Trial to Investigate Intensified Neoadjuvant Chemotherapy in Locally Advanced Pancreatic Cancer (NEOLAP)

This study is currently recruiting participants. (see Contacts and Locations)

Verified July 2015 by AIO-Studien-gGmbH

Sponsor:
AIO-Studien-gGmbH

Collaborators:
Celgene Corporation
ClinAssess GmbH

Information provided by (Responsible Party):
AIO-Studien-gGmbH

ClinicalTrials.gov Identifier:
NCT02125136

First received: April 11, 2014
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History of Changes

Purpose

The aim ot the study is to investigate the efficacy and safety of tw o new intensified chemotherapy regimens (gemcitabine (Gem)/nab-paclitaxel (PAC), FOLFIRINOX) as neoadjuvant chemotherapy protocol in locally advanced, non-metastatic pancreatic cancer (LAPC) and consecutive conversion of the tumor to resectability.

Condition	Intervention	Phase
Ductal Adenocarcinoma of the Pancreas	Drug: Gem/nab-Pac Drug: FOLFIFINOX	Phase 2

Study Type: Interventional
Study Design: Allocation: Randomized
Endpoint Classification: Efficacy Study
Intervention Model: Parallel Assignment
Masking: Open Label
Primary Purpose: Treatment

Official Title: Prospective Randomized Multicenter Phase II Trial to Investigate Intensified Neoadjuvant Chemotherapy in Locally Advanced Pancreatic Cancer

Resource links provided by NLM:

Genetics Home Reference related topics: breast cancer

MedlinePlus related topics: Cancer Pancreatic Cancer

Genetic and Rare Diseases Information Center resources: Pancreatic Cancer

U.S. FDA Resources

Further study details as provided by AIO-Studien-gGmbH:

Primary Outcome Measures:

- Conversion Rate [Time Frame: approx. 10 month] [Designated as safety issue: No]

To compare the effect of intensified neoadjuvant chemotherapy on conversion rate to resectability in LAPC.

Secondary Outcome Measures:

- Safety [Time Frame: approx. 22 month] [Designated as safety issue: Yes]

  evaluate safety and tolerability of intensified neoadjuvant chemotherapy

  - Exposure to study drugs
  - Type, incidence, and severity of adverse events
  - Dose reduction or discontinuation of study drugs due to adverse events
  - Laboratory parameters

- objective tumour response rate [Time Frame: approx. 22 month] [Designated as safety issue: No]

  assess objective tumour response rate (ORR) to intensified neoadjuvant chemotherapy Baseline tumor measurement(s) w ill be performed w ithin 4 w eeks before the first dose of study drug w ith either computed tomography (CT) including spiral CT or MRI according to investigator's choice and clinical practice at the respective trial site as done routinely also outside of clinical trial situations.The same method used at baseline must be used consistently for response assessment to neoadjuvant chemotherapy at the first restaging (after the first part of neoadjuvant chemotherapy) and the second restaging (after the second part of neoadjuvant chemotherapy) and thereafter.

- disease control rate (DCR) [Time Frame: approx. 22 month] [Designated as safety issue: No]

  assess disease control rate (DCR) after intensified neoadjuvant chemotherapy

- CA 19-9 change [Time Frame: 10 month] [Designated as safety issue: No]

  Assess carbohydrate antigen 19-9 (CA 19-9) change during/after neoadjuvant chemotherapy. In this trial, CA 19-9 change to neoadjuvant chemotherapy w ill be evaluated as decrease to the baseline level at the 1st and 2nd restaging.

- R0 and R1 resections [Time Frame: 10 month] [Designated as safety issue: No]

  assess rate of R0 and R1 resections

- pathological responses [Time Frame: approx. 22 month] [Designated as safety issue: No]

  assess rate of grade 3 + 4 pathological responses according to grading scheme of treatment responses by Evans in resected patients.

