**An open labelled phase III adjuvant trial of disease-free survival in patients with resected pancreatic ductal adenocarcinoma randomized to allocation of oxaliplatin- or gemcitabine-based chemotherapy by standard clinical criteria or by a transcriptomic treatment specific stratification signature**

**AIO-assoziierte Studie**

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| Studiennummer/-Code: | **AIO-PAK-0121/ass - ESPAC-6** |
| Status: | in Vorbereitung, Voten erhalten |
| Rekrutierungszeit: | von: Q2/2024 bis: Q3/2027 |
| Anzahl Zentren: | geplant: 30 (in Deutschland + 6 Zentren in Schweden;<br>aktuell initiiert: 0 aktiv rekrutierend: 0 |
| Weitere Zentren: | auf Anfrage |
| Anzahl Patienten: | geplant: 394 aktuell eingeschlossen: 0 |
| Letzte Aktualisierung | 18.03.2024 |

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| STUDY TYPE | Open labelled phase III multicentre randomized trial |
| PRINCIPAL INVESTIGATOR | Lead Coordinating Investigator:<br>Prof. Dr. Dr. med. Christoph Springfeld<br>University Hospital Heidelberg<br>Abteilung für Allgemeine, Viszerale und Transplantationschirurgie<br>Im Neuenheimer Feld 420<br>69120 Heidelberg |
| TRIAL OFFICE | Frankfurt Institute of Clinical Cancer Research IKF GmbH<br>at Northwest Hospital<br>Steinbacher Hohl 2-26<br>60488 Frankfurt am Main |
| SPONSOR | Ruprecht-Karls-University Heidelberg, Medical Faculty represented by Universitätsklinikum Heidelberg and Commercial Director<br>Im Neuenheimer Feld 672<br>69120 Heidelberg |
| CONDITION | Pancreas |
| DESIGN | Open labelled phase III multicentre randomized trial. |
| INDICATION | Pancreatic ductal adenocarcinoma (PDAC)<br>MedDRA code: 10033575<br>Concept ID: C0346647<br>ICD-O-3 site C25 |
| OBJECTIVE(S) | **Primary Objective**<br>The main purpose of the study is to determine whether disease free survival in patients with resected pancreatic ductal adenocarcinoma (PDAC) treated with standard adjuvant chemotherapy regimens (oxaliplatin- or gemcitabine-based), is superior using allocation based on a treatment specific signature (TSS), compared to the same chemotherapy regimens allocated according to standard clinical criteria.<br><br>The primary estimand for the primary objective is defined as follows:<br>Population: all patients fulfilling the in- and exclusion criteria. |

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| | Variable/Endpoint: disease-free survival, defined as time from randomisation to disease recurrence (growth or metastasis) or death from any cause.<br><br>Post-randomisation events: death from any cause is incorporated into the variable definition (composite strategy); changes in treatment and termination of treatment before the end of the 24 weeks treatment will be ignored (treatment policy strategy); event-free patients at the end of the follow-up period will be censored and drop-outs will be censored at the last observation (hypothetical strategy).<br><br>Summary measure: hazard ratio for the endpoint disease-free survival between the two treatment arms.<br><br>**Secondary Objectives**<br>Secondary objectives of the study are to assess overall survival (median, 3 year survival rate), metastasis free survival; survival based on targeted signatures (TSS) in test versus control arms, and survival using targeted therapies initially on relapse compared to standard first-line therapies on relapse. |
| INTERVENTION(S) | All medication within the study is used within clinical routine.<br>Therapeutic intervention of standard adjuvant chemotherapy comprising oxaliplatin- or gemcitabine-based regimens based on standard clinical criteria, compared to selection using a treatment specific signature and prediction model. |
| OBJECTIVES of OPTIONAL TRANSLATIONAL RESEARCH | The ESPAC-6 translational research programme will generate a rich resource of archival patient material, Patient-Derived Organoids (PDOs) and prospective data (randomised and controlled). The translational research protocol will utilise patient tissues including blood and primary resectable and recurrent locally advanced or metastatic tissue to exhaustively characterise the molecular mechanisms underpinning response to adjuvant therapy.<br><br>ESPAC-6 will co-ordinate the sequencing and analysis of all patient material, included in the trial, and harmonise efforts to generate PDOs. ESPAC-6 is funded to sequence all patient material (RNA and DNA) with additional supplementary funding for PDO generation.<br><br>ESPAC-6 will, where possible, complement existing translational research programmes currently being undertaken by partner organisations and does not wish to act as a competing interest. Partner organisations may contribute material to the ESPAC-6 translational research programme at their discretion, however, all data generated/funded by ESPAC-6 must be made available to all contributing partner organisations. |
| BACKROUND/RATIONALE | At present selection of therapy is based entirely on clinical criteria. It is becoming increasingly apparent that different tumour types respond differently to gemcitabine based versus non- gemcitabine-based regimens. For example, tumours expressing high levels of hENT1 are more likely to be associated with longer survival from gemcitabine whilst tumours expressing high levels of GATA6 are more likely to be associated with longer survival from 5FU.<br><br>The use of a Treatment Specific Signature based on RNAseq may also select patients with pancreatic cancer more likely to respond to either oxaliplatin-based or gemcitabine-based therapy. At the present time the best that can be expected for resectable PDAC with resection and adjuvant therapy using standard clinical criteria is say 20-50%. By selecting patients with specific transcriptomic signatures the upper level could be increased to say 70%. This |

