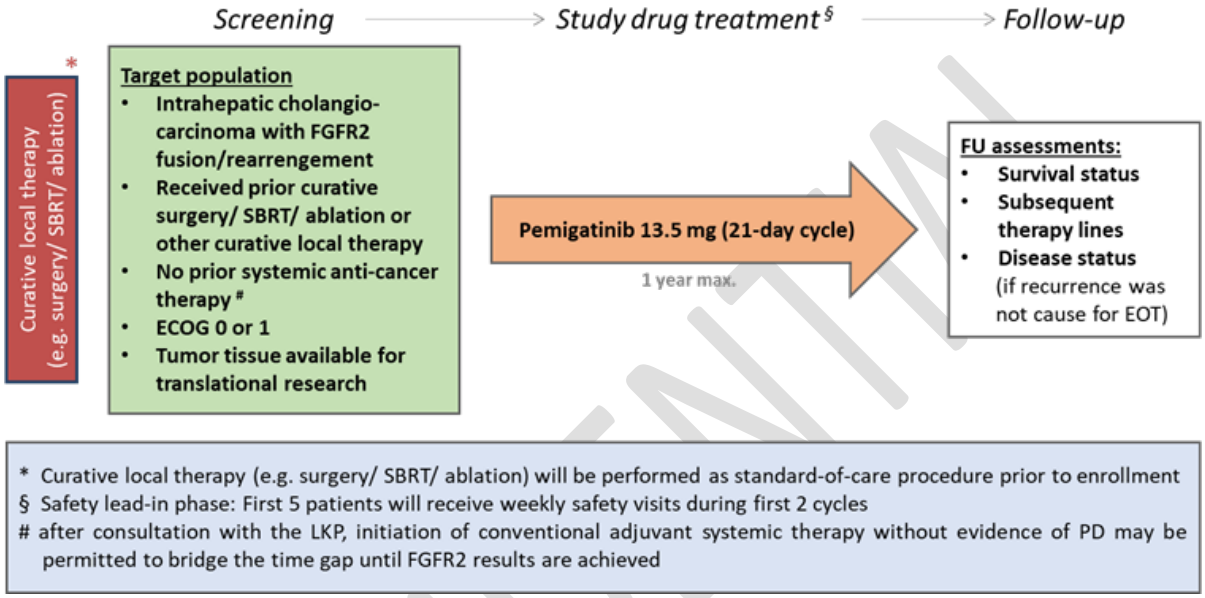
PEARLDIFER Protocol Synopsis

Study title	A Phase II study of **pe**miga**a**tinib after cu**r**ative local therapy in **l**ocally a**d**vanced **i**ntrahepatic cholangiocarcinoma (iCCA) harboring **F**GFR2 fusions/r**e**a**r**rangements - PEARLDIFER
Study type	Single arm, multicenter, open label, exploratory phase II study
Trial overview	
Objectives / endpoints	The aim of this phase II study is to determine whether pemigatinib is clinically efficacious after curative local therapy such as surgery/ SBRT or ablation in iCCA patients harboring FGFR2 fusion/rearrangement and to assess the safety profile to support the continuation of the concept in a large, randomized trial for further development. **Primary Objective** To assess the efficacy of pemigatinib administered after curative local therapy in treatment-naïve patients with resectable intrahepatic biliary tract cancer. **Corresponding endpoint** Recurrence free survival rate at 12 months (RFS@12)**Secondary Objectives** To assess the efficacy by overall survival (OS) and recurrence free survival (RFS); to assess safety of the treatment (AEs, impact on liver function, use of subsequent therapies); to assess quality of life (QoL). Corresponding Endpoints

