another location, he/she must notify the sponsor in writing of the new responsible person and/or the new location.

13.10 Compensation

Subjects will not be paid for participating in this clinical trial.

14. Trial Sponsorship and Financing

The University Medical Center Hamburg-Eppendorf is the legal sponsor of the trial and finances the trial. Financial support for the conduction of the trial is granted by the Deutsche Krebshilfe e.V. (Grant No: 110215) and medac GmbH.

15. Trial Insurance

For all subjects participating in the trial the sponsor has taken out a liability insurance policy (mentioned below) according to the respective national law (e.g. § 40 (1) Nr. 8 und (3) German drug law (AMG)) which covers the sponsor, the investigator and his co-workers against liability in the event that a subject's health is injured during the course of the clinical trial. The insurance policy provides benefits, even when no one else is liable for the damage death of or injury to any subject during the trial.

A certificate of insurance and conditions will be provided to the investigators and the subjects.

16. Trial Registration

The trial is registered at Clinical Trials Gov (NCT02170090).

17. Publication Policy

After receiving the biometrical results a final report will be published and further publications (abstracts etc.) will be done. First author of the final publication will be the principal investigator of the study. All participating sites recruiting at least 10% of the patients will become a co-authorship if possible according to the publication policy of the journal. Persons involved in planning, conducting and evaluating the trial will be offered co-authorships. All co-authors will get the option to comment on the manuscript before publication.

Appendix A: Bibliography

Anderson, C. and R. Kim (2009). "Adjuvant therapy for resected extrahepatic cholangiocarcinoma: a review of the literature and future directions." Cancer Treat Rev **35**(4): 322-327.

Choi, S. B., K. S. Kim, J. Y. Choi, S. W. Park, J. S. Choi, W. J. Lee and J. B. Chung (2009). "The prognosis and survival outcome of intrahepatic cholangiocarcinoma following surgical resection: association of lymph node metastasis and lymph node dissection with survival." Ann Surg Oncol **16**(11): 3048-3056.

de Jong, M. C., H. Nathan, G. C. Sotiropoulos, A. Paul, S. Alexandrescu, H. Marques, C. Pulitano, E. Barroso, B. M. Clary, L. Aldrighetti, C. R. Ferrone, A. X. Zhu, T. W. Bauer, D. M. Walters, T. C. Gamblin, K. T. Nguyen, R. Turley, I. Popescu, C. Hubert, S. Meyer, R. D. Schulick, M. A. Choti, J. F. Gigot, G. Mentha and T. M. Pawlik (2011). "Intrahepatic cholangiocarcinoma: an international multi-institutional analysis of prognostic factors and lymph node assessment." J Clin Oncol **29**(23): 3140-3145.

Duffy, A., M. Capanu, G. K. Abou-Alfa, D. Huitzil, W. Jarnagin, Y. Fong, M. D'Angelica, R. P. Dematteo, L. H. Blumgart and E. M. O'Reilly (2008). "Gallbladder cancer (GBC): 10-year experience at Memorial Sloan-Kettering Cancer Centre (MSKCC)." J Surg Oncol **98**(7): 485-489.

Eckel, F. and R. M. Schmid (2007). "Chemotherapy in advanced biliary tract carcinoma: a pooled analysis of clinical trials." Br J Cancer **96**(6): 896-902.

Edeline, J., F. Bonnetain and J. M. Phelip (2017). "Gemox versus surveillance following surgery of localized biliary tract cancer: Results of the PRODIGE 12-ACCORD 18 (UNICANCER GI) phase III trial. ." J Clin Oncol **35**(no 4 suppl): abstr 225.

Ercolani, G., G. Vetrone, G. L. Grazi, O. Aramaki, M. Cescon, M. Ravaioli, C. Serra, G. Brandi and A. D. Pinna (2010). "Intrahepatic cholangiocarcinoma: primary liver resection and aggressive multimodal treatment of recurrence significantly prolong survival." Ann Surg **252**(1): 107-114.

Ferlay, J., H. R. Shin, F. Bray, D. Forman, C. Mathers and D. M. Parkin (2010). "Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008." Int J Cancer **127**(12): 2893-2917.

Freidlin, B., E. L. Korn and R. Gray (2010). "A general inefficacy interim monitoring rule for randomized clinical trials." Clin Trials **7**(3): 197-208.

Goetze, T. O. and V. Paolucci (2012). "The prognostic impact of positive lymph nodes in stages T1 to T3 incidental gallbladder carcinoma: results of the German Registry." Surg Endosc **26**(5): 1382-1389.

Gold, D. G., R. C. Miller, M. G. Haddock, L. L. Gunderson, F. Quevedo, J. H. Donohue, S. Bhatia and D. M. Nagorney (2009). "Adjuvant therapy for gallbladder carcinoma: the Mayo Clinic Experience." Int J Radiat Oncol Biol Phys **75**(1): 150-155.

Guglielmi, A., A. Ruzzenente, T. Campagnaro, S. Pachera, A. Valdegamberi, P. Nicoli, A. Cappellani, G. Malfermoni and C. Iacono (2009). "Intrahepatic cholangiocarcinoma: prognostic factors after surgical resection." World J Surg **33**(6): 1247-1254.

Horgan, A. M., Amir, E. (2011). "Adjuvant therapy in the treatment of biliary tract cancer (BTC): A systematic review and meta-analysis." J Clin Oncol **29**(suppl): abstr 4050.

Hughes, M. A., D. A. Frassica, C. J. Yeo, T. S. Riall, K. D. Lillemoe, J. L. Cameron, R. C. Donehower, D. A. Laheru, R. H. Hruban and R. A. Abrams (2007). "Adjuvant concurrent chemoradiation for adenocarcinoma of the distal common bile duct." Int J Radiat Oncol Biol Phys **68**(1): 178-182.

Hundal, R. and E. A. Shaffer (2014). "Gallbladder cancer: epidemiology and outcome." Clin Epidemiol **6**: 99-109.

Jarnagin, W. R., Y. Fong, R. P. DeMatteo, M. Gonen, E. C. Burke, B. J. Bodniewicz, B. M. Youssef, D. Klimstra and L. H. Blumgart (2001). "Staging, resectability, and outcome in 225 patients with hilar cholangiocarcinoma." Ann Surg **234**(4): 507-517; discussion 517-509.

Jarnagin, W. R., L. Ruo, S. A. Little, D. Klimstra, M. D'Angelica, R. P. DeMatteo, R. Wagman, L. H. Blumgart and Y. Fong (2003). "Patterns of initial disease recurrence after resection of gallbladder carcinoma and hilar cholangiocarcinoma: implications for adjuvant therapeutic strategies." Cancer **98**(8): 1689-1700.

Koeberle, D., P. Saletti, M. Borner, D. Gerber, D. Dietrich, C. B. Caspar, W. Mingrone, K. Beretta, F. Strasser, T. Ruhstaller, O. Mora and R. Herrmann (2008). "Patient-reported outcomes of patients with advanced biliary tract cancers receiving gemcitabine plus capecitabine: a multicenter, phase II trial of the Swiss Group for Clinical Cancer Research." J Clin Oncol **26**(22): 3702-3708.

Kriston, L., I. Scholl, L. Holzel, D. Simon, A. Loh and M. Harter (2010). "The 9-item Shared Decision Making Questionnaire (SDM-Q-9). Development and psychometric properties in a primary care sample." Patient Educ Couns **80**(1): 94-99.

Li, S. Q., L. J. Liang, Y. P. Hua, B. G. Peng, Q. He, M. D. Lu and D. Chen (2009). "Long-term outcome and prognostic factors of intrahepatic cholangiocarcinoma." Chin Med J (Engl) **122**(19): 2286-2291.

Mayo, S. C., A. D. Shore, H. Nathan, B. Edil, C. L. Wolfgang, K. Hirose, J. Herman, R. D. Schulick, M. A. Choti and T. M. Pawlik (2010). "National trends in the management and survival of surgically managed gallbladder adenocarcinoma over 15 years: a population-based analysis." J Gastrointest Surg **14**(10): 1578-1591.

Murakami, Y., K. Uemura, T. Sudo, Y. Hashimoto, A. Nakashima, N. Kondo, R. Sakabe, H. Ohge and T. Sueda (2010). "Prognostic Factors After Surgical Resection for Intrahepatic, Hilar, and Distal Cholangiocarcinoma." Ann Surg Oncol.

Neoptolemos, J. P., D. D. Stocken, H. Friess, C. Bassi, J. A. Dunn, H. Hickey, H. Beger, L. Fernandez-Cruz, C. Dervenis, F. Lacaine, M. Falconi, P. Pederzoli, A. Pap, D. Spooner, D. J. Kerr and M. W. Buchler (2004). "A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer." N Engl J Med **350**(12): 1200-1210.

Nuzzo, G., F. Giuliante, F. Ardito, A. M. De Rose, M. Vellone, G. Clemente, C. Chiarla and I. Giovannini (2010). "Intrahepatic cholangiocarcinoma: prognostic factors after liver resection." Updates Surg **62**(1): 11-19.

Oettle, H., S. Post, P. Neuhaus, K. Gellert, J. Langrehr, K. Ridwelski, H. Schramm, J. Fahlke, C. Zuelke, C. Burkart, K. Gutberlet, E. Kettner, H. Schmalenberg, K. Weigang-Koehler, W. O. Bechstein, M. Niedergethmann, I. Schmidt-Wolf, L. Roll, B. Doerken and H. Riess (2007). "Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial." JAMA **297**(3): 267-277.

Primrose, J., R. Fox and D. H. Palmer (2017). "Adjuvant capecitabine for biliary tract cancer: The BILCAP randomized study." J Clin Oncol **35**(suppl): abstr 4006.

Saxena, A., T. C. Chua, A. Sarkar, F. Chu and D. L. Morris (2010). "Clinicopathologic and treatment-related factors influencing recurrence and survival after hepatic resection of intrahepatic cholangiocarcinoma: a 19-year experience from an established Australian hepatobiliary unit." J Gastrointest Surg **14**(7): 1128-1138.

Scholl, I., L. Kriston, J. Dirmaier, A. Buchholz and M. Harter (2012). "Development and psychometric properties of the Shared Decision Making Questionnaire--physician version (SDM-Q-Doc)." Patient Educ Couns **88**(2): 284-290.

Scholl, I., L. Kriston, J. Dirmaier and M. Harter (2012). "Comparing the nine-item Shared Decision-Making Questionnaire to the OPTION Scale - an attempt to establish convergent validity." Health Expect.

Seehofer, D., C. Kamphues and P. Neuhaus (2008). "Management of bile duct tumors." Expert Opin Pharmacother **9**(16): 2843-2856.

Shinohara, E. T., N. Mitra, M. Guo and J. M. Metz (2008). "Radiation therapy is associated with improved survival in the adjuvant and definitive treatment of intrahepatic cholangiocarcinoma." Int J Radiat Oncol Biol Phys **72**(5): 1495-1501.

Su, C. H., S. H. Tsay, C. C. Wu, Y. M. Shyr, K. L. King, C. H. Lee, W. Y. Lui, T. J. Liu and K. P'Eng F (1996). "Factors influencing postoperative morbidity, mortality, and survival after resection for hilar cholangiocarcinoma." Ann Surg **223**(4): 384-394.

Takada, T., H. Amano, H. Yasuda, Y. Nimura, T. Matsushiro, H. Kato, T. Nagakawa and T. Nakayama (2002). "Is postoperative adjuvant chemotherapy useful for gallbladder carcinoma? A phase III multicenter prospective randomized controlled trial in patients with resected pancreaticobiliary carcinoma." Cancer **95**(8): 1685-1695.

Tamandl, D., B. Herberger, B. Gruenberger, H. Puhalla, M. Klinger and T. Gruenberger (2008). "Influence of hepatic resection margin on recurrence and survival in intrahepatic cholangiocarcinoma." Ann Surg Oncol **15**(10): 2787-2794.

Ueno, H., T. Kosuge, Y. Matsuyama, J. Yamamoto, A. Nakao, S. Egawa, R. Doi, M. Monden, T. Hatori, M. Tanaka, M. Shimada and K. Kanemitsu (2009). "A randomised phase III trial comparing gemcitabine with surgery-only in patients with resected pancreatic cancer: Japanese Study Group of Adjuvant Therapy for Pancreatic Cancer." Br J Cancer **101**(6): 9 08-915.

Ustundag, Y. and Y. Bayraktar (2008). "Cholangiocarcinoma: a compact review of the literature." World J Gastroenterol **14**(42): 6458-6466.

Valle, J., H. Wasan, D. H. Palmer, D. Cunningham, A. Anthoney, A. Maraveyas, S. Madhusudan, T. Iveson, S. Hughes, S. P. Pereira, M. Roughton and J. Bridgewater (2010). "Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer." N Engl J Med **362**(14): 1273-1281.

Wang, S. J., A. Lemieux, J. Kalpathy-Cramer, C. B. Ord, G. V. Walker, C. D. Fuller, J. S. Kim and C. R. Thomas, Jr. (2011). "Nomogram for Predicting the Benefit of Adjuvant Chemoradiotherapy for Resected Gallbladder Cancer." J Clin Oncol.

Yang, J. and L. N. Yan (2008). "Current status of intrahepatic cholangiocarcinoma." World J Gastroenterol **14**(41): 6289-6297.

Appendix B: WHO performance status scale

Grade	Performance scale
0	Able to carry out all normal activity without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out light work.
2	Ambulatory and capable of all self-care but unable to carry out any work; up and about more than 50% of waking hours.
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair.

Appendix C: Common Terminology Criteria for Adverse Events (CTCAE)

In the present study, adverse events and/or adverse drug reactions will be recorded according to the

Common Terminology Criteria for Adverse Events (CTCAE), version 4.03.

At the time this protocol was issued, the full CTC document was available on the NCI web site, at the following address: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

Another option is via the EORTC Headquarters web site www.eortc.be, which provides a link to the appropriate CTC web site. This link will be updated if the CTC address is changed.

Appendix D: EORTC QLQ-C30, QLQ-BIL21, INFO 25, PEF-FB-9, PEF-FB-Doc

ENGLISH

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:
Your birthdate (Day, Month, Year):
Today's date (Day, Month, Year): 31

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4
16.	Have you been constipated?	1	2	3	4

Please go on to the next page

ENGLISH

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

ENGLISH

EORTC QLQ – BIL21

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:	Not at all	A little	Quite a bit	Very much
31. Have you had trouble with eating?	1	2	3	4
32. Have you felt full up too quickly after beginning to eat?	1	2	3	4
33. Have you had problems with your sense of taste?	1	2	3	4
34. Were you restricted in the types of food you can eat as a result of your disease or treatment?	1	2	3	4
35. Have your skin or eyes been yellow (jaundiced)?	1	2	3	4
36. Have you had itching?	1	2	3	4
37. Have you been worried about your skin being yellow?	1	2	3	4
38. Have you been less active than you would like to be?	1	2	3	4
39. Have you felt "slowed down"?	1	2	3	4
40. Have you felt lacking in energy?	1	2	3	4
41. Did you have pain during the night?	1	2	3	4
42. Have you had pain in your stomach area?	1	2	3	4
43. Have you had pain in your back?	1	2	3	4
44. Did you have a bloated feeling in your abdomen?	1	2	3	4
45. Have you felt stressed?	1	2	3	4
46. Have you felt less able to enjoy yourself?	1	2	3	4
47. Have you worried about your health in the future?	1	2	3	4
48. Were you worried about your family in the future?	1	2	3	4
49. To what extent have you been troubled with side-effects from your treatment?	1	2	3	4
50. Have you had difficulties with drainage tubes/ bags?	1	2	3	4
51. Have you worried about losing weight?	1	2	3	4

ENGLISH

EORTC QLQ – INFO25

We are interested in the information you have received about aspects of your disease and its treatment, in order to improve your health care. Please answer ALL the questions yourself by *circling* the number that best applies to you. There are no right or wrong answers. The information that you provide will remain strictly confidential.

	During your current disease or treatment, how much information have you received on:	Not at all	A little	Quite a bit	Very much
31.	The diagnosis of your disease?	1	2	3	4
32.	The extent (spread) of your disease?	1	2	3	4
33.	The possible causes of your disease?	1	2	3	4
34.	Whether the disease is under control?	1	2	3	4
35.	The purpose of any medical tests you have had or may undergo?	1	2	3	4
36.	The procedures of the medical tests?	1	2	3	4
37.	The results of the medical tests you have already received?	1	2	3	4
38.	The medical treatment (chemotherapy, radiotherapy, surgery or other treatment modality)?	1	2	3	4
39.	The expected benefit of the treatment?	1	2	3	4
40.	The possible side-effects of your treatment?	1	2	3	4
41.	The expected effects of the treatment on disease symptoms?	1	2	3	4
42.	The effects of the treatment on social and family life?	1	2	3	4
43.	The effects of the treatment on sexual activity?	1	2	3	4
44.	Additional help outside the hospital (e.g. help with daily activities, self help groups, district nurses)?	1	2	3	4
45.	Rehabilitation services (e. g. physiotherapy, occupational therapy)?	1	2	3	4

Please go to the next page

ENGLISH

During your current disease or treatment, how much information have you received on:	Not at all	A little	Quite a bit	Very much
46. Aspects of managing your illness at home?	1	2	3	4
47. Possible professional psychological support?	1	2	3	4
48. Different places of care (hospitals/outpatient services/home)?	1	2	3	4
49. Things that you can do to help yourself get well (rest, contact with others..)?	1	2	3	4

50. Have you received written information?	**Yes**	**No**
51. Have you received information on CD or tape / video?	**Yes**	**No**

	Not at all	A little	Quite a bit	Very much
52. Were you satisfied with the amount of information you received?	1	2	3	4

53. a) Do you wish to receive more information? **Yes** **No**

b) If yes, please specify on which topics?

_____

54. a) Do you wish that you had received less information? **Yes** **No**

b) If yes, please specify on which topics?

_____

	Not at all	A little	Quite a bit	Very much
55. Overall has the information you have received been helpful?	1	2	3	4

The 9-item Shared Decision Making Questionnaire (SDM-Q-9)

[Example] **Please indicate which health complaint/problem/illness the consultation was about:**

[Example] **Please indicate which decision was made:**

Nine statements related to the decision-making in your consultation are listed below. For each statement please indicate how much you agree or disagree.

1.	**My doctor made clear that a decision needs to be made.**					
	completely disagree ❑	strongly disagree ❑	somewhat disagree ❑	somewhat agree ❑	strongly agree ❑	completely agree ❑
2.	**My doctor wanted to know exactly how I want to be involved in making the decision.**					
	completely disagree ❑	strongly disagree ❑	somewhat disagree ❑	somewhat agree ❑	strongly agree ❑	completely agree ❑
3.	**My doctor told me that there are different options for treating my medical condition.**					
	completely disagree ❑	strongly disagree ❑	somewhat disagree ❑	somewhat agree ❑	strongly agree ❑	completely agree ❑
4.	**My doctor precisely explained the advantages and disadvantages of the treatment options.**					
	completely disagree ❑	strongly disagree ❑	somewhat disagree ❑	somewhat agree ❑	strongly agree ❑	completely agree ❑
5.	**My doctor helped me understand all the information.**					
	completely disagree ❑	strongly disagree ❑	somewhat disagree ❑	somewhat agree ❑	strongly agree ❑	completely agree ❑
6.	**My doctor asked me which treatment option I prefer.**					
	completely disagree ❑	strongly disagree ❑	somewhat disagree ❑	somewhat agree ❑	strongly agree ❑	completely agree ❑
7.	**My doctor and I thoroughly weighed the different treatment options.**					
	completely disagree ❑	strongly disagree ❑	somewhat disagree ❑	somewhat agree ❑	strongly agree ❑	completely agree ❑
8.	**My doctor and I selected a treatment option together.**					
	completely disagree ❑	strongly disagree ❑	somewhat disagree ❑	somewhat agree ❑	strongly agree ❑	completely agree ❑
9.	**My doctor and I reached an agreement on how to proceed.**					
	completely disagree ❑	strongly disagree ❑	somewhat disagree ❑	somewhat agree ❑	strongly agree ❑	completely agree ❑

The 9-item Shared Decision Making Questionnaire (SDM-Q-Doc, physician version)

[Example] **Please indicate which health complaint/problem/illness the consultation was about:**

[Example] **Please indicate which decision was made:**

Nine statements related to the decision-making in the above mentioned consultation are listed below. For each statement please indicate how much you agree or disagree.

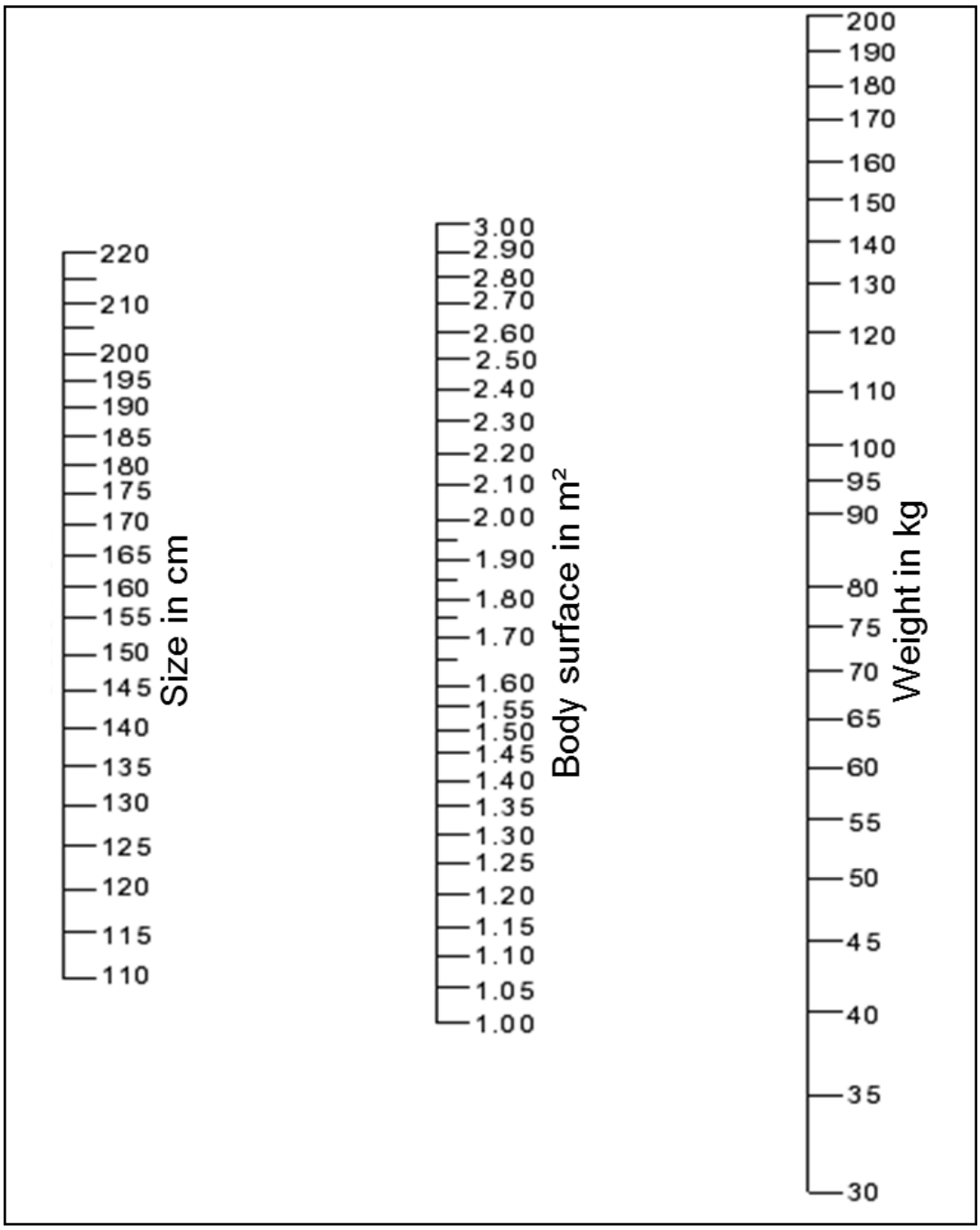
1.	**I made clear to my patient that a decision needs to be made.**					
	completely disagree ❑	strongly disagree ❑	somewhat disagree ❑	somewhat agree ❑	strongly agree ❑	completely agree ❑
2.	**I wanted to know exactly from my patient how he/she wants to be involved in making the decision.**					
	completely disagree ❑	strongly disagree ❑	somewhat disagree ❑	somewhat agree ❑	strongly agree ❑	completely agree ❑
3.	**I told my patient that there are different options for treating his/her medical condition.**					
	completely disagree ❑	strongly disagree ❑	somewhat disagree ❑	somewhat agree ❑	strongly agree ❑	completely agree ❑
4.	**I precisely explained the advantages and disadvantages of the treatment options to my patient.**					
	completely disagree ❑	strongly disagree ❑	somewhat disagree ❑	somewhat agree ❑	strongly agree ❑	completely agree ❑
5.	**I helped my patient understand all the information.**					
	completely disagree ❑	strongly disagree ❑	somewhat disagree ❑	somewhat agree ❑	strongly agree ❑	completely agree ❑
6.	**I asked my patient which treatment option he/she prefers.**					
	completely disagree ❑	strongly disagree ❑	somewhat disagree ❑	somewhat agree ❑	strongly agree ❑	completely agree ❑
7.	**My patient and I thoroughly weighed the different treatment options.**					
	completely disagree ❑	strongly disagree ❑	somewhat disagree ❑	somewhat agree ❑	strongly agree ❑	completely agree ❑
8.	**My patient and I selected a treatment option together.**					
	completely disagree ❑	strongly disagree ❑	somewhat disagree ❑	somewhat agree ❑	strongly agree ❑	completely agree ❑
9.	**My patient and I reached an agreement on how to proceed.**					
	completely disagree ❑	strongly disagree ❑	somewhat disagree ❑	somewhat agree ❑	strongly agree ❑	completely agree ❑

Appendix E: MDRD formula

Formula:

GFR (ml/min/1,73m^2) = 186 x Serum-Creatinine $^{-1,154}$ x age $^{-0,203}$ [x 0,742 only in women] [x 1,21 in patients with black skin color]

Correction on body surface area: divide GFR by body surface area from nomogram



Appendix F: Primary efficacy analysis and sample size calculation

Stage 1+2 Gemcitabine/cisplatin vs. Standard of care (observation +/- capecitabine) (Power calculation)
Two-Sample Logrank Test (Two-Sided)

Null hypothesis H_0: hazard ratio = 1
Formula of Schoenfeld (Biometrika, 1981, 316-319) used for the calculation of the number of events.

A single stage (fixed sample size) design was chosen.
For specified $\alpha = 0.05$, event rates $\pi_1 = 0.491$, $\pi_2 = 0.398$ at time 24 (hazard ratio = 0.752) the power (1 - β) is 89.9% if the logrank test is performed at the number of accumulated (pooled) events given in the column of the table entitled "events".
The computation assumes an allocation ratio $(n_2/n_1) = 1.0$.
Assuming an accrual time of 48 and a follow-up time of 24 time units a total of 765.0 patients is expected to yield the necessary number of events if the accrual rate is constant. Under these assumptions, the time points of interim analyses should be as given in the column entitled "observ. time". This yields the stagewise number of patients given in the last column of the table where this calculation assumes dropout rates $\varphi_1 = 0$, $\varphi_2 = 0$ at time 24 (see the ADDPLAN documentation for further details).

Information rate	bounds accept H_0	bounds reject H_0	sign.level one-sided	α spent	β spent	power achieved	observ. time	events	cum. observations
1.0	1.960	1.960	0.0250	0.0500	-	0.8992	72.00	513.5	765.0

Stage 1 Gemcitabine/cisplatin vs. Observation (Power calculation)
Two-Sample Logrank Test (Two-Sided)

Null hypothesis H_0: hazard ratio = 1
Formula of Schoenfeld (Biometrika, 1981, 316-319) used for the calculation of the number of events.

A single stage (fixed sample size) design was chosen.
For specified $\alpha = 0.05$, event rates $\pi_1 = 0.55$, $\pi_2 = 0.4$ at time 24 (hazard ratio = 0.640) the power (1 - β) is 79.0% if the logrank test is performed at the number of accumulated (pooled) events given in the column of the table entitled "events".
The computation assumes an allocation ratio $(n_2/n_1) = 1.0$.
Assuming an accrual time of 12 and a follow-up time of 60 time units a total of 187.0 patients is expected to yield the necessary number of events if the accrual rate is constant. Under these assumptions, the time points of interim analyses should be as given in the column entitled "observ. time". This yields the stagewise number of patients given in the last column of the table where this calculation assumes dropout rates $\varphi_1 = 0$, $\varphi_2 = 0$ at time 24 (see the ADDPLAN

documentation for further details).

Information rate	bounds accept H_0	bounds reject H_0	sign.level one-sided	α spent	β spent	power achieved	observ. time	events	cum. observations
1.0	1.960	1.960	0.0250	0.0500	-	0.7903	72.00	153.5	187.0

Stage 2 Gemcitabine/cisplatin vs. Capecitabine (Sample size calculation)
Two-Sample Logrank Test (Two-Sided)

Null hypothesis H_0: hazard ratio = 1
Formula of Schoenfeld (Biometrika, 1981, 316-319) used for the calculation of the number of events.