- relapse-free survival (RFS) [Time Frame: approx. 22 month] [Designated as safety issue: No]

  assess relapse-free survival (RFS): Relapse-free survival is the time from Day 1 after pancreatic resection to the date of relapse, defined as Day 1 after pancreatic resection to either local relapse of pancreatic cancer or occurrence of distant metastases. For each patient w ho is not know n to have had a relapse as of the data-inclusion cut-off date for a particular analysis, time to relapse w ill be censored for that analysis at the date of the patient's last study visit prior to that cut-off date.

- Progression-free survival (PFS) [Time Frame: approx. 2 years] [Designated as safety issue: No]

  PFS is the time from Day 1 of the first cycle of neoadjuvant chemotherapy to date of objective disease progression or to death of any cause. For each patient w ho is not know n to have had a progression as of the data-inclusion cut-off date for a particular analysis, time to progressive disease w ill be censored for that analysis at the date of the patient's last study visit prior to that cut-off date.

- perioperative morbidity and mortality [Time Frame: 60 days] [Designated as safety issue: No]

  assess perioperative morbidity and mortality

- Tolerability [Time Frame: 10 month] [Designated as safety issue: Yes]

  evaluate safety and tolerability of intensified neoadjuvant chemotherapy (see safety measure)

- Overall Survival (OS) [Time Frame: approx. 22 month] [Designated as safety issue: No]

  OS is the time from Day 1 of the first cycle of neoadjuvant chemotherapy to date of death from any cause. The rate of patients w ho have died from any cause after one year and tw o years, respectively w ill be assessed. For each patient for w hom it is not know n w hether he died or is still alive until the data-inclusion cut-off date for a particular analysis, time to death of any cause w ill be censored for that analysis at the date of the patient's last study visit prior to that cut-off date.

Estimated Enrollment: 168

Study Start Date:	November 2014
Estimated Study Completion Date:	December 2017
Estimated Primary Completion Date:	December 2017 (Final data collection date for primary outcome measure)

Arms	Assigned Interventions
Experimental: Gem/nab-Pac 2 further cycles Gem/nab-Pac (duration of each cycle 28 days)	Drug: Gem/nab-Pac All patient receive: 2 cycles gemcitabine/nab-paclitaxel ([Gem/nab-Pac]; duration of each cycle 28 days) Then: Nab-paclitaxel 125 mg/m2, IV infusion over 30 minutes, followed by gemcitabine 1000 mg/m2 as a 30-minute IV infusion on D1, D8, D15 of each 28-day cycle
Experimental: FOLFIFINOX 4 cycles combination therapy with 5-fluorouracil/folinic acid, irinotecan, oxaliplatin (FOLFIFINOX) - duration of each cycle 14 days	Drug: FOLFIFINOX All patient receive: 2 cycles gemcitabine/nab-paclitaxel ([Gem/nab-Pac]; duration of each cycle 28 days) Then: Oxaliplatin 85 mg/m2, given as a 2-hour intravenous infusion D1 Folinic acid 400 mg/m2, given as a 2-hour intravenous infusion D1 Irinotecan 180 mg/m2, given as a 90-minutes intravenous infusion D1 (application through a Y-connector parallel to infusion of folinic acid or 30 minutes after start of folinic acid possible) Fluorouracil 400 mg/m2, administered by intravenous bolus, followed by a continuous intravenous infusion of fluorouracil 2400 mg/m2 over a 46-hour period D1. To be repeated on D1 of each cycle.

Detailed Description:
This is a prospective open randomized multicenter phase II trial with two arms.

Patients suffering from histologically confirmed LAPC (and assessed as unresectable or borderline resectable according to National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines "pancreatic adenocarcinoma" version 1.2013) without metastases will receive two different neoadjuvant treatment regimens:

First all patients receive two cycles Gem/nab-PAC (duration of each cycle 28 days) as neoadjuvant chemotherapy in equal measure and a first restaging is performed after these two cycles based on imaging criteria. If there is no progression according to Response evaluation criteria in solid tumors (RECIST 1.1) criteria at the first restaging, the patients are randomized in a 1:1 relation to:

Two further cycles Gem/nab-PAC (duration of each cycle 28 days). or Four further cycles FOLFIRINOX (duration of each cycle 14 days). After the neoadjuvant chemotherapy a 2nd restaging is performed based on imaging criteria. All patients without progression at this restaging or at an earlier time point undergo obligatory exploratory laparotomy irrespective of imaging criteria to assess resectability. If they are evaluated as converted to resectable during this exploratory laparotomy, pancreas resection in curative intent will be performed. All patients with successful R0 or R1 pancreatic resection will receive three further cycles adjuvant chemotherapy with Gem/nab-PAC. Adjuvant chemotherapy will start within 4 to 8 weeks after pancreatic resection surgery.