	• Incidence, treatment relationship, seriousness, and severity of all AEs, SAEs according to CTCAE V5.0 • Overall survival (OS) • Recurrence free survival (RFS) • Effect of therapy on global health status/quality of life and on other symptoms and scales of the EORTC-QLQ-C30, EORTC-QLQ-BIL21 and EQ-5D-5L after 6 and 12 months (proportion of patients with a better, stable, or worse score)
Study design	This is a prospective, exploratory, single-arm, non-randomized, open-label phase II study to investigate whether pemigatinib is clinically efficacious after curative local therapy including surgery/ SBRT or ablation in iCCA patients with FGFR2 fusion/rearrangements and to assess the safety profile to support the continuation of the concept in a large, randomized trial for further development. In this initial trial phase, 20 patients will be enrolled to receive pemigatinib 13.5 mg oral once daily (21-day cycle; two weeks on, one week off) until disease recurrence, unacceptable toxicity, withdrawal of consent, or physician decision, but no longer than 12 months (max. 18 cycles). Tumor assessment (CT/MRI scans) will be performed before enrollment and then every 6 weeks during therapy and the first year and every 12 weeks during follow-up until recurrence, death or end of follow-up, whichever comes first.
Rationale	Biliary tract cancer (BTC), or cholangiocarcinoma (CCA), is a rare malignancy arising from epithelial cells of the biliary tree, which is associated with poor prognosis and limited SOCs options. [1,2] The incidence of biliary tract cancer is increasing, perhaps associated with an increasing incidence of gallstone disease. Although surgical resection is the primary treatment of choice for these tumors, many patients' tumors are inoperable when they are detected or relapse quickly after resection is attempted. [3-6] Potentially curative resection is feasible in only 20% of presenting patients, [7] and increasing centralisation of often complex surgery in specialist hepatopancreatobiliary centres aims to improve outcomes. [8,9] However, the postoperative median overall survival is reported to be 18-30 months, [10] while a recurrence rate of up to 70% has been observed after curative surgery. Due to progressive tumor disease the mortality rate after relapse is about 100%. [11-13] The high relapse rate in the minority of patients who undergo potentially curative surgery is reflected by an estimated five-year survival rate that varies with stage:

50% for American Joint Committee on Cancer (AJCC) stage I, 30% for stage II, 10% for stage III, and 0% for stage IV. [14-16]

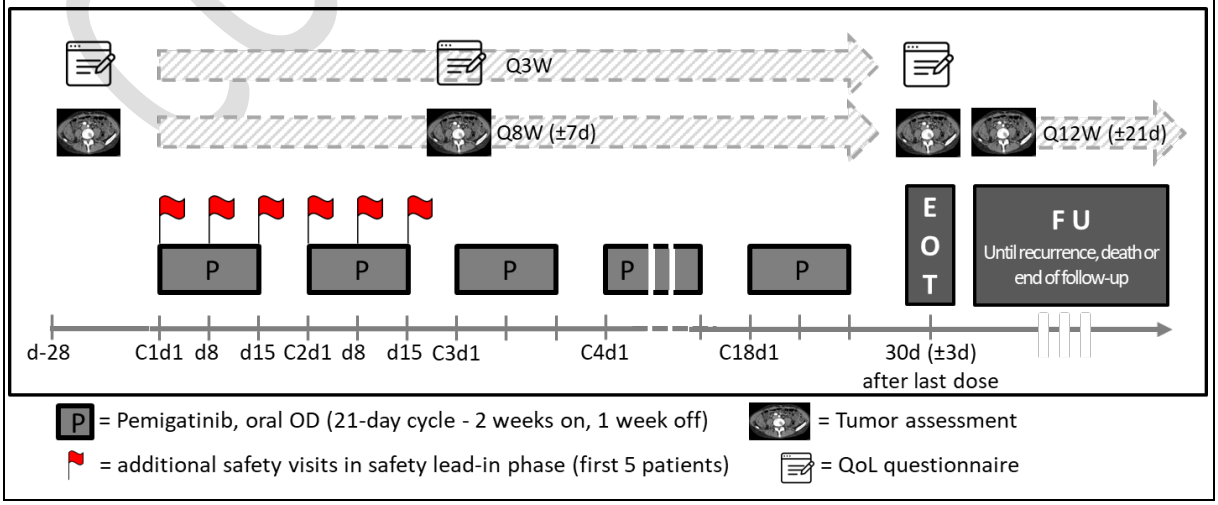
So far, data regarding adjuvant therapy in CCA after surgical resection are conflicting. Gemcitabine alone or in combination with oxaliplatin (GEMOX) showed no benefit compared to the observation group for patients with resected CCA in the French PRODIGE 12-ACCORD 18-UNICANCER GI-study and the Japanese BCAT, respectively. [17,18] Although, the BILCAP-study did not meet its primary endpoint of improving overall survival in the intention-to-treat population, the prespecified sensitivity and per-protocol analyses suggested that capecitabine can improve overall survival in patients with resected biliary tract cancer when used as adjuvant chemotherapy following surgery and authors concluded that capecitabine could be considered as standard of care. [19] However, due to the lack of sufficient alternatives, there is an unmet medical need for a more effective adjuvant regimen in CCA.