A design with a maximum of K = 2 stages was chosen.
The critical values and the test characteristics of the group sequential test design were calculated for the O'Brien and Fleming design.
For specified α = 0.05, event rates π_1= 0.491, π_2= 0.398 at time 24 (hazard ratio = 0.752) the power (1 - β) is 80.0% if the logrank test is performed at the number of accumulated (pooled) events given in the column of the table entitled "events".
The computation assumes an allocation ratio (n_2/n_1) = 1.0.
Assuming an accrual time of 48 and a follow-up time of 24 time units a total of 577.5 patients is expected to yield the necessary number of events if the accrual rate is constant. Under these assumptions, the time points of interim analyses should be as given in the column entitled "observ. time". This yields the stagewise number of patients given in the last column of the table where this calculation assumes dropout rates $\varphi_1 = 0$, $\varphi_2 = 0$ at time 24 (see the ADDPLAN documentation for further details).
For comparison, the sample size in a fixed sample size design is $n_1 + n_2 = 573.1$.
Thus, the maximum sample size in the group sequential test design is 1.008 times the sample size in a fixed sample size design.
The expected (average) number of events under the alternative hypothesis is 347.1, under a value midway between H_0 and H_1 it is 380.7, and under the null hypothesis it is 386.7.
The expected study duration under H_1 is 65.8, under H_0 it is 71.8 time units. The expected number of patients under H_1 is 563.8, under H_0 it is 577.2.

Information rate	bounds accept H_0	bounds reject H_0	sign.level one-sided	α spent	β spent	power achieved	observ. time	events	cum. observations
0.5	-	2.797	0.0026	0.0052	-	0.2096	42.54	193.8	511.8
1.0	1.977	1.977	0.0240	0.0500	-	0.8000	72.00	387.7	577.5

Appendix G: Translational research working instructions

(to be adapted in respective language version or replaced by the respective national lab manual)

Contact/Questions: acticca@uke.de

For patients included in the enrolement and treatment phase

Blood draw

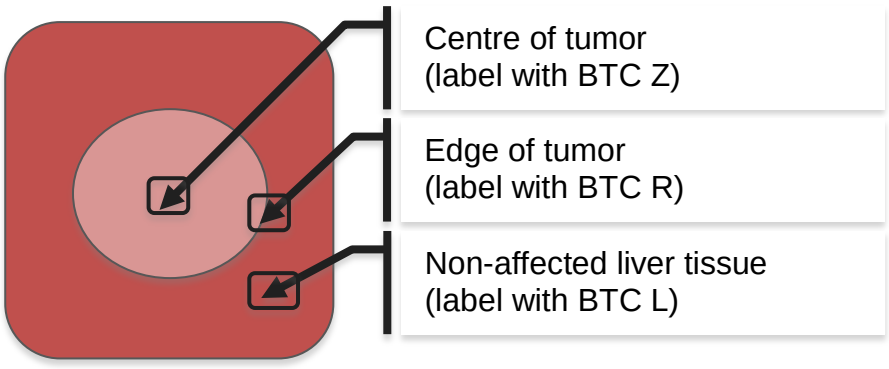
- **preoperatively and postoperatively (7-14 days after resection)**
  - 15ml plain tubes
    - Within 30 minutes after blood collection, place the tube into the centrifuge and spin at 1000 x g for 15 minutes. Immediately transfer the serum (max. 2 ml per tube, as much tubes as possible) into the labeled tubes (note the patient- and site-no., and the start time of blood draw) Lab kits are provided. Place the storage tube immediately upright into the freezer at -80°C (optional -20°C).
  - 15ml in 2 VERIDEX tubes for immediate shipment (only Germany)

- **baseline (within 4 weeks before treatment) and after recurrence**
  - 15ml plain tubes
    - Within 30 minutes after blood collection, place the tube into the centrifuge and spin at 1000 x g for 15 minutes. Immediately transfer the serum (max. 2 ml per tube, as much tubes as possible) into the labeled tubes (note the patient- and site-no., and the start time of blood draw) Lab kits are provided. Place the storage tube immediately upright into the freezer at -80°C (optional -20°C).

Tissue (fresh frozen and/or paraffin embedded)

Take the following samples of tumor-tissue

1) **Primary tumor 3 samples each (overall 9)**
   - **Out of centre** (label each with: BTC Z),
   - **Out of the edge** (label each with: BTC R) and
   - **Out of non-affected liver- tissue** (label each with: BTC L)



Atypical resection, if possible. Small tumors should possibly be obtained as a whole (edge to centre).

2) **Lymph nodes 2 samples each (overall 4)**
   - **Out of an affected lymph node**; if available (label each with: BTC NT)
   - **Out of (first) adjacent tumor-free lymph node** (label each with: BTC NF)

Within a maximum of 30 minutes, samples must be stored in freezer for fresh frozen tissue. Please provide number of liver segment on identification form.

Blood and tissue will both be stored locally and identification forms will be send by fax or mail to ACTICCA study coordination unit at University Hospital Hamburg-Eppendorf

Fax: +49-40-741053563
Mail: acticca@uke.de

For patients included directly in the treatment phase

Blood draw

- **baseline (within 4 weeks before treatment) and after recurrence**
  - 15ml plain tubes
    - Within 30 minutes after blood collection, place the tube into the centrifuge and spin at 1000 x g for 15 minutes. Immediately transfer the serum (max. 2 ml per tube, as much tubes as possible) into the labeled tubes (note the patient- and site-no., and the start time of blood draw) Lab kits are provided. Place the storage tube immediately upright into the freezer at -80°C (optional -20°C).

