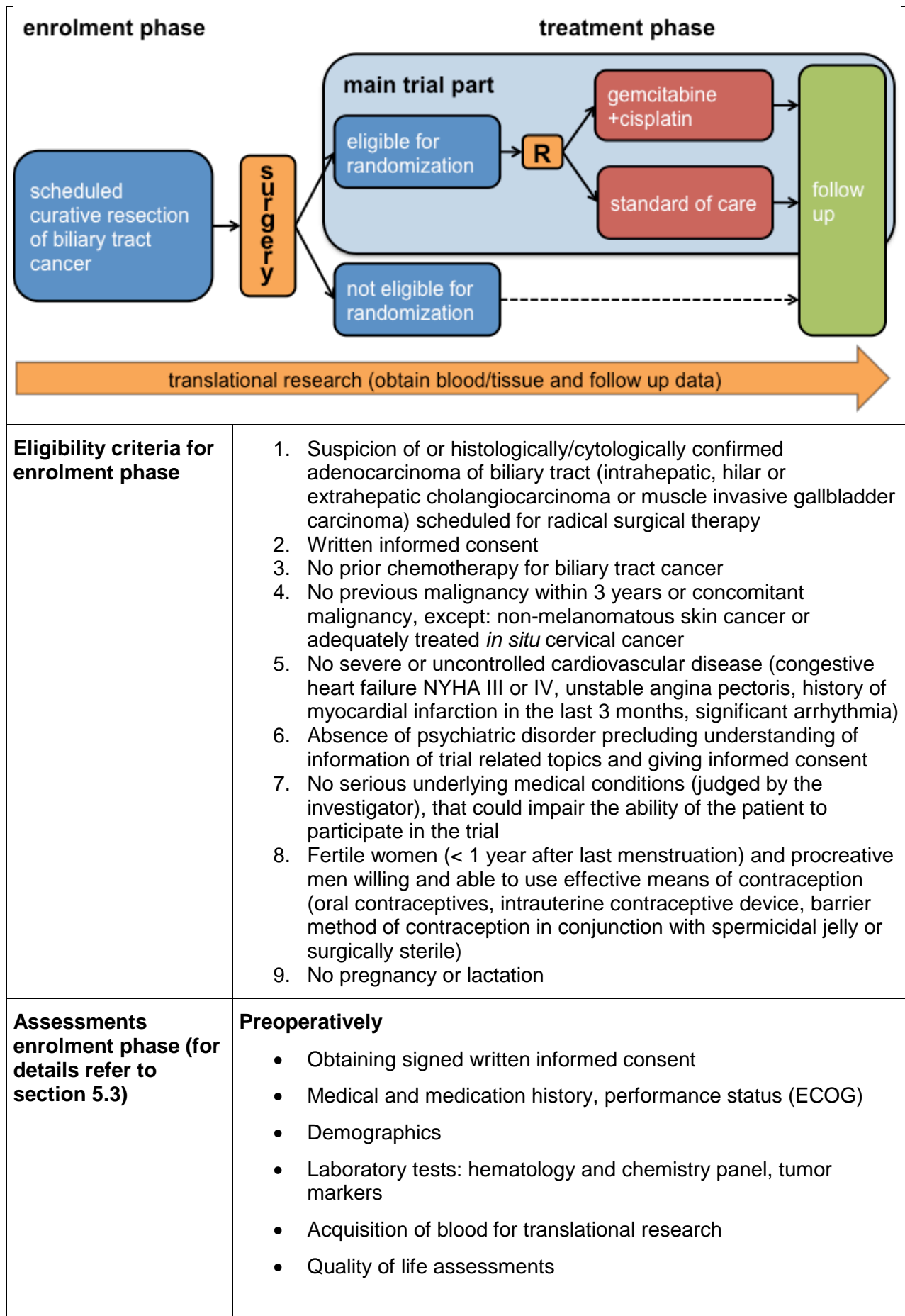


## Synopsis

<b>Title</b>	<p><b>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).</b></p> <p><b>A randomized, multidisciplinary, multinational AIO/DGAV/DGVS phase III trial.</b></p>
<b>Design</b>	Randomized, controlled, two stage, multicenter phase III trial
<b>Indication</b>	Patients after curative intent resection of cholangiocarcinoma (intrahepatic, hilar or distal) or muscle invasive gallbladder carcinoma (without evidence of metastatic disease).
<b>Sample size</b>	781 patients to be randomized, 187 in stage 1 and 594 in stage 2
<b>Study Duration</b>	<p>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).</p> <p>Expected total duration: 72 plus further 36 months follow up for overall survival (maximum of 5 years per individual patient)</p>
<b>Endpoints</b>	<p><u>Primary endpoints:</u></p> <ul style="list-style-type: none"> <li>• Disease free survival (DFS)</li> </ul> <p><u>Secondary endpoints:</u></p> <ul style="list-style-type: none"> <li>• Disease free survival rate at 24 months (DFSR@24)</li> <li>• Recurrence free survival</li> <li>• Overall survival (OS)</li> <li>• Safety and tolerability of adjuvant chemotherapy</li> <li>• Quality of life (QoL)</li> <li>• Function of biliodigestive anastomosis (in terms of surgical revision, requirement for PTCD)</li> <li>• Rate and severity of biliary tract infections</li> <li>• Patterns of disease recurrence</li> <li>• Locoregional control</li> </ul>



	<p><b>Intraoperatively</b></p> <ul style="list-style-type: none"> <li>• Acquisition of tissue for translational research</li> </ul> <p><b>Postoperatively</b></p> <ul style="list-style-type: none"> <li>• Acquisition of blood for translational research (during second postoperative week)</li> <li>• Evaluation of feasibility for treatment phase</li> </ul>
<p><b>Eligibility criteria for treatment phase (before randomization)</b></p>	<p>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.</p> <ol style="list-style-type: none"> <li>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)</li> <li>2. Macroscopically complete resection (R0/1) within 6 (-16) weeks before scheduled start of chemotherapy</li> <li>3. ECOG 0-1</li> <li>4. Age <math>\geq 18</math> years</li> <li>5. Adequate hematologic function: ANC <math>\geq 1.5 \times 10^9/L</math>, platelets <math>\geq 100 \times 10^9/L</math>, hemoglobin <math>\geq 9</math> g/dl or <math>\geq 5.59</math> mmol/L</li> <li>6. Adequate liver function as measured by serum transaminases (AST and ALT) <math>\leq 5 \times</math> ULN and bilirubin <math>\leq 3 \times</math> ULN</li> <li>7. Adequate renal function, i.e. serum creatinine <math>\leq 1.5 \times</math> ULN, glomerular filtration