The standard of care for patients with unresectable CCA has been established as cisplatin and gemcitabine, suggesting that CCA are chemosensitive malignancies. [20,21] However, there is no established SOC after failure of first-line chemotherapy, and the efficacy of second-line chemotherapy regimens for advanced biliary cancer remains low. [11,22]

Therefore, the development of novel technical strategies to optimize outcome of CCA patients without the burden of surgical complications and recurrence rate after surgery and ineffective adjuvant therapy is urgently required.

Comprehensive genomic profiling (CGP) has identified several potentially actionable oncogenic alterations in patients with CCA including in genes encoding fibroblast growth factor receptor (FGFR). FGFR2 fusions and rearrangements are found almost exclusively in intrahepatic cholangiocarcinoma, occurring in 10–16% of patients. [23,24] Somatic alterations in FGFR can lead to aberrant FGFR signalling, which can drive tumorigenesis by enhancing cellular proliferation, migration, survival, and invasion, as well as angiogenesis. [25] Consequently, in addition to other targeted agents, FGFR inhibitors are gaining interest as potential therapeutics for cholangiocarcinoma. [2]

Several FGFR-targeted inhibitors such as derazantinib and pemigatinib are currently undergoing clinical trials. Several of these agents have revealed promising anticancer efficacy in phase I clinical trials. Most recently, data from the FIGHT-202 study, one of the largest studies so far in BTC, has been published. In this study, patients who had progressed after at least

	one prior systemic therapy and had FGFR2 fusions or rearrangements, pemigatinib elicited an objective response rate (ORR) of 35.5% and a disease control rate of 82%; median duration of response (DoR) was 7.5 months and median progression free survival (PFS) was 6.9 months. [26] This encouraging antitumor activity was observed irrespective of the number of prior treatments and granting of a conditional marketing authorization by the European Medicines Agency (EMA) has led to an approval of pemigatinib (Pemazyre) intended for the second-line treatment of advanced or metastatic cholangiocarcinoma with FGFR2 fusion or rearrangements in 2021. A main problem after curative local therapy in CCA is a systemic relapse. Thus, an approach combining local control with direct systemic control via a potent tailored systemic therapy seems promising. Administration of pemigatinib, currently the most potent drug in the subgroup of patients harboring FGFR2 fusions/rearrangements, after previous curative local therapy will be the optimal approach to prevent disease recurrence.
Treatment plan	Patients who previously received curative surgery/ SBRT or ablation or other local curative therapy will receive pemigatinib 13.5 mg oral once daily (21-day cycle; two weeks on, one week off) until disease recurrence, unacceptable toxicity, withdrawal of consent, or physician decision, but no longer than 12 months (max. 18 cycles). All patients will be followed up for 12 months after end of therapy or until death, withdrawal of consent, or loss to follow-up (whichever occurs first). Tumor assessment (CT/MRI scans) will be performed before enrollment and then every 8 weeks during therapy and the first year and every 12 weeks during follow-up until recurrence, death, or end of follow-up, whichever comes first.
Treatment Overview	d – day, C – cycle, Q3/8/12W – every 3/8/12 weeks, EOT – end of treatment, FU – follow up  P = Pemigatinib, oral OD (21-day cycle - 2 weeks on, 1 week off) = Tumor assessment = additional safety visits in safety lead-in phase (first 5 patients) = QoL questionnaire

