AIO-PAK-0219xx: Intensified treatment in patients with local operable but oligometastatic pancreatic cancer - multimodal surgical treatment versus systemic chemotherapy alone: a randomized controlled phase 3 trial [METAPANC]

AIO-Studie		
Studiennummer/-Code:	AIO-PAK-0219xx - ACO/AIO-19 - METAPANC	
Status:	Förderung durch DFG, vor Einreichung	
Rekrutierungszeitraum:	geplanter Beginn: I Q 2022 – geplantes Ende IV Q 2027	
Anzahl Patienten:	geplant: 400	aktuell randomisiert: noch nicht gestartet
Anzahl Zentren:	geplant: 25	aktuell initiiert: noch nicht gestartet
Weitere Zentren:	In Evaluation	
Letzte Aktualisierung	Nov. 2021	

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Medical condition	Patients with locally resectable but oligometastatic pancreatic cancer
Trial-Office	Johanna Kreutzer, M.A. (Study Coordinator); University Medical Center Göttingen, Trial Office of Dept. of General and Visceral Surgery; Robert-Koch-Str. 40, 37075 Göttingen, Germany; Tel. +49 551 67825, Fax +49 551 67861, email: studiensek-chirurgie@med.uni-goettingen.de
Hypothesis	Overall survival in patients with oligometastases in pancreatic cancer and intensified chemotherapy is superior after complete surgical resection compared to chemotherapy alone.
Participants / study population	Key inclusion criteria: Age ≥ 18 years and ≤ 75 years; histologically confirmed metastatic adenocarcinoma of the pancreas; medical and technical operability of the primary tumor defined tumor board assessment; limited metastatic status (≤ 3 resectable liver metastases); adequate hematological (WBC ≥3000/µL, absolute neutrophil count ≥1500 /µL, platelets ≥100.000/µL, hemoglobin ≥8 g/dL), hepatic (bilirubin ≤2.5 x mg/dl) and renal function (creatinine clearance >50ml/min) parameters; ECOG performance status ≤ 1; signed study-specific consent form prior to therapy; measurable disease according to RECIST v1.1. Key exclusion criteria:

	Unresectable pancreatic cancer; prior chemotherapy within 6 months or prior radiation therapy within 28 days; significant comorbidity (e.g. cardiovascular, pulmonary); peritoneal carcinomatosis or > three liver metastases or ~~non-~~ extrahepatic metastasis; inability to understand the study and/or comply with the protocol procedures.
Trial type	Interventional trial: [X]
Treatments / procedures	Experimental intervention: Chemotherapy (modified FOLFIRINOX at least 8 cycles) followed by surgery followed by additive 5-FU-based chemotherapy for 3 months Control intervention: Chemotherapy (modified FOLFIRINOX at least 8 cycles) followed by 5-FU based maintenance therapy (FOLFIRI or capecitabine) for three months or until progression Follow-up per patient: minimum of 2 years from randomization. Duration of intervention per patient: approx. 8 months
Endpoint(s)	Primary endpoint: Overall Survival (OS, time from randomization to death from any cause) Secondary endpoint(s): Progression-free survival (time of randomization to cancer progression or death) according RECIST and clinical data; Quality of life (EORTC QLQ-C30, PAN-26, Q-TWIST); Exploratory/Translational: Tissue samples: Genetic profiling, molecular subtyping Liquid biopsy samples: Analysis of cell-free DNA/RNA/proteins Radiomics: machine-learning model to preoperative CT images for non-invasive subtype prediction and therapy response. Assessment of safety: Standard reporting for adverse events (AEs) and serious adverse events (SAEs). AEs and SAEs will be summarized by frequencies and percentage for each treatment group. AEs will be coded according to MedDRA, analyzed, and presented following ICH E3 Structure and Content of Clinical Study Reports. Events of special interest (e.g. toxicities, post-operative complications) will be summarized in the same manner.
Trial duration	First patient in to last patient out (months): maximum of 92 Duration of the entire trial (months): maximum of 98 Recruitment period (months): maximum of 60
Statistical analysis	Statistical methods used to compare groups for primary and secondary outcomes: The primary outcome survival will be analyzed by a Cox proportional hazards regression. The treatment effect will be reported as hazard ratio with 95% confidence intervals and p-value testing the null hypothesis of no effect. Patients withdrawing from study medication will be followed up for endpoints. Withdrawal from the study will be dealt with as independent right censoring in the primary analysis. If withdrawal from study is substantial and differential between the treatment groups, supporting analyses will explore the impact of the independent censoring assumption by use of shared frailty models for time to death and time to withdrawal from study. The analyses of the time-to-event outcomes among the secondary endpoints will follow the same lines as the analyses of the primary endpoint. Methods for additional analyses, such as subgroup analyses and adjusted analyses: Planned subgroup analyses include metastasis status (synchronous/metachronous), mGPS score. We will use an adaptive design. A sample size review verifying planning assumptions such as the overall event and dropout rate will be conducted. Furthermore, a futility analysis will be carried out.

Sample size	To be assessed for eligibility: (approx. n = 400, informed consent) To be assigned to the trial: (n = 272) To be analyzed: (n= 272 ITT, including 218 completers)
Participating sites	No. of cities to be involved (planned): 20 German (AIO/ACO group network), 5 Netherlands (from DPCG network), Finland, Norway No. of centres to be involved: approx. 25 high-volume centers in GER/NL//FIN/NOR Names of cities and centres: approx. 25/25