Further treatment of patients with PD after 1st or 2nd restaging as well as patients with unresectable status based on exploratory laparotomy is under the discretion of the local investigators (e.g. second-line chemotherapy in case of distant relapse or local radiochemotherapy in case of local progression or definitive irresectability).

All patients are followed up for local recurrence, progression and survival until death or for at least one year after last application of study drugs whichever is sooner.

The translational research conducts exploratory analyses for potential biomarkers of possible prognostic or predictive value for efficacy of neoadjuvant chemotherapy in LAPC; including analyses of circulating tumor cells, molecular pathways of pancreatic adenocarcinoma including SPARC expression.

Eligibility

Ages Eligible for Study:	18 Years to 75 Years
Genders Eligible for Study:	Both
Accepts Healthy Volunteers:	No

Criteria
Inclusion Criteria:

- Adult patients ≥ 18 years and ≤ 75 years of age
- Histologic or cytologic proven ductal adenocarcinoma of the pancreas (histologic confirmation of diagnosis is preferred)
- No distant metastases

- De novo, treatment-naïve unresectable or borderline resectable LAPC; evaluation of unresectable and borderline resectable status according to NCCN- Clinical Practice Guidelines in Oncology "pancreatic adenocarcinoma" version 1.2013. Applicable criterion/criteria have to be indicated.
- Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1
- Total bilirubin ≤ 2 mg/dL. Patients with a biliary stent may be included provided that bilirubin level after stent insertion decreased to ≤ 2 mg/dL and there is no cholangitis.
- Adequate renal, hepatic and bone marrow function, defined as
- Serum creatinine ≤ 1.25 x Upper limit of normal (ULN)
- Calculated creatinine clearance ≥ 60 mL/min according to Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula
- Aspartate aminotransferase (AST)/(serum glutamic oxaloacetic transaminase)GOT and/or Alanine aminotransferase (ALT)/serum glutamic pyruvic transaminase (GPT) ≤ 2.5 x ULN
- Partial thromboplastin time (PTT) ≤ 1.5 x ULN and Quick value ≥ 70%
- Absolute neutrophil count (ANC) ≥ 1.5 x 109/L
- Haemoglobin ≥ 8g/dL
- Platelets ≥ 100 x 109/L
- Females of childbearing potential (FCBP) must have a negative pregnancy test within 7 days of the first application of study treatment and must agree to use effective contraceptive birth control measures (Pearl Index < 1) during the course of the trial and for at least 1 month after last application of study treatment.

A female subject is considered to be of childbearing potential unless she is age ≥ 50 years and naturally amenorrhoeic for ≥ 2 year, or unless she is surgically sterile.

- Males must agree not to father a child during the course of the trial and for at least 6 months after last administration of study drugs.
- Signed and dated informed consent before the start of any specific protocol procedures
- Patient's legal capacity to consent to study participation

Exclusion Criteria:

- Evidence of distant metastases. In case of radiological suspicion of peritoneal carcinomatosis or ascites histological or cytological verification is required e.g. by means of exploratory laparoscopy
- Local relapse of the pancreatic adenocarcinoma prior treated with surgical resection
- Any previous treatment of the pancreatic carcinoma (radiotherapy, chemoradiotherapy, chemotherapy, targeted tumor therapy, local ablative therapy)
- Contraindication for pancreas resection (pancreatic head resection, distal pancreatectomy with splenectomy, or complete pancreatectomy)
- Larger surgical interventions within 4 weeks before study enrolment and/or diagnostic laparotomy with or without gastroenterostomy and with or without biliodigestive anastomosis within 2 weeks before first application of study treatment. Wound healing must be also completed before first application of study treatment.
- Known chronic diarrhoea
- