AIO-HEP-0118/ass: Neoadjuvant chemotherapy with gemcitabine plus cisplatin followed by radical liver resection versus immediate radical liver resection alone with or without adjuvant chemotherapy in incidentally detected gallbladder carcinoma after simple cholecystectomy or in front of radical resection of BTC (ICC/ECC) – A phase III study utilizing the German Registry of Incidental Gallbladder Carcinoma Platform (GR) – The AIO/ CALGP/ ACO- GAIN-Trial -

AIO-assoziierte Studie		
Studiennummer/-Code:	AIO-HEP-0118/ass - GAIN/GEM/CIS	
Status:	Voten erhalten; Förderantrag der DFG ist genehmigt, über die Hälfte der Zentren ist initiiert, Rekrutierung ist angelaufen	
Rekrutierungszeitraum:	Q2/2019, 4 Jahre Rekrutierung	
Zentren:	geplant: 50	initiiert:37
Patienten:	geplant: 300	aktuell eingeschlossen: 32
Weitere Zentren:	sind sehr erwünscht	
Letzte Aktualisierung	28.03.2022	

STUDY TYPE	Multicenter, randomized, open label phase III study
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CONDITION	Cholangiocarcinoma
DESIGN	This is a multicenter, randomized, controlled, open-label phase III study including patients with incidentally discovered gallbladder carcinomas (IGBC/ 70% of all GBC`s) after simple cholecystectomy and patients with resectable/ borderline resectable cholangiocarcinomas (ICC/ ECC) scheduled to receive perioperative chemotherapy or surgery alone. Potential study participants will be assessed for eligibility during a 28-day screening period. Eligible patients will be enrolled and randomized to perioperative chemotherapy (Arm A) or immediate surgery alone with or without adjuvant chemotherapy (investigator's choice) (Arm B). Randomization will occur in a 1:1 ratio with stratification by clinical tumor

stage (T1 and T2 vs. T3 and T4), ECOG (0 and 1 vs. 2) and localization of the primary (ICC vs. ECC vs. IGBC(GBC)).
Neoadjuvant chemotherapy with gemcitabine plus cisplatin will be administered for 3 cycles preoperatively followed by radical liver resection versus immediate radical liver resection alone with or without adjuvant chemotherapy (investigator's choice) in incidentally detected gallbladder carcinoma after simple cholecystectomy or in front of radical resection of Biliary Tract Cancer (ICC/ECC). After the radical tumor resection again 3 cycles postoperative chemotherapy will be administered in the experimental arm. In the standard (control) arm no perioperative chemotherapy will be administered. After surgery adjuvant chemotherapy can be administered by investigator's choice.

Arm A (gemcitabine plus cisplatin)
Patients assigned to arm A will receive gemcitabine (1000 mg/m^2) plus cisplatin (25 mg/m^2) every three weeks on days 1 and 8 intravenously. Treatment with gemcitabine plus cisplatin will be administered for 3 cycles preoperatively (neoadjuvant part) and for 3 cycles postoperatively (adjuvant part). In case of progressive or recurrent disease, unacceptable toxicity, or withdrawal of consent, treatment will be terminated.

Arm B (standard postoperative management)
Patients assigned to arm B will receive surgery immediately, without receiving perioperative chemotherapy (Standard of Care / SOC). After surgery adjuvant chemotherapy can be administered by investigator's choice.

In both of the treatment arms, tumor assessments (CT or MRI) are performed before randomization and prior to surgery. Therefore, in patients randomized to Arm A (surgery + chemotherapy) there will be an additional staging before the surgical procedure, after completing 3 cycles of chemotherapy. After surgery, tumor assessments are performed every 3 months until progression/relapse, death or end of follow-up. A change from CT into MRI in the follow up period is possible at any time.
During treatment, clinical visits (blood cell counts, detection of toxicity) occur prior to every treatment dose. Safety of Cis/ Gem will be monitored continuously by careful monitoring of all adverse events (AEs) and serious adverse events (SAEs) reported.

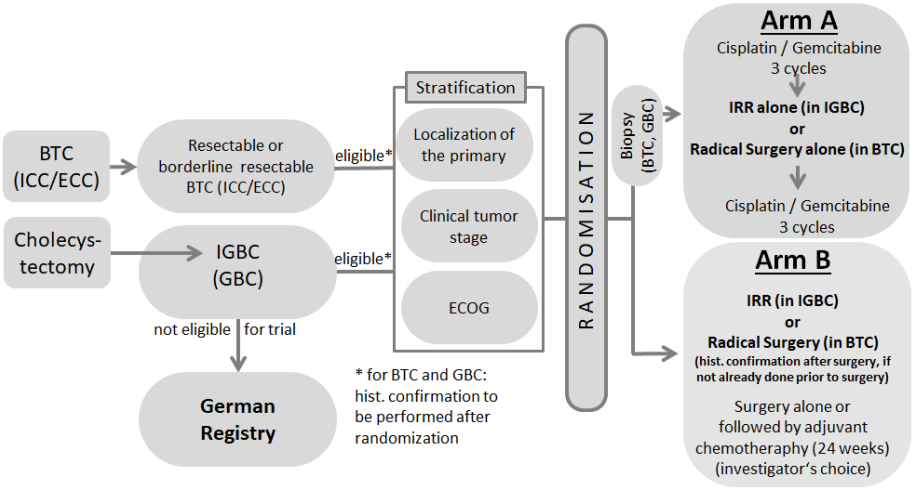

Figure 1: Study Scheme. BTC (ICC/ ECC) = Biliary Tract cancer (Intrahepatic Cholangiocarcinoma/ Extrahepatic Cholangiocarcinoma); IGBC = Incidental Gallbladder Carcinoma; GBC = Gallbladder Carcinoma; IRR = Immediate Radical Re-resection

INDICATION	Incidental gallbladder carcinoma (IGBC) or in front radical resection in biliary tract cancer (BTC) (intrahepatic cholangiocarcinoma (ICC)/ extrahepatic cholangiocarcinoma (ECC))
OBJECTIVE(S)	The aim of the study is to investigate whether induction chemotherapy followed by radical re-resection (and - if possible - postoperative chemotherapy) in incidental gallbladder carcinoma (IGBC) or in front radical resection in biliary tract cancer (BTC) (intrahepatic cholangiocarcinoma (ICC)/ extrahepatic cholangiocarcinoma (ECC)) prolongs overall survival without impaired quality of life compared to immediate radical surgery alone with or without adjuvant chemotherapy (investigator's choice) in patients with IGBC, or BTC (ICC/ECC). One of the most important secondary objectives is to raise awareness for the necessity of a radical second surgery as well as to improve the adherence to the treatment guidelines in IGBC. Further secondary objectives are safety and tolerability of the treatment as well as quality of life. <u>Safety Objectives</u> • To evaluate the safety and tolerability of neoadjuvant, respectively perioperative chemotherapy plus surgery compared with immediate surgery alone with or without adjuvant chemotherapy (investigator's choice) in patients with incidentally detected gallbladder carcinoma after simple cholecystectomy in front of radical re- resection in IGBC or in front of radical resection in BTC (ICC/ECC), focusing on serious adverse events, National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Grade ≥ 3 adverse events, and Grade ≥ 3 laboratory toxicities • To evaluate the perioperative morbidity and mortality
INTERVENTION(S)	<u>Arm A (gemcitabine plus cisplatin)</u> Patients assigned to arm A will receive treatment with gemcitabine plus cisplatin. Chemotherapy will be administered for 3 cycles preoperatively (neoadjuvant part) and for 3 cycles postoperatively (adjuvant part). In case of progressive or recurrent disease, unacceptable toxicity, or withdrawal of consent, treatment will be terminated. • Cisplatin (25 mg/m^2) every three weeks on days 1 and 8 intravenously, in 1000 ml 0.9% saline with KCl 20 mmol and MgSO4 8 mmol during the one hour cisplatin infusion followed by 500 ml 0.9% saline over 30 minutes prior to gemcitabine; with adequate pre- and posthydration. In case of reduced glomerular filtration rate the dose must be adjusted according to guideline or local standards. • Gemcitabine (1000 mg/m^2) in 250-500 ml 0.9% saline every three weeks on days 1 and 8 intravenously <u>Arm B (standard postoperative management)</u> Patients assigned to arm B will receive surgery directly, without receiving perioperative chemotherapy (Standard of Care / SOC). After surgery adjuvant chemotherapy can be administered by investigator's choice. In case of progressive or recurrent disease, unacceptable toxicity, or withdrawal of consent, adjuvant treatment will be terminated.
BACKROUND /RATIONALE	Currently, complete surgical resection represents the only potentially curative treatment option for Biliary tract cancer (BTC; Intrahepatic Cholangiocarcinoma/ Extrahepatic Cholangiocarcinoma) and Gallbladder Carcinoma, and is therefore the treatment of choice if the respective tumor is deemed resectable (Bridgewater et al., 2014). However, more than 50% of patients already exhibit unresectable disease at the time of diagnosis (Glimelius et al., 1996; Sharma et al., 2010). Even after curative resection, 5-year overall survival (OS) is only 20–40 %

	(Anderson & Kim, 2009; Choi et al., 2009; Guglielmi et al., 2009; Li et al., 2009; Murakami et al., 2011; Nuzzo et al., 2010; Saxena, Chua, Sarkar, Chu, & Morris, 2010; Tamandl et al., 2008). Van der Gaag and colleagues evaluated the long-term outcome of 175 consecutive patients with resected extrahepatic CCA (Cholangiocarcinoma) (van der Gaag et al., 2012). In this study, the 2-year OS was 50% and declined to 26% after five years. In summary, following complete resection of CCA, patients had DFS rates of 48 to 65% after one year and 23 to 35% after three years without adjuvant treatment (Choi et al., 2009; Takada et al., 2002; Tamandl et al., 2008). Patients with a positive nodal status (N1) and/or vascular invasion (V1) at time of resection had an even higher risk of disease recurrence. Gallbladder carcinoma is relatively rare, but still the fifth most common neoplasm of the digestive tract and even the most frequent cancer of the biliary system (Goetze, 2015). Gallbladder carcinoma is suspected preoperatively in only 30% of all patients (Goetze & Paolucci, 2006; Paolucci, Neckell, & Goetze, 2003), while the majority of cases are discovered incidentally by the pathologist (IGBC) after cholecystectomy for a benign indication. All reported cases of IGBC in Germany are registered in the “German Registry of Incidental Gallbladder Carcinoma” also known as “CAES-/ CAMIC- Zentralregister”, the largest casebook of gallbladder carcinomas in Europe, overseen by the principal investigator of this proposal protocol (Goetze & Paolucci, 2006, 2008a, 2008b, 2009, 2010, 2012, 2013, 2014a, 2014b; C. N. Gutt et al., 2013; Paolucci et al., 2003). The GR shows that surgical management of gallbladder cancer remains inadequate despite widely published guidelines (Goetze & Paolucci, 2008a). Less than 50% of the patients received stage adjusted therapy according to the GR (Goetze & Paolucci, 2014c). Stage adjusted therapy according to the S3 Guidelines contains liver resection in the form of wedge resection of the gallbladder bed with a 3 cm margin in the liver, or a resection of liver segments 4b and 5, always combined with dissection of the regional lymph nodes along the hepatoduodenal ligament in cases of T2 (T1b, respectively – according to the new S3-Guidelines effective from 2017) or more advanced carcinomas (C. Gutt et al., 2018). Using the data of n = 930 IGBC patients contained in the GR, our group has shown that there is no need for an IRR in T1a- stage carcinomas. But – strikingly – in T1b-stage there is a significant improvement of OS (45% vs. 75%) after IRR. This applies also for T2- (22% vs. 38%) and T3- (12% vs. 18%) stages (Goetze & Paolucci, 2014a, 2014b). Gallbladder neoplasms shows a high incidence of locoregional failure after surgical resection, with early spread to celiac, retropancreatic, and aortocaval nodes and occult liver spread (Endo et al., 2004) in formally R0 patients after simple cholecystectomy (SC). The rate of positive lymphatic nodes is 31.2% in T2- and 45.5% in T3-stage carcinomas (Bartlett, Fong, Fortner, Brennan, & Blumgart, 1996; Endo et al., 2004). Lymphatic spread beyond the hepatoduodenal ligament generally represents distant metastatic disease, and a cure of such patients by a pure surgical concept does not seem to be achievable. Therefore, there is a need for a systemic therapy as early as possible in the course of treatment in IGBC`s and also in BTC (ICC/ECC). The landmark trial, UK ABC-02 by Valle et al. (Valle et al., 2010) compared gemcitabine/cisplatin with gemcitabine alone in locally advanced or metastatic cholangio- and gallbladder carcinomas and showed clear superiority of the combination, with significant improvements for PFS (8 vs. 5 months, $p<0.001$) and OS (8.1 vs. 11.7 months, $P<0.001$). Basically, the study indicates the sensitivity of this disease towards chemotherapy and provides a rationale for the use of this chemotherapeutic doublet in the present study. For improving disease control and cure rates in BTC (ICC/ ECC) and of IRR in IGBC`s, it is meaningful to implement early additional systemic therapy. The earliest moment to apply chemotherapy would be directly after simple cholecystectomy in IGBC`s and right before surgery in ICC/ECC. The