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| | would have major impact in the treatment in the disease. It would also facilitate the introduction RNAseq into routine clinical practice. Potentially this principle could be extended to other difficult-to-treat cancer types. |
| KEY EXCLUSION CRITERIA | 1. Solid pseudopapillary neoplasm, neuroendocrine neoplasm, pancreatoblastoma, bile duct cancer, and ampullary cancer.<br>2. Distant metastases, including ascites or malignant pleural effusion.<br>3. Macroscopic incomplete tumour removal (R2 resection).<br>4. Post-operative CA 19-9 > 180 U / ml before randomization on study.<br>5. Cardiomyopathy or congestive heart failure, NYHA III-IV or coronary heart disease symptoms.<br>6. Major comorbidity that may preclude the delivery of treatment or known active infection (HIV or untreated chronic hepatitis B or active hepatitis C) or uncontrolled diabetes.<br>7. Pre-existing neuropathy, Gilbert's disease or known genotype UGT1A1*28 /*28.<br>8. Inflammatory disease of the colon or rectum, or intestinal obstruction, or severe postoperative uncontrolled diarrhoea.<br>9. Known severe dihydropyrimidine dehydrogenase (DPD) deficiency (activity score <1). There are clear guidelines for dose reductions for patients with a score of 1 and 1,5 (2 is normal activity).<br>10. Pregnancy and lactation.<br>11. Participation in other clinical trials or observation period of competing trials, respectively.<br>12. History of hypersensitivity or other known contraindication to the investigational medicinal product or to any drug with similar chemical structure or to any excipient present in the pharmaceutical form of the investigational medicinal product.<br>13. Past or current history of other malignancies not curatively treated and without evidence of disease for more than 5 years, except for curatively treated basal cell carcinoma of the skin and in situ carcinoma of the cervix or bladder, or low/intermediate risk prostate cancer (Gleason score ≤7) with normal PSA levels.<br>14. Any other concurrent antineoplastic treatment including irradiation |
| KEY INCLUSION CRITERIA | 1. Histologically proven pancreatic ductal adenocarcinoma including variants, and pancreatic acinar cell carcinoma.<br>2. Patient had provided tumour tissue at resection for RNAseq<br>3. Macroscopically complete resection (R0 or R1 resection).<br>4. Female and male Patients aged from 18 to 79 years.<br>5. WHO performance status 0-1.<br>6. No prior radiotherapy and no previous chemotherapy for pancreatic cancer.<br>7. Full recovery from surgery and patient able to receive chemotherapy: adequate oral nutrition of ≥ 1500 calories per day and free of significant nausea and vomiting.<br>8. Adequate hematologic function: Absolute neutrophil count ≥ 1,500 cells/$mm^3$, platelets ≥ 100,000<br>cells/$mm^3$ and haemoglobin ≥ 8 g/L (transfusion permitted).<br>9. Serum total bilirubin ≤ 1.5 times the institutional upper limit of normal.<br>10. Creatinine clearance ≥ 50 mL/min.<br>11. Patient of child-bearing potential (for female patient: study entry after a menstrual period and a negative pregnancy test) must agree to use highly effective methods of contraception during the study and for 6 months after the last study treatment for women and 6 months for men.<br>12. Intended interval since surgery between 21 and 84 days at date of randomization. |

