locally advanced intrahepatic cholangiocarcinoma (iCCA) / 1st line

PEARLDIFER:
A Phase II study of pemigatinib in combination with SBRT (Stereotactic Body Radiation Therapy) as definitive organ preserving therapy in locally advanced intrahepatic cholangiocarcinoma (iCCA) harboring FGFR2 fusions/rearrangements

AIO-assoziierte-Studie

Studiennummer/-Code:	**AIO-HEP-0122/ass / PEARLDIFER**
Status:	in Vorbereitung
Rekrutierungszeit:	von: Q3/2022 bis: Q3/2023
Anzahl Zentren:	geplant: 40 aktuell initiiert: 0 aktiv rekrutierend: 0
Weitere Zentren:	sind sehr erwünscht
Anzahl Patienten:	geplant: 20 aktuell eingeschlossen: 0
Letzte Aktualisierung	18.02.2022

STUDY TYPE	Single arm, multicenter, open label, phase II study
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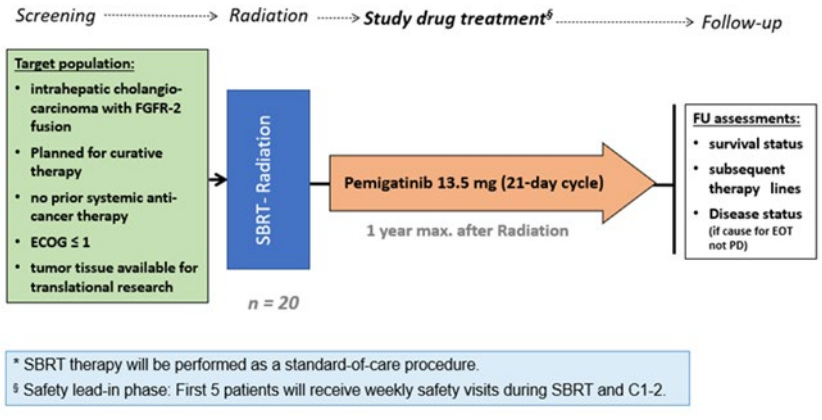
CONDITION	locally advanced intrahepatic cholangiocarcinoma (iCCA)
DESIGN	

INDICATION	locally advanced intrahepatic cholangiocarcinoma (iCCA)
OBJECTIVE(S)	The aim of this phase II study is to determine whether a combination of pemigatinib with SRBT in iCCA patients harboring FGFR2 fusion/rearrangement is clinically efficacious or whether the combination potentially improves toxicity profile with comparable efficacy 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 standard-of-care SBRT in treatment-naïve patients with resectable intrahepatic biliary tract cancer **Secondary Objectives** To assess the efficacy by recurrence free survival (RFS) and overall survival (OS); to assess safety of the combination treatments (AEs, impact on liver function, use of subsequent therapies); to assess quality of life (QoL).
INTERVENTION(S)	Patients will receive SBRT treatment via IMRT or VMAT. They will be treated with three to twelve fractions, depending on the proximity to organs at risk (OARs), mostly the stomach and the intestine. Three fraction regimens (typically 3×16 Gy) are preferred in patients with lesions at distance from critical structures, twelve fraction regimens (typically 12×4-5.5 Gy) are preferred in patients with direct contact to OARs, and five fraction regimens (typically 5×7-10 Gy) in all other cases, so that the dose constraints can be respected. Within 14 days after the last SBRT treatment, patients will receive pemigatinib 13.5 mg oral once daily (21-day cycle; two weeks on, one week off) until disease progression, 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 6 weeks during therapy and the first year and every 8 weeks during follow-up until progression/relapse, death, or end of follow-up, whichever comes first.
OBJECTIVES of OPTIONAL TRANSLATIONAL RESEARCH	To collect tumor biopsies that enable to perform correlation analysis between selected molecular parameters and clinical data to identify molecular biomorakers predictive for RFS and OS at a later timepoint <u>Markers will be evaluated for their predictive and prognostic value:</u> o Tumour blocks or slides of all patients confirming diagnosis of iCCA will be collected o Tumour blocks may be used to analyse immune cell infiltration before therapy o Sites will be asked to consider a re-biopsy at the timepoint of tumor relapse. If so, sites are asked to priovde tumor blocks for molecular analysis. However, it is the responsibility of the trial site to evaluate if such biopsy has to be obtained for individual patients as a part of clinical standards Details on the accompanying translational research will be provided in a separate translational research manual.
BACKROUND/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 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 chemotherapy (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 garnering 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 FGR2 fusion or rearrangements in 2021. A main problem in CCA after curative resection is a systemic relapse. Thus, an approach combining local control with direct systemic control via a potent tailored systemic therapy seems promising. Stereotactic Body Radiation

