Zusammenfassende Ergebnisberichte/Schlussberichte für IIT	7.3.10 Anlage 02 Stand: 18.09.2020

Name of Sponsor/Company: University Hospital Hamburg Eppendorf, Martinistr 52, 20246 Hamburg	Individual Study Table Referring to Part of the Dossier Volume: 4.7 Page:69-70	*(For Competent Authority only)*
Name of Finished Product: n/a		
Name of Active Ingredient: Gemcitabine- based RCTx		

Title of Study	Sequential Neoadjuvant Chemoradiotherapy (CRT) Followed by Curative Surgery vs. Primary Surgery Alone for Resectable, Non-metastasized Pancreatic Adenocarcinoma
Principal Investigator	Prof. Dr. med. Prof. h. c. Dr. h. c. Jakob R. Izbicki, Head of the Department of General, Visceral and Thoracic Surgery of the University Hospital Hamburg-Eppendorf, Germany
Study centre(s)	University Hospital Hamburg Clinic Darmstadt St. Josef Hospital Bochum Staedtisches Klinikum Karlsruhe University Hospital Freiburg University Schleswirg Holstein, Campus Kiel and Campus Lübeck SRH Clinic Gera Technical University Munich University Hospital Heidelberg Saarland University, Homburg University Hospital Augsburg Hospital Stuttgart University Hospital Jena University Hospital Rostock Ludwig-Maximilians - University of Munich Dresden-Friedrichstadt Hospital
Publication (reference)	MC Cancer . 2014 Jun 7;14:411. doi: 10.1186/1471-2407-14-411. Sequential neoadjuvant chemoradiotherapy (CRT) followed by curative surgery vs. primary surgery alone for resectable, non-metastasized pancreatic adenocarcinoma: NEOPA- a randomized multicenter phase III study (NCT01900327, DRKS00003893, ISRCTN82191749. Michael Tachezy, Florian Gebauer, Cordula Petersen, Dirk Arnold, Martin Trepel, Karl Wegscheider, Phillipe Schafhausen, Maximilian Bockhorn, Jakob Robert Izbicki 1 ,

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	Emre Yekebas	
Studied period (years):	Date of first enrolment: Julil 4th, 2014	
	Date of last completed: November 22, 2016	
Phase of development	IIIb	
Objectives	Efficacy of neoadjuvant CRT in improving 3-year survival probability from 30% in the control arm undergoing upfront surgery without neoadjuvant CRT to 42% (relative increase of 40%) in the study arm undergoing CRT. The underlying guess of a 30% 3-year survival probability in the control group derives from an assumed median overall survival (MOS) of 20.7 months which corresponds with a MOS of 17.9 months to 23.6 months reported in several randomized trials.	
Methodology	The underlying hypothesis of this randomized, two-armed, open-label, multicenter, phase III trial is that neoadjuvant CRT increases the three-year overall survival by 12% compared to patients undergoing upfront surgery for resectable pancreatic cancer. A rigorous, standardized technique of histopathologically handling Whipple specimens will be applied at all participating centers. Overall, 410 patients (n = 205 in each study arm) will be enrolled in the trial, taking into regard an expected drop out rate of 7% and allocated either to receive neoadjuvant CRT prior to surgery or to undergo surgery alone. Circumferential resection margin status, i.e. R0 and R1 rates, respectively, surgical resectability rate, local and distant disease-free and global survival, and first site of tumor recurrence constitute further essential endpoints of the trial.	

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Number of patients (planned and analysed)	410 planned, 30 analyzed	
Indication and main in- and exclusion criteria	Key inclusion criterion is the biopsy-proven, non-metastasized, adenocarcinoma of the pancreatic head/uncinate process larger than two centimeter in size (≥cT2) and/or in close contact with the mesenterico-portal axis and superior mesenteric artery (SMA) (less than 3 mm). Inclusion Criteria: ○ Resectable adenocarcinoma of the pancreatic head/uncinate process or pancreatic body treted with an extended pancreatic head resection with a tumor size greater 2 cm (≥cT2) and/or close contact to the superior mesenteric vessels (≤3 mm in preoperative staging). ○ Histologic/ Cyologic verification or patients with a highly suspected pancreatic head carcinoma with elevated CA19-9 (>100U/ml), Hyperbilirubinemia, B-symptoms, and an interdisciplinary treatment recommendation ○ No evidence of metastasis to distant organs (liver, peritoneum, lung, others). ○ For determination of resectability, a multi-detector CT (MDCT) with at least 16 rows applying both oral and intravenous contrast media is performed. MDCT-based imaging focuses on the upper abdomen with native, arterial, and parenchyma phase, where the parenchyma phase should include the pelvis. Imaging criteria derived from the recent consensus definition of the Society of Surgical Oncology, the American Society of Clinical Oncology and the American Hepato-Pancreatico-Biliary Association [1] are applied for preoperative assessment of local resectability. ○ Potential Resectability: visualizable fat plane around celiac and superior mesenteric arteries, and patent	

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superior mesenteric/portal vein (SMV/PV).