Tissue

Obtain paraffin embedded tissue.

Blood and tissue will both be stored locally and identification forms will be send by fax or mail to ACTICCA study coordination unit at University Hospital Hamburg-Eppendorf

Fax: +49-40-741053563
Mail: acticca@uke.de

Please refer to translational research manual for further information and identification forms.

Appendix H: Surgery

All patients should have had radical surgical treatment. All macroscopic disease must be removed and an attempt made to achieve microscopic clearance.

- In the case of intrahepatic bile duct cancer, surgery should take the form of a radical liver resection.
- With extrahepatic/hilar cholangiocarcinoma, a liver resection, usually in the form of a hepatectomy (sometimes extended) should be performed together with segment I resection and a radical lymphadenectomy extending at least to the hepatic artery territory.
- With muscle invasive gallbladder cancer, a resection of segments IV and V should be performed and an extended R hepatectomy advised in cases with 10 mm or more liver invasion. A radical lymphadenectomy as described above should be performed. The bile duct may be removed if required for oncological reasons.
- In the event of a laparoscopic cholecystectomy having been performed for an undiagnosed gallbladder cancer, in addition to a liver resection the port sites should where possible be excised.
- Patients with gallbladder cancer which has not extended to involve the muscle layers or lymph nodes are not eligible for recruitment to the trial.
- In the case of cancer of the distal bile duct a Whipples procedure should be performed.

Appendix I: Calculation of capecitabine doses

The following table for dose calculations, taken from the Summary of Product Characteristics (SmPC) for capecitabine.

Capecitabine Dose Calculations

Standard and reduced dose calculations according to body surface area for a starting dose of Capecitabine of 1250 mg/m^2

	Dose level 1250 mg/m^2 (twice daily)				
	Full dose **1250 mg/m^2**	**Number of 150 mg tablets and/or 500 mg tablets per administration (each administration to be given morning and evening)**		**Reduced dose (75%)** **950 mg/m^2**	**Reduced dose (50%)** **625 mg/m^2**
Body Surface Area (m^2)	Dose per administration (mg)	150 mg	500 mg	Dose per administration (mg)	Dose per administration (mg)
≤ 1.26	1500	-	3	1150	800
1.27 - 1.38	1650	1	3	1300	800
1.39 - 1.52	1800	2	3	1450	950
1.53 - 1.66	2000	-	4	1500	1000
1.67 - 1.78	2150	1	4	1650	1000
1.79 - 1.92	2300	2	4	1800	1150
1.93 - 2.06	2500	-	5	1950	1300
2.07 - 2.18	2650	1	5	2000	1300
≥ 2.19	2800	2	5	2150	1450

Appendix J: Capecitabine patient diary

Dear Patient,

Please use this sheet to keep a record of your capecitabine (Xeloda) tablets as you take them. You will be taking capecitabine tablets twice a day (morning and evening) for 14 days, followed by a gap of 7 days with no capecitabine.

Each dose of ..... **mg** is made up from: ..... **x 500 mg tablet(s)**

..... **x 150 mg tablet(s)**

Swallow the tablets with water within 30 minutes after the end of a meal. Please record the time that you take each dose. If you miss a dose, record this by writing "missed" on the sheet. Do not take the missed dose at all and do not double the next one. Instead continue with your standard dosing schedule and check with your doctor.

If you develop diarrhoea or any other severe side-effect it may be necessary to stop taking the capecitabine tablets. Please phone your 24-hour telephone advice number if this happens.

Date: (nurse to complete)	**Day:**	**Morning Dose:** please record time taken	**Evening Dose:** please record time taken
___ / ___ / ___	1	_____ : _____ am	_____ : _____ pm
___ / ___ / ___	2	_____ : _____ am	_____ : _____ pm
___ / ___ / ___	3	_____ : _____ am	_____ : _____ pm
___ / ___ / ___	4	_____ : _____ am	_____ : _____ pm
___ / ___ / ___	5	_____ : _____ am	_____ : _____ pm
___ / ___ / ___	6	_____ : _____ am	_____ : _____ pm
___ / ___ / ___	7	_____ : _____ am	_____ : _____ pm
___ / ___ / ___	8	_____ : _____ am	_____ : _____ pm
___ / ___ / ___	9	_____ : _____ am	_____ : _____ pm
___ / ___ / ___	10	_____ : _____ am	_____ : _____ pm
___ / ___ / ___	11	_____ : _____ am	_____ : _____ pm
___ / ___ / ___	12	_____ : _____ am	_____ : _____ pm
___ / ___ / ___	13	_____ : _____ am	_____ : _____ pm
___ / ___ / ___	14	_____ : _____ am	_____ : _____ pm
___ / ___ / ___	15	_____ : _____ am	
___ / ___ / ___ to ___ / ___ / ___		**No capecitabine tablets taken on these days**	

Page 2 of 3

BILCAP Trial Capecitabine Patient Diary. Version 1, 23rd August 2006 Cancer Research UK Trials Unit, Birmingham

Additional Notes: (e.g. please note any side effects or any reasons for missing a dose)