rate <math>\geq 50</math> ml/min</li> <li>8. No active uncontrolled infection, except chronic viral hepatitis under antiviral therapy</li> <li>9. No concurrent treatment with other experimental drugs or other anti-cancer therapy, treatment in a clinical trial within 30 days prior to randomization</li> <li>10. Negative serum pregnancy test within 7 days of starting study treatment in pre-menopausal women and women <math>&lt; 1</math> 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)</li> </ol> <p><b>Criteria for initial study enrolment</b></p> <ol style="list-style-type: none"> <li>11. Written informed consent</li> <li>12. No prior chemotherapy for biliary tract cancer</li> <li>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 <i>in situ</i> cervical cancer</li> <li>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)</li> <li>15. Absence of psychiatric disorder precluding understanding of information of trial related topics and giving informed consent</li> <li>16. No serious underlying medical conditions (judged by the investigator), that could impair the ability of the patient to</li> </ol>

	<p>participate in the trial</p> <p>17. Fertile women (&lt; 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)</p> <p>18. No pregnancy or lactation</p>
<p><b>Treatment, Dosage and Administration</b></p>	<p>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.</p> <p><b>Arm A: Gemcitabine/cisplatin and observation</b></p> <p>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).</p> <p><b>Arm B: Capecitabine and observation</b></p> <p>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).</p> <p><b>Observation</b></p> <p>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.</p> <p><b>Duration of treatment</b></p> <p>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.</p>
<p><b>Assessments treatment phase (for details refer to section 5.3)</b></p>	<p><b>Baseline (within 4 weeks before treatment start – informed consent may be obtained before)</b></p> <ul style="list-style-type: none"> <li>• Review of selection criteria, (obtaining signed written informed consent, if not previously enrolled)</li> <li>• Medical and medication history, physical examination, performance status (ECOG)</li> <li>• Demographics</li> <li>• Laboratory tests: hematology and chemistry panel, tumor markers</li> <li>• Acquisition of blood for translational research</li> <li>• Optional audiometry including audiogram recommended (loss of hearing according to RÖ 73, loss of hearing according to RÖ 80, Highfrequency-Audiogram loss of &gt;20db in 4 frequencies )</li> <li>• Disease and quality of life assessment</li> <li>• Hand out and reply of EORTC INFO25, SDM-Q-9 (PEF-FB-9)</li> </ul>