	encouraging results of neoadjuvant/perioperative concepts in esophagogastric, stomach, rectal, and other malignancies provide an additional rationale to use this treatment in the early phase of IGBC management and even ICC/ECC. However, due to the fact that 2/3 of gallbladder carcinomas are incidental findings after SC, an earlier start of a systemic therapy in IGBC will be not realizable. Furthermore, preoperatively discovered gallbladder carcinomas are usually too advanced for neoadjuvant/perioperative concepts. Recently the results of two randomized trials were presented which evaluate the role of either gemcitabine and oxaliplatin (PRODIGE 12) or capecitabine (BILCAP) compared to observation alone. The primary endpoint of PRODIGE 12 trial was Relapse-Free Survival. The study showed no significant benefit according to Relapse-Free Survival and Overall Survival. Therefore, the authors conclude that there was no benefit for GEMOX over surveillance in the adjuvant setting and GEMOX chemotherapy was not recommended in the adjuvant setting (Edeline et al., 2017). The most recent results of the BILCAP trial ("Capecitabine Extends Survival for Biliary Tract Cancer," 2017) in 447 patients showed a significantly improved OS again only in the PP-population. In a sensitivity analysis, adjusting for further prognostic factors (nodal status, disease grade and gender) there was a significant benefit for adjuvant chemotherapy. However, in the overall ITT-population the trial was negative and there was no significance for the delta of 15 months even if the authors define a new standard, describing a gain in OS of 15 months due to adjuvant therapy. To conclude there are trends for an improvement in OS due to adjuvant therapy, but data showing a significant improvement for adding adjuvant therapy after a curative resection are lacking. Because of high rates of disease recurrence and poor survival rates in IGBC and ICC/ECC following surgical resection and the inadequacy of treatment modalities in the pure adjuvant therapy there is a need for an earlier intervention in the course of the disease. Due to the prognostic improvements of patients in other tumor entities (gastric, colorectal e.g. (Al-Batran et al., 2016; Cunningham et al., 2006) treated with neoadjuvant or perioperative therapy there is a strong rationale to use these concepts in biliary and gallbladder cancers.
KEY EXCLUSION CRITERIA	1. Known hypersensitivity against gemcitabine or cisplatin 2. Other known contraindications to gemcitabine or cisplatin 3. Clinically significant valvular defect 4. Past or current history of other malignancies not curatively treated and without evidence of disease for more than two years, except for curatively treated basal cell carcinoma of the skin, in situ carcinoma of the cervix, and prostate cancer 5. Locally unresectable tumor or metastatic disease: - Radiological evidence suggesting inability to resect with curative intent whilst maintaining adequate vascular inflow and outflow, and sufficient future liver remnant - Radiological evidence of direct invasion into adjacent organs - Radiological evidence of extrahepatic metastatic disease 6. Other severe internal disease or acute infection 7. Chronic inflammatory bowel disease 8. Receiving chronic antiplatelet therapy, including aspirin (Once-daily aspirin use (maximum dose 325 mg/day) is permitted), nonsteroidal anti-inflammatory drugs (including ibuprofen, naproxen, and others), dipyridamole or clopidogrel, or similar agents. 9. History of deep vein thrombosis, pulmonary embolism, or any other significant thromboembolism (venous port or catheter thrombosis or superficial venous thrombosis are not considered “significant”) during 3

