- CONFIDENTIAL -

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Synopsis pro-duct002-trial

Sponsor	Charité - Universitätsmedizin Berlin Chariteplatz 1, 10117 Berlin, Germany Chirurgische Klinik Campus Charité Mitte | Campus Virchow-Klinikum
Principal Investigator	Prof. Dr. med. Johann Pratschke (LKP) Charité - Universitätsmedizin Berlin Chirurgische Klinik Campus Charité Mitte | Campus Virchow-Klinikum Augustenburger Platz 1, 13353 Berlin, Germany Phone: +49 30 450-552001, Fax: +49 30 450-552900 e-mail: johann.pratschke@charite.de
Coordinating Investigator	Prof. Dr. med. Wenzel Schöning Charité - Universitätsmedizin Berlin Chirurgische Klinik Campus Charité Mitte | Campus Virchow-Klinikum Augustenburger Platz 1, 13353 Berlin, Germany Phone: +49 30 450-552001, Fax: +49 30 450-552900 e-mail: wenzel.schoening@charite.de
Project Management	Charité - Universitätsmedizin Berlin Chirurgische Klinik Campus Charité Mitte | Campus Virchow-Klinikum Studienbüro Augustenburger Platz 1, 13353 Berlin, Germany Phone: +49 30 450-552072, Fax: +49 30 450-552962 e-mail: andrea.koepke@charite.de
Data management	Michael Hippler-Benscheidt Charité - Universitätsmedizin Berlin Chirurgische Klinik Campus Charité Mitte | Campus Virchow-Klinikum Augustenburger Platz 1, 13353 Berlin, Germany Phone: +49 30 450- 552378 , Fax: +49 30 450-552900 e-mail: michael.hippler-benscheidt@charite.de
Biometry	Stefanie Ernst Berlin Institute of Health (BIH)/Clinical Research Unit (CRU) Campus Charité Mitte Charitéplatz 1, 10117 Berlin, Germany Phone: +49 30 450 643 546, FAX:+49 30 450 7 643 546 e-mail: stefanie.ernst@charite.de
Monitoring	Charité - Universitätsmedizin Berlin Chirurgische Klinik Campus Charité Mitte | Campus Virchow-Klinikum Studienbüro Augustenburger Platz 1, 13353 Berlin, Germany Phone: +49 30 450-552072, Fax: +49 30 450-552962 e-mail: andrea.koepke@charite.de
Funding	Internal funding
Data Monitoring Committee	PD Dr. med. Uwe Pelzer Charité - Universitätsmedizin Berlin Medizinische Klinik mit Schwerpunkt Hämatologie, Onkologie und Tumorimmunologie Campus Virchow-Klinikum

	Augustenburger Platz 1, 13353 Berlin, Germany Phone: +49 30 450-553727, Fax: ++49 30 450-553959 e-mail: marianne.sinn@charite.de PD Dr. med. Tobias Müller Charité - Universitätsmedizin Berlin Medizinische Klinik mit Schwerpunkt Hepatologie und Gastroenterologie Campus Virchow-Klinikum Augustenburger Platz 1, 13353 Berlin, Germany Phone: +49 30 450-553770, Fax: ++49 30 450-553930 e-mail: tobias.mueller@charite.de
Concomitant Scientific Projects	Not applicable

Synopsis

Title of the trial	*Microscopic Tumor Clearance after Liver Transplantation for **Pro**ximal Bile **Duct** Cancer **(pro-duct002**).*
Acronym	pro-duct002
Indication	Perihilar cholangiocarcinoma (Bismuth-Corlette type III/IV)
Primary goal of the trial/ primary endpoint	**Primary endpoint:** • Rate of microscopic tumor clearance (R0) after liver transplantation This study is designed as pilot study to achieve data on liver transplantation for perihilar cholangiocarcinoma using strict patient selection criteria. It is hypothesized that liver transplantation for perihilar cholangiocarcinoma is associated with a high rate of microscopic tumor clearance and good long-term survival.
Secondary goals of the trial/ secondary endpoints	**Secondary endpoints:** • Overall survival (OS) at 36 months • Recurrence free survival (RFS) at 36 months • Postoperative complication rate (grade III-V) • Percentage of patients after liver transplantation, in which chemotherapy could not be initiated as scheduled (on an individual basis) or had to be terminated ahead of schedule
Trial design	Prospective, multi-center, non-randomized, non-blinded single-arm trial Data from patients with Bismuth-Corlette type III/IV perihilar cholangiocarcinoma considered surgically resectable with a curative intent will be collected by a tumor registry.
Trial population	Patients with Bismuth-Corlette type III/IV perihilarcholangicarcinoma (with or without PSC) considered surgically unresectable or only with a high probability of R1-resection or postoperative liver failure **Key inclusion criteria:** • Protocol defined diagnosis of perihilarcholangiocarcinoma in patients with primary sclerosing cholangitis (PSC): i.e. histological diagnosis of cholangiocarcinoma (obtained via ERC) or dominant