	<p>and SDM-Q-Doc (PEF-FB-Doc)</p> <p><b>During treatment (at start of treatment and every 3 weeks, previous to any new cycle) (may be performed up to 3 days before treatment)</b></p> <ul style="list-style-type: none"> <li>• Physical examination, performance status (ECOG), assessment of toxicity, concomitant medication, issue and collect capecitabine patient diary</li> <li>• Laboratory tests (additional blood count on day 8 only for arm A)</li> </ul> <p><b>Final staging (end of postoperative treatment)</b></p> <p>When any subject discontinues dosing of all study treatment, the following assessments should be made:</p> <ul style="list-style-type: none"> <li>• Physical examination, performance status (ECOG), assessment of toxicity, concomitant medication</li> <li>• Laboratory tests</li> <li>• CA 19-9, (CEA optional)</li> <li>• Disease and quality of life assessment</li> </ul> <p><b>Follow-up for disease recurrence</b></p> <p>All subjects will be evaluated for disease recurrence every 3 to 6 months (+/-28 days), irrespective of treatment arm:</p> <ul style="list-style-type: none"> <li>• Physical examination, performance status (ECOG), assessment of toxicity</li> <li>• Laboratory tests:</li> <li>• CA 19-9, (CEA optional)</li> <li>• Disease and quality of life assessment</li> <li>• Acquisition of blood for translational research (at recurrence)</li> </ul> <p><b>After disease recurrence every 3-6 months (+/-28 days) only for (optional: via telephone):</b></p> <ul style="list-style-type: none"> <li>• Survival and disease status including further therapy</li> </ul> <p><b>Tumor and disease assessment</b></p> <p>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.</p> <p>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.</p> <p>All radiological tumor assessments will be collected and retrospectively reviewed.</p> <p><b>Safety</b></p>
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	<p>Safety assessments will include physical examinations with vital signs (blood pressure, heart rate, respiratory rate), performance status (ECOG), clinical laboratory profile and adverse events.</p> <p>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.</p> <p>Treatment related serious adverse events rate (SAE), defined as SAEs considered possibly, probably or definitely related to treatment, will be determined.</p>
<p><b>Translational Research</b></p>	<p>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.</p> <p>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.</p> <p>At baseline and at disease recurrence 15 ml of blood will be collected and used for serum preparation and stored.</p> <p>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.</p> <p>For tissue and blood sampling working instructions refer to appendix G or the respective national lab manual.</p>
<p><b>Statistical Considerations</b></p>	<p>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.</p> <p><b>Overall statistical analysis (stage 1+2) - gemcitabine/cisplatin vs. standard of care (observation +/- capecitabine)</b></p> <p>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%</p>

(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:

#### Stratification criteria

	<ul style="list-style-type: none"><li>• intrahepatic vs. hilar/distal cholangiocarcinoma vs. gallbladder cancer</li><li>• lymph node positivity vs. negativity</li><li>• R0 vs. R1 resection</li></ul>
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## 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 <sup>15</sup>	Arm A only: day 8 every 3 wks <sup>16</sup>		every 3/6 <sup>11</sup> months, until recurrence	every 3/6 <sup>11</sup> months, after recurrence <sup>4</sup>
Informed consent	X			(X) <sup>10</sup>					
Medical history, demographics	X			X					
Physical examination <sup>1</sup>				X	X		X	X	(X)
Vital signs <sup>2</sup>				X	X		X	X	(X)
Performance status (ECOG)	X			X	X		X	X	(X)
Obtain tumor tissue		X <sup>5</sup>		X <sup>6</sup>					
Audiometry optional				X <sup>9</sup>					
Blood draw transl. research	X		X	X				X <sup>13</sup>	
Laboratory determinations <sup>3</sup>	X			X	X	X <sup>12</sup>	X	X	(X)
Treatment (chemotherapy)					X	X			
Capecitabine patient diary (Arm B only)					X <sup>17</sup>		X <sup>17</sup>		
Tumor markers (CA 19-9, CEA optional)	X			X			X	X	(X)
Tumor assessment <sup>11</sup>				X			X	X	(X)
Quality of life assessment <sup>8</sup>	X			X			X	X	
EORTC INFO 25, SDM-Q-9 and SDM-Q-Doc	X <sup>7</sup>			X <sup>7,10</sup>					
Concomitant medication				X	X	X	X	X <sup>14</sup>	
AE monitoring								X <sup>14</sup>	
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-9 and 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)