	months prior to randomization. 10. Cirrhosis at a level of Child-Pugh B (or worse) or cirrhosis (any degree) and a history of hepatic encephalopathy or ascites. 11. On-treatment participation in another clinical study 30 days or five half-lives (whichever is longer) prior to inclusion and during the study 12. Pregnant or breast feeding patient, or patient is planning to become pregnant within 7 months after the end of treatment. 13. Patients in a closed institution according to an authority or court decision (AMG § 40, Abs. 1 No. 4) 14. Any other concurrent antineoplastic treatment including irradiation
KEY INCLUSION CRITERIA	1. Incidental gallbladder carcinoma (IGBC), gallbladder carcinoma (GBC) or Biliary tract cancer (BTC) (intrahepatic, hilar or distal Cholangiocarcinoma (CCA)) scheduled for complete resection (mixed tumor entities with hepatocellular carcinoma are excluded). 2. No prior partial or complete tumor resection for BTC (intrahepatic, hilar or distal CCA), for IGBC/GBC prior Cholecystectomy is allowed. 3. Exclusion of distant metastases by CT or MRI of abdomen, pelvis, and thorax, bone scan or MRI (if bone metastases are suspected due to clinical signs). Exclusion of the infiltration of any adjacent organs or structures by CT or MRI, indicating an unresectable situation. 4. ECOG performance status of 0, 1, or 2. 5. Estimated life expectancy > 3 months. 6. Female and male patients ≥18 years. 7. Patient able and willing to provide written informed consent and to comply with the study protocol and with the planned surgical procedures 8. No previous or preceding cytotoxic or targeted therapy for BTC or IGBC/GBC. 9. No previous malignancy within two years or concomitant malignancy, except for curatively treated basal cell carcinoma of the skin, in situ carcinoma of the cervix, and prostate cancer 10. No severe or uncontrolled cardiovascular disease (congestive heart failure NYHA III or IV, unstable angina pectoris, history of myocardial infarction in the last three months, significant arrhythmia). 11. Absence of psychiatric disorder precluding understanding of information of trial related topics and giving informed consent. 12. No serious underlying medical conditions (judged by the investigator), that could impair the ability of the patient to participate in the trial. 13. A) Females of childbearing potential must agree to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of <1% per year during the treatment period and for at least 7 months after the last study treatment. A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (has not had ≥12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus). Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, hormonal implants, established, proper use of combined oral or injected hormonal contraceptives, and certain intrauterine devices. The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception. B) Males must agree to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agree to refrain from

	donating sperm, as defined below: With female partners of childbearing potential or pregnant female partners, men must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of 1% per year during the treatment period and for at least 6 months after the last dose of study treatment to avoid exposing the embryo. Men must refrain from donating sperm during this same period. Men with a pregnant partner must agree to remain abstinent or to use a condom for the duration of the pregnancy. 14. No pregnancy or lactation. 15. Adequate hematologic function: ANC ≥ 1.5 × 109/L, platelets ≥ 100 × 109/L, hemoglobin ≥ 9 g/dl or ≥ 5.59 mmol/L; prior transfusions for patients with low hemoglobin are allowed 16. Adequate liver function as measured by serum transaminases (AST and ALT) ≤ 5 x ULN and bilirubin ≤ 3 x ULN. 17. Adequate renal function, i.e. serum creatinine ≤ 1.5 x institutional ULN, a calculated glomerular filtration rate ≥ 30 mL/min 18. Adequate coagulation functions as defined by International Normalized Ratio (INR) ≤ 1.5, and a partial thromboplastin time (PTT) ≤ 5 seconds above the ULN (unless receiving anticoagulation therapy). Patients receiving warfarin/ phenprocoumon must be switched to low molecular weight heparin and have achieved stable coagulation profile prior to randomization. 19. No active uncontrolled infection, except chronic viral hepatitis under antiviral therapy (patients on long-term antibiotics are eligible provided signs of active infection have been resolved). 20. No concurrent treatment with other experimental drugs or other anti-cancer therapy, treatment in a clinical trial within 30 days or five half-lives (whichever is longer) prior to randomization. 21. Negative serum pregnancy test within 7 days of starting study treatment in pre-menopausal women and women <1 year after the onset of menopause Please note that after randomization for patients in Arm A the histological confirmation of BTC or GBC must be performed before administering chemotherapy. For IGBC histological confirmation should already have been performed. For Arm B patients the histological confirmation can be performed after surgery with material from the surgery.
OUTCOME(S)	<u>Primary efficacy endpoint</u> • Primary efficacy endpoint is overall survival (OS) <u>Secondary efficacy endpoints</u> • Quality of life (EORTC QLQ- C30) • PFS rates at 3 and 5 years • OS rates at 3 and 5 years • progression free survival (PFS) • R0- resection rate • Toxicity, graded using CTC adverse events criteria version CTCAE V 5.0 • perioperative morbidity and mortality (30 days and 90 days mortality/morbidity)

SAMPLE SIZE	A total of n = 333 patients with IGBC/GBC or BTC(ICC/ECC) will be included in the study with 10% drop out expected. Therefore, 300 patients will be allocated to the trial and analyzed as intention-to-treat basis.
TRIAL DURATION	Recruitment period (months): 4 years (48 months) Duration of follow-up: overall 2 years (24 months), every 3 months Duration of the entire trial (first patient in to last patient out): 6 years (72 months). The study can be analyzed earlier or later depending on the number of events.
PARTICIPATING CENTERS	Up to 50 sites in Germany
NUMBER of PATIENTS	N=300