	stenosis plus cytological diagnosis of severe dysplasia or two subsequent cytological results of severe dysplasia or carcinoma whereby the second has been obtained after 2 weeks of antibiotic treatment to exclude inflammatory changes • Protocol defined diagnosis of perihilar cholangiocarcinoma in patients without PSC: clinical diagnosis of proximal bile duct cancer based on ERC plus a second method (CT or MRI), cytology is obtained during ERC, but a cytological result of carcinoma or severe dysplasia is not mandatory • tumor not curatively resectable as judged by an experienced hepatobiliary surgeon (> 50 liver resections for perihilar cholangiocarcinoma) • on-line review of defined patient data and acceptance for priority listing by an Eurotransplant expert panel consisting of two experts recruited from the Eurotransplant Liver Allocation Committee; in case of split decision addition of a third expert for definite decision on priority listing with a respective matchMELD. • obligatory staging laparotomy before priority listing (see SOP staging laparotomy, chapter 7.5.1.4) • age between 18 and 70 years • negative pregnancy test • informed consent before study enrolment (all other procedures are clinical routine procedures in the management of these patients) **Key exclusion criteria:** • locally very advanced, unresectable tumor infiltrating adjacent other organs, the main trunk of the hepatic artery • a visible tumor mass on CT or MRI scan larger than 3 cm in diameter • highly elevated CA 19-9 levels (> 1000 U/ml) • Decompression of the bile ducts by external drainage (PTCD) • tumors suspicious for gallbladder cancer • known lymph node or distant metastasis (determined mandatory by CT scan/MRI and laparotomy, further investigations if deemed necessary, a PET scan is recommended) • patients undergoing multi-organ transplantation or have undergone previous solid organ or bone marrow transplantation • previous photodynamic therapy, radiation, brachytherapy or combinations of these procedures • previous tumor biopsy (except via ERC) systematic lymphadenectomy (except SOP defined staging laparotomy), surgical preparation at the region of the hepatoduodenal ligament (except cholecystectomy for other reasons) or previous completed or attempted surgery for hilar cholangiocarcinoma • pregnancy or breastfeeding

	• patients unwilling to consent to saving and propagation of pseudonymized medical data for study reasons • general contraindications for liver transplantation • subjects who are legally detained in an official institute
Sample size	Given an expected rate of microscopic tumor clearance (R0) of approximately 95% after liver transplantation in contrast to ~80% after liver resection, a sample size of at least 50 patients is required to achieve a significance level of 5% and a power of ≥90%. Sample size calculation was carried out with nQuery Advisor 7.0 using one group Chi2 test. To be assessed for eligibility: n = 150 To be listed for transplantation: n = 60 **To undergo liver transplantation: n = 55** **To be analyzed (confirmed histology): n = 50**
Therapy	**Experimental intervention:** Liver transplantation (either deceased or living donor) for perihilar cholangiocarcinoma (Bismuth-Corlette type III/IV) **Follow up per patient:** 3 years After liver transplantation, 4-weekly visits will be conducted until month 3. All patients will undergo visits every 3 months until 2 years after transplantation. This includes laboratory test including CA 19-9 levels and a CT scan of the abdomen and thorax. For study purposes afterwards only the date of recurrence (and if available primary site of recurrence) and the date and reason of death are recorded until 3 years after liver transplantation. The required data are at least checked by telephone visits on a yearly basis. Of the patients, who underwent screening investigations but are otherwise not candidates for liver transplantation 1, 2 and 3 year survival rates and reason of death will be recorded in a Registry.
Biometry	**Efficacy:** To understand the clinical effectiveness regarding response rate defined as rate of microscopic tumor clearance (R0) after liver transplantation. **Description of the primary efficacy analysis and population:** Primary response rate will be assessed and 95% confidence interval will be given. If appropriate response rate will be analyzed separate for known prognostic factors. **Safety:** Descriptive analysis of (serious) adverse reactions/events and lab values. Annual safety reports. **Secondary endpoints:**

	Analyzed in a descriptive manner by appropriate methods depending on the scale of the endpoint.
Trial Duration	**First patient in to last patient out (years):** 8 years (01/2018 to 12/2025) **Duration of the entire trial (years) including preparation and analysis:** 10 years (7/2017 to 6/2027) **Recruitment period (years)** 5 years

Hypothesis	Liver transplantation for perihilar cholangiocarcinoma is associated with a high rate of microscopic tumor clearance and good long-term survival
Rationale	This study is designed as pilot study to create data on liver transplantation for proximal bile duct cancer using strict patient selection. (Neo)-adjuvant chemotherapy can be initiated on an individual basis. It is intended to offer patients, who are not or not likely curatively resectable, the possibility to undergo liver transplantation within a controlled trial in view of the otherwise unfavorable prognosis (median survival without surgery 8 - 12 months (Valle, J et al., 2010). Strict selection of patients undergoing liver transplantation for perihilar cholangiocarcinoma is associated with a 5-year survival rate of 60%, based on the available data (Mantel, HT et al., 2016). Additionally, the trial will produce preliminary data on recurrence rates after liver transplantation. Therefore, the study serves as pilot investigation to evaluate, if the obtained survival rates justify a subsequent larger controlled trial using the same treatment algorithm.
Strategy	**Screening investigations/ listing for transplantation:** All patients will undergo ERC with brush cytology using standard operative procedures (SOP; see chapter 7.5.1. ff.) or tumor biopsy (via ERC only). If all protocol criteria for the diagnosis of proximal bile duct cancer (see below) are given and metastatic disease could be excluded by staging investigations (see below), all patients undergo staging laparotomy with lymph node retrieval (using defined SOP, see chapter 7.5.1. ff.) before listing for liver transplantation. This is also to exclude peritoneal tumor spread or other intraabdominal metastatic manifestations. **Liver transplantation:** Liver transplantation either deceased donation or living donation is intended within 3 months after listing. All patients will undergo liver transplantation with extrahepatic bile duct resection and regional lymphadenectomy using standard operative procedures (SOP). In case of deceased donor liver transplantation, the recipient operation is started immediately (as soon as the recipient is arrived in the hospital and prepared for laparotomy) to exclude extra hepatic tumor growth in the abdominal cavity If extrahepatic manifestations are detected, Eurotransplant is informed immediately and the donor liver is allocated otherwise A maximum number of 10 patients transplanted are allowed for each center, thereafter no further priority listing will be permitted.

Staging laparotomy	• the laparotomy has to be performed by an experienced hepatobiliary surgeon • meticulous inspection of the whole peritoneal cavity (all quadrants) • examination of the hepatoduodenal ligament, the foramen of Winslow, the liver hilum and the course of the common hepatic artery and the coeliac trunk for lymphadenopathy • inspection of the gallbladder (evidence of gallbladder cancer ?) • suspicious findings are removed or biopsied and sent for histological investigation • if additional procedures are required those should be performed according to individual findings • At least one lymph node at the right and left side of the hepatoduodenal ligament is removed and investigated histologically (see figure, written report of ≥ 2 negative and no positive lymph nodes has to be available and presented to the review panel at listing for liver transplantation).
Liver transplantation	• Inspection of the abdominal cavity • If the lymph nodes are suspicious for tumor growth a frozen section investigation is obtained (if organizationally possible) • Systematic lymphadenectomy is performed at the common hepatic artery and at both sides of the bile duct • If feasible, the lymphadenectomy is continued until the coeliac nodes • If this “extended” lymphadenectomy is considered as too dangerous, a biopsy of the coeliac nodes is sufficient, to see if these nodes (N2) are positive • Lymphadenectomy is performed only at the distal part of the hepatoduodenal ligament • No surgical preparation close to the tumor region • The proper hepatic artery and the portal vein can be prepared/dissected close (approximately 10-15 mm) to their origin • The bile duct is dissected immediately above the pancreatic head. • If considered necessary and organizationally possible a frozen section of the distal bile duct margin is obtained • Reconstruction of the biliary continuity is achieved by bilioenteric anastomosis using preferentially hepaticojejunostomy with Roux-Y reconstruction
Postoperative course	**Chemotherapy:** • Patients with histologically proven perihilar cholangiocarcinoma will be scheduled for (neo-)adjuvant chemotherapy on an individual basis **Primary immunosuppression:** • There are **no general restrictions** with regard to individual combinations of immunosuppressive drugs • Induction therapy with anti-lymphocyte or other antibodies is permitted • Combinations of a calcineurin inhibitor (tacrolimus or cyclosporin A) with mTOR (mechanistic Target of Rapamycin) inhibitors/ MMF (Mycophenolate-Mofetil) are strongly recommended • In case of graft rejection antibody therapy is permitted

	• Azathioprine should only be used if deemed necessary • The lowest possible level of immunosuppression should be used **Maintanance of immunosuppression:** • maintenance immunosuppression should be reduced to the lowest possible level (during individual adjuvant chemotherapy) to prevent severe side effects • steroids should be tapered as early as possible - patients should receive steroid free immunosuppresion 3 to 4 months after transplantation or earlier (if possible, if not e.g. in PSC patients, reduction as far as possible)
Discontinuation criteria	**Criteria for premature termination of the whole clinical study:** • 1 year recurrence free survival less than 30 % in the whole liver transplant population after the first 25 patients • new scientific evidence provided during the study that could affect the patient's safety (benefit-risk analysis no longer positive) • unjustifiable risk and toxicity in risk-benefit analysis (decision taken by principal Investigator) **Criteria for premature termination in individual patients:** • personal wish of the patient, withdrawal of consent • occurrence of severe infections (according to the investigators decision) • pregnancy or inadequate contraception in a woman of childbearing potential • any other circumstance that makes the investigator believe that in the patient's own interest he/she should no longer participate in the trial. • significant violation of the study protocol • subsequent occurrence of exclusion criteria (after enrolment) • if a patient is likely to benefit more from an alternative treatment according to the investigator's discretion

1 Study Flow-Chart