- Borderline Resectability: substantial superior mesenteric/portal vein impingement, tumor abutment on the SMA < 180°, GDA encasement up to the origin of the hepatic artery, or colonic/mesenteric root invasion.
- Karnofsky performance status ≥ 80%
- Serum creatinine level ≤ 3.0 mg/dl
- Serum total bilirubin level ≤ 3.0 mg/dl in the absence of biliary obstruction (In the event of biliary obstruction, patients allocated to the CRT group must undergo interventional endoscopy or percutaneous drainage for biliary decompression. Post-interventionally, bilirubin levels should be ≤ 3.0 mg/dl before patients are subjected to CRT. In control patients undergoing upfront surgery, serum total bilirubin levels ≤ 10.0 mg/dl are tolerated, unless clinical and laboratory signs of severe cholangitis take place. Patients with serum total bilirubin level > 10.0 mg/dl undergo preoperative biliary decompression, preferentially by interventional endoscopy)
- White blood cell count ≥ 3.5 x 109/ml, platelet count ≥ 100 x 109/ml
- Ability to understand and willingness to consent to formal requirements for study participation
- Written informed consent

Exclusion Criteria:

- Age ≤ 18 years
- Neuroendocrine, acinar cancer
- Cancers of the pancreatic body or tail, i.e. lesions left to the SMV, that would be treated with an pancreatic tail resection
- Recurrent disease
- Infiltration of extrapancreatic organs (except duodenum and transverse colon)

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	○ Persistent cholestasis/cholangitis despite adequate biliary stenting ○ Gastric outlet obstruction, especially in the event of endoscopically evidenced tumor invasion into the gastroduodenal mucosa. ○ Tumor specific pre-treatment ○ History of gastrointestinal perforation, e.g. perforated colonic diverticulitis, abdominal abscess or intestinal fistula within 6 months prior to potential study participation ○ Radiographic evidence of severe portal hypertension/cavernomatous transformation that may, at the discretion of the participating investigators, hamper surgery ○ Other concurrent malignancies except for basal cell cancer of the skin and in-situ cervical cancer ○ Premalignant hematologic disorders, e.g. myelodysplastic syndrome ○ Severe organ dysfunctions (e.g. Liver cirrhosis ≥ Child B; Cardio-pulmonal diseases (NYHA ≥III, arrhythmia Lown III/IV, global respiratory insufficiency); Ascites; Acute pancreatitis; bleeding diathesis, coagulopathy, need for full-dose anticoagulation or INR > 1.5; other severe diseases that might prevent completion of the treatment regimen) ○ Chronic infectious diseases, especially immune deficiency syndromes, e.g. HIV infection, active tuberculosis within 12 months prior to potential study participation ○ History of severe neurologic disorders, e.g. cerebrovascular ischemia ○ History of prior deep venous thrombosis or pulmonary embolism ○ Pregnant or nursing women are ineligible and patients of reproductive potential must agree to use an effective	

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	contraceptive method during participation in this trial and for 6 months following the trial ○ Serious medical, psychological, familial, sociological or geographical conditions or circumstances potentially hampering compliance with the study protocol and follow-up Participation in other clinical trials during the last 6 months before allocation to trial	
Test product, dose and mode of administration, batch number	Neoadjuvant CRT will receive Gemcitabine 300 mg/m2/weekly for 6 weeks combined with 3-D-conformal external beam radiotherapy (EBRT)	
Duration of treatment	6 weeks	
Reference therapy, dose and mode of administration, batch number	Upfront PD followed by adjuvant CTx	
Criteria for evaluation	Safety: An advisory Data and Safety Monitoring Board (DSMB) evaluates the risk to the patients on the accrued data provided by the sponsor and the monitor. The multicentre character of the study poses special challenges as to quality control performed on an ad hoc or real-time basis or quarterly, as appropriate. The DSMB will especially focus on inter-institutional differences in diagnostic work-up, clinical staging accuracy, surgery, histopathologic reporting, and non-surgical therapy. A further major task of the DSMB is to check for potentially elevated surgical morbidity in CRT patients (intraoperative blood loss, anastomotic leakage rates, etc.). All SAEs or follow-up information to SAEs will be reported to the sponsor during the entire course of the study, from informed consent until end of study visit plus an additional safety observation period of 30 days. After the safety observation period, the investigator shall report to the sponsor only serious adverse events that are related to the study medication. The investigator must promptly report to his Institutional Review Board / Independent Ethics Committee (IEC) all unanticipated problems	