	Therapy (SBRT) is a promising treatment showing high local control rates in CCA. 27,28 Thus, the combination of SBRT and pemigatinib, currently the most potent drug in the subgroup of patients harboring FGFR2 fusions/rearrangements, will be the optimal approach to be evaluated for an organ preservation concept with only surgery on demand. Such combination of two strong therapies has the potential to cure patients without the need of a detrimental surgical procedure with a significant mortality, severe morbidity, and a substantial impact on the quality of life (QoL). We propose a "surgery as needed" (Salvage Surgery) approach after completion of SBRT and the start of pemigatinib therapy accompanied by an imagining guided control every 6 weeks for the 1st year followed by a bimonthly imaging approach. Surgical resection would be offered only to those patients in whom a locoregional persistence is highly suspected or proven by radiological imaging and in the absence of any signs of distant dissemination. Such an organ-preserving strategy would clearly have great advantages. Our hypothesis is that our concept is superior to the traditional surgery, because of three points: a) no surgical mortality and morbidity. At least one complication occurred in 22.6% of patients within 30 days after liver resection and a mortality rate after major hepatic procedures in high volume liver centers of at least 10.4% has been reported. 29 Thus, a nonsurgical treatment strategy in patients with a clinically complete response after SBRT theoretically saves 10% mortality and 20% severe morbidity in this patient group and leads to b) better systemic effect, and c) better QoL. Therefore, these results provide a rationale to reconsider and study the necessity of standard liver resection in the subgroup of patients harboring FGFR2 fusions/rearrangements after SBRT and subsequent application of pemigatinib.
KEY EXCLUSION CRITERIA	1. Pretreatment with any systemic anti-cancer therapy. 2. Patients who meet at least one of the following criteria are not eligible for trial participation: 3. 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. 4. Metastatic biliary tract cancer (intrahepatic, hilar, or distal CCA as well as gallbladder carcinoma) disease. 5. Simultaneous, ongoing systemic immunotherapy, chemotherapy, or hormone therapy not described in the study protocol. 6. Simultaneous treatment with a different anti-cancer therapy other than that provided in the study (excluding palliative radiotherapy only for symptom control). 7. Previous therapy with an FGFR- inhibitor. 8. 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. 9. Known allergic / hypersensitive reactions to at least one of the treatment components. 10. Other serious illnesses or medical ailments within the last 12 months prior to the start of the study.

	11. 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. 12. 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). 13. History of hypovitaminosis D requiring supraphysiologic doses (eg, 50,000 UI/weekly) to replenish the deficiency. NOTE: Participants receiving vitamin D supplements are eligible . 14. 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). 15. Presence of an active, uncontrollable infection. 16. Has active infection with SARS-CoV-2 (positive antigen test in routine testing at site). 17. Chronic inflammatory bowel disease. 18. Active disseminated intravascular coagulation. 19. 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. 20. On-treatment participation in another interventional clinical study in the period 30 days prior to inclusion and during the study. 21. Patient pregnant or breast feeding, or planning to become pregnant 22. Patient in a closed institution according to an authority or court decision (AMG § 40, Abs. 1 No. 4). 23. Subjects that are depending on the Sponsor/CRO or investigational site as well as on the investigator.
KEY INCLUSION CRITERIA	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) with a maximum of 5 cm in diameter, without signs of metastatic disease, and proven FGRF2- fusions/ rearrangements, identified by routine FISH or by NGS testing. 4. Patients of reproductive age must be prepared to use a suitable contraceptive method during the study and up to 1 week after the end of treatment. A suitable method of contraception is defined as surgical sterilization (eg, bilateral fallopian tube ligation, vasectomy), hormonal contraception (implantable, patch, oral), and double barrier methods (each two-fold combination of intrauterine pessary, condom for men, or women with spermicidal gel, Diaphragm, contraceptive sponge, cervical cap). Women of child-bearing potential must have a negative pregnancy test within the last 7 days prior to the start of study therapy. 5. ECOG performance status 0-1. 6. Appropriate hematological, hepatic and renal function: a. Absolute number of neutrophils ≥ 1.5 x 109/L b. Platelets ≥ 100 x 109/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.

	7. 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). 8. 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. 9. Patients must be able to take oral medications. 10. 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. 11. 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. 12. 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 13. 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.
OUTCOME(S)	**<u>Primary Endpoint</u>** • Objective Response Rate (ORR [assessed every 6 weeks (±7 days) during the first year and every 8 weeks (±7 days) thereafter]): Objective response rate (ORR) according to investigator-based RECIST 1.1 assessment, defined as the proportion of allocated subjects with best response of complete or partial response within 12 months after the date of first administration of study treatment. Patients who receive anti-cancer treatment other than the study medication for any reason before reaching a complete or partial response will be identified as nonresponders in the assessment of ORR **<u>Secondary Endpoints</u>** • Incidence, treatment relationship, seriousness, and severity of all AEs, SAEs according to CTCAE V5.0 • Percentage of patients. with complete response after completion of SBRT + pemigatinib treatment • Percentage of patients with Salvage Surgery • Duration of response (DoR) • Recurrence free survival (RFS) • Overall survival (OS)

STATISTICAL ANALYSIS	This is a signal detection trial with the scope to determine whether a combination of pemigatinib with SBRT in iCCA is clinically efficacious or if the combination potentially improves toxicity profile with comparable efficacy to support the continuation the concept in a large, randomized trial for further development. The possible large, randomized trial is going to compare in a 1:1 fashion current SOC surgery only with SBRT followed by pemigatinib.
SAMPLE SIZE	In the initial pilot trial phase, only n=20 patients will be enrolled.
TRIAL DURATION	The estimated study 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).f The end of this study is defined as the date when the last patient, last visit (LPLV) occurs, i.e., when all enrolled patients have either been followed-up for the maximum duration of 12 months after treatment or have died, withdrawn consent, are lost to follow up, or if Sponsor decides to terminate the trial, whichever occurs first. 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).
PARTICIPATING CENTERS	Up to 40 site in Germany
FURTHER CENTERS DESIRED?	Yes (Participating centers will be recruited from the national HCC trials group of the AIO.)
NUMBER of PATIENTS	N = 20
CURRENT NUMBER of PATIENTS	Recruitment not yet started.