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| | 13. Public or private health insurance cover.<br>14. Ability of subject to understand character and individual consequences of the clinical trial.<br>15. Not legally incapacitated.<br>16. Written informed consent. |
| OUTCOME(S) | Primary<br>Disease free survival, time from randomization to disease recurrence or death from any cause<br><br>Secondary<br>• Overall survival<br>• Metastasis free survival<br>• Overall survival from recurrence<br>• Quality of Life (EORTC QLQ C-30)<br>• Survival based on targeted signatures (TSS) in arm A (test) versus arm B (control).<br>• Response to targeted therapies<br>• Assessment of safety: toxicity according to NCI-CTC v.5.0; adverse and serious adverse events |
| STATISTICAL ANALYSIS | Primary endpoint analysis and population: Analysis of the primary endpoint disease free survival will be carried out using a Cox regression model. The Cox model allows evaluation of differences in the hazards between the test and control arm while accounting for the strata resection status (R0 vs. R1) and "post-operative serum Carbohydrate Antigen (CA) 19-9 levels <37KU/L (yes/no)". Hereby, the robust sandwich estimate of the covariance matrix proposed by Lin and Wei (1989) 11 is used for the test for treatment effect. This test allows valid statistical inference also in situations where the proportional hazards assumption is violated, which may be the case in the current situation. The two-sided significance level is set to α= 0.05. The hazard ratio for the treatment effect will be estimated alongside a 95% confidence interval. Kaplan-Meier curves will be created, median, and 3-year disease free survival rates will be calculated with 95% confidence intervals. The analysis of the primary endpoint will be conducted on the full analysis set (including all randomized patients following the intention-to-treat principle). Death, as intercurrent event occurring after randomization, is handled by inclusion into the definition of the primary endpoint which reflects a composite strategy (according to the ICH E9 (R1) addendum). Patients with incomplete observation time due to lost to follow-up or early drop-out will be censored at last observation (hypothetical strategy). Further post-randomization events (e.g. treatment discontinuation due to toxicities) will be ignored. This reflects a treatment policy approach.<br>Safety: The proportion of grade 3 and 4 toxicity will be compared across treatments using time to event methods and frequency counts. Adverse and serious adverse events are collected throughout the study and will be tabulated and compared between study arms.<br>Secondary endpoint analysis: Overall-survival (OS) will be tested in a hierarchical manner if the null hypothesis regarding the primary endpoint was rejected. If not, OS will be analysed as the other secondary outcomes in a descriptive manner which means that p-values will not be interpreted in a confirmatory sense. Time to event endpoints will be analysed analogously to the primary endpoint. Quality of life will be assessed over time and treatment groups compared using longitudinal analysis. Joint modelling of quality-adjusted survival analysis will be undertaken to allow a simultaneous assessment of quality of life and survival. |
| SAMPLE SIZE | To be assessed for eligibility: n= approximately 600<br>To be allocated to study: n=394<br>To be analysed: n=394 |

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| | The sample size was calculated for the primary endpoint disease free survival (DFS) based on a two-sided significance level of α = 5 % and a power 1-β of 80 %, assuming an accrual time of 36 months and a follow-up time of 36 months (including the 6 months of treatment). Based on previous studies (ESPAC-4, PRODIGE) we assume a 35 % 3 year-disease free survival rate for the control arm. We expect a hazard ratio (HR) of 0.710 which corresponds to a 3 year- disease free survival rate of 47.45 % in the test arm. Furthermore, we expect an exponentially distributed drop-out rate of 10 %. This results in 394 patients to be included in the study to observe the necessary 268 events. The use of a Cox regression model adjusting for covariates is expected to yield an additional increase in power due to less unexplained variance. ADDPLAN v6.1.1 and the formula by Schoenfeld (1981) 12 were used to calculate the sample size. |
| TRIAL DURATION | Recruitment period (months): 40<br>Follow-up for each patient from date of randomization, at least (months): 36<br>First patient in, to last patient out (months):76<br>Time for data clearance and analysis (months): 6<br>Duration of the entire study (months): 82 |
| PARTICIPATING CENTERS | To be involved n= 30 sites approximately in Germany & 6 sites in Sweden |
| FURTHER CENTERS DESIRED? | on request |
| NUMBER of PATIENTS | 394 |
| CURRENT NUMBER of PATIENTS | Not applicable, recruitment not yet started |
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