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	involving risks to patients. This includes all SAEs and death from any cause within 180 days (6 months) after last administration of study-related drug or procedure.	
	Efficacy: Description of the primary efficacy analysis and population: ITT population, log-rank test, 4-stage group-sequential design according to O'Brien-Fleming Safety: AEs and SAEs will be presented by their National Cancer Institute Common Toxicity Criteria Adverse Event (NCI-CTCAE) grade and by preferred terms nested within the System Organ Class using the Medical Dictionary for Regulatory Activities (MedDRA). Exploratory two-sided 95% CIs will be calculated for the incidence of AEs. Secondary endpoints: All secondary endpoints will be analyzed at end of trial in the ITT population. Two-sample tests adequate for the specific scale of the endpoint will be applied. Supportive analyses will include the repetition of the analysis in a per-protocol subpopulation, statistical model building based on Cox or other regression models and sensitivity analyses for loss-to-follow-up. A subgroup survival analysis stratifying patients deemed potentially resectable vs. those deemed borderline resectable will be performed. Sample size calculation: For the group sequential design, required sample size of 2 x 205=410 patients to be recruited over 3 years at a rate of 12 patients/ month was calculated.	
Statistical methods	The primary analysis will consist of a log-rank test comparing the survival between groups. Patients who do not experience a primary event will be censored at their last day at risk observed in the study. A 4-stage group-sequential design of the O'Brien-Fleming type will be applied with a total alpha spent of 5%.	

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	Maximum 4 log-rank tests at levels of 0.36/1.40/2.58/3.98% with boundaries 5.816/4.916/4.460/4.112 will be preformed after 50%/75%/85%/100% of the information was collected, i.e. after 154/215/261/307 deaths were observed. All secondary endpoints will be analyzed at end of trial only. Two-sample tests adequate for the specific scale of the endpoint will be applied. If baseline determinations are available, an analysis of covariance (ANCOVA) will be considered after suitable transformation. All analysis will at first be performed in the intention-to-treat population that covers all consenting patients randomized. To avoid missing values, all possible efforts will be made to collect data of patients who discontinued trial therapy or were temporarily lost to follow-up. For the primary analysis drop-outs will be treated as censored at their last observation day. However, several imputation methods will be applied to missing values in different sensitivity analyses of the primary outcome. At second, all analyses will be repeated in a per-protocol population containing only patients without major protocol violations. Additional analyses will be performed by statistical model building, e.g. Cox proportional hazard models including baseline covariates and interaction terms for the primary endpoint. A proper subgroup survival analysis stratifying patients deemed potentially resectable vs. those deemed borderline resectable will be performed by including a corresponding interaction term to the Cox model. A detailed statistical analysis plan (SAP) will be adopted before the first comparative outcome analysis is performed.	
SUMMARY-CONCLUSIONS		
Efficacy results	Due to early determination no efficacy analysis was feasible	

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Safety results	Due to the early determination of the study, no robust and statistically analysable data regarding the safety of the therapy were generated.	
Conclusion	Only 30 (out of 410 planned) patients were included and therefor, no scientific reliable conclusion can be drawn.	
Date of Report:	September 18th, 2020	

PRINCIPAL OR COORDINATING INVESTIGATOR(S) SIGNATURE(S) OR SPONSOR'S RESPONSIBLE MEDICAL OFFICER

STUDY TITLE: Sequential Neoadjuvant Chemoradiotherapy (CRT) Followed by Curative Surgery vs. Primary Surgery Alone for Resectable, Non-metastasized Pancreatic Adenocarcinoma

STUDY AUTHOR(S): Michael Tachezy (MD)

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study

Prof. Dr. J. Izbicki

INVESTIGATOR OR SPONSORS RESPONSIBLE MEDICAL OFFICER

SIGNATURE(S)

AFFILIATION: _____

DATE: 20.01.2021