Inclusion criteria	Patients who meet all of the following criteria are eligible for trial participation: 1. Signed informed consent form (ICF). 2. Patients*, age ≥ 18 years at the time of signing the informed consent form. 3. Histologically proven and curatively treatable localized intrahepatic biliary tract cancer (iCCA only), without signs of metastatic disease, and proven FGRF2-fusions/rearrangements, identified by routine FISH or by NGS testing. *NOTE: Only CE-IVD marked NGS-tests are applicable which cover FGFR2 fusions and rearrangements.* 4. Patients previously received local therapy for iCCA in form of curative surgery/ SBRT/ ablation or other local curative therapy up to 12 weeks prior to enrollment (*initiation of conventional adjuvant systemic therapy without signs of PD might be permitted for bridging the time gap to achieve FGFR2-results* - ***only after consultation with the LKP***). 5. Female patients who are considered as woman of childbearing potential (WOCBP) as well as male patients who are sexually active with WOCBP must use any contraceptive method with a failure rate of less than 1% per year during the treatment as well as up to 1 week after the last dose of pemigatinib. Female patients who are not of childbearing potential (i.e., who are postmenopausal or surgically sterile, see section 13.5) as well as azoospermic male patients do not require contraception. Female patients considered as WOCBP must have a negative pregnancy test within the last 7 days prior to the start of study therapy. 6. ECOG performance status 0-1. 7. Appropriate hematological, hepatic and renal function: a. Absolute number of neutrophils ≥ 1.5 x 10^9/L b. Platelets ≥ 100 x 10^9/L c. Hemoglobin ≥ 9 g/dL (5.58 mmol/L) d. Total bilirubin ≤ 1.5 times the upper limit of normal (ULN) e. AST (SGOT) and ALT (SGPT) ≤ 2.5 x ULN without existing liver metastases, or ≤ 5 x ULN in the presence of liver metastases; AP ≤ 5 x ULN. 8. Serum creatinine ≤ 1.5 x ULN or creatinine clearance (measured by 24h urine) ≥ 40 mL/min (i.e., if the serum creatinine level is > 1.5 x ULN, then a 24-h urine test must be performed to check the creatinine clearance to be determined).

	9. Adequate coagulability, as determined by the International Normalized Ratio (INR) ≤ 1.5 and partial thromboplastin time (PTT) ≤ 5 s above the ULN (unless anti-coagulation therapy has been given). Patients receiving warfarin / Phenoprocoumon must be switched to low molecular weight heparin before starting any study-specific procedures. 10. Patients must be able to take oral medications. 11. For patients with active hepatitis B virus (HBV): • HBV DNA ≤ 500 IU/mL obtained within 28 days prior to initiation of study treatment, AND • Anti-HBV treatment (per local standard of care e.g. entecavir) prior to study entry and willingness to continue treatment for the length of the study. 12. For patients with active hepatitis C virus (HCV): • Patients positive for HCV antibody are eligible, also if polymerase chain reaction testing is positive for HCV RNA • However, anti-viral therapy against HCV is only allowed prior to trial but not during the trial. 13. Patients infected with human immunodeficiency virus (HIV) are eligible if they meet all the following criteria: a) CD4 count is ≥350 cells/uL, viral load is undetectable, and not taking prohibited cytochrome (CYP)-interacting medications b) Probable long-term survival with HIV if cancer were not present c) Stable on a highly active antiretroviral therapy (HAART) regimen for ≥4 weeks and willing to adhere to their HAART regimen with minimal overlapping toxicity and drug-drug interactions with the experimental agents in this study d) HIV is not multi-drug resistant e) Taking medication and/or receiving antiretroviral therapy that does not interact or have overlapping toxicities with the study medication 14. Subject is willing and able to comply with the protocol (including contraceptive measures) for the duration of the study including undergoing treatment, and scheduled visits and examinations including follow up. *There are no data that indicate special gender distribution. Therefore, patients will be enrolled in the study gender-independently.
Exclusion criteria	Patients who meet at least one of the following criteria are not eligible for trial participation:

	1. Presence of tumors other than biliary tract cancer or a secondary tumor other than squamous or basal cell carcinomas of the skin or in situ carcinomas of the cervix which have been effectively treated. The Sponsor decides to include patients who have received curative treatment and have been disease-free for at least 3 years. 2. Metastatic biliary tract cancer (intrahepatic, hilar, or distal CCA as well as gallbladder carcinoma) disease. 3. Pretreatment with any systemic anti-cancer therapy. *NOTE: initiation of conventional adjuvant systemic therapy without signs of PD for bridging the time gap to achieve FGFR2-results might be permitted* - ***only after consultation with the LKP****.* 4. Simultaneous, ongoing systemic immunotherapy, chemotherapy, or hormone therapy not described in the study protocol. 5. Simultaneous treatment with a different anti-cancer therapy other than that provided in the study (excluding palliative radiotherapy only for symptom control). 6. Previous therapy with an FGFR- inhibitor. 7. Stage B cirrhosis according to Child-Pugh criteria (or worse) or cirrhosis (of any grade) with a history of hepatic encephalopathy or clinically significant ascites resulting from cirrhosis. Clinically significant ascites is defined as ascites resulting from cirrhosis requiring diuretics or paracentesis. 8. Known allergic / hypersensitive reactions to at least one of the treatment components. 9. Other serious illnesses or medical ailments within the last 12 months prior to the start of the study. 10. Current evidence of clinically significant corneal (including but not limited to bullous/band keratopathy, corneal abrasion, inflammation/ulceration, and keratoconjunctivitis) or retinal disorder (including but not limited to central serous retinopathy, macular/retinal degeneration, diabetic retinopathy, retinal detachment) as confirmed by ophthalmologic examination. 11. History of calcium and phosphate hemostasis disorder or systemic mineral imbalance with ectopic calcification of soft tissues (exception: commonly observed calcifications in soft tissues, such as the skin, kidney, tendons or vessels due to injury, disease, and aging, in the absence of systemic mineral imbalance). 12. History of hypovitaminosis D requiring supraphysiologic doses (eg, 50,000 UI/weekly) to replenish the deficiency. NOTE: Participants receiving vitamin D supplements are eligible.

	13. Use of any potent CYP3A4 inhibitors or inducers or moderate CYP3A4 inducers within 14 days or 5 half-lives (whichever is longer) before the first dose of study treatment. NOTE: Moderate CYP3A4 inhibitors are not prohibited (refer to section 24.3 Appendix 3 for a list of CYP3A4 inhibitors and inducers). 14. Presence of an active, uncontrollable infection. 15. Has active infection with SARS-CoV-2 (positive antigen test in routine testing at site). 16. Chronic inflammatory bowel disease. 17. Active disseminated intravascular coagulation. 18. Any other serious concomitant or medical condition that, in the opinion of the investigator, presents a high risk of complications to the patient or reduces the likelihood of clinical effect. 19. On-treatment participation in another interventional clinical study in the period 30 days prior to inclusion and during the study. 20. Patient pregnant or breast feeding, or planning to become pregnant 21. Patient in a closed institution according to an authority or court decision (AMG § 40, Abs. 1 No. 4). 22. Subjects that are depending on the Sponsor/CRO or investigational site as well as on the investigator.
Sample size	This is a signal detection trial with the scope to determine whether a treatment with pemigatinib in the adjuvant setting after curative surgery/ SBRT/ ablation or other local curative therapy in iCCA is clinically efficacious or if it potentially improves the toxicity profile with comparable efficacy to support the continuation of this concept in a large, randomized trial for further development. In the initial pilot trial phase, only n=20 patients will be enrolled. In this trial, the primary endpoint will be the recurrence free survival rate at 12 months (RFS@12). We assume that this rate will be at 75%, which is clinically relevant and would lead to further consideration of the concept in registrational trials. Because of the exploratory nature of the trial, no formal sample size calculation is performed. If the target rate of recurrence free survival at 12 months of 75% is achieved, the enrollment of 20 subjects would lead to a 95% exact confidence interval of 51% - 91%, which is considered enough to generate a signal and pursue the concept in a larger trial.
Duration of the study (planned)	The estimated trial duration at the trial sites is 36 months (12 months recruitment, 12 months maximum therapy duration, and 12 months follow-up after last patient last treatment).

	The end of this trial is defined as the date of database closure to ensure the collection of survival data of patients and the active involvement of sites in the data cleaning process (e.g., additional source data may be requested, or an additional monitoring visit may be necessary. In addition, the Sponsor may decide to terminate the study at any time (refer to protocol section 12.2.3 for criteria for early trial termination). The trial will be conducted at approximately 20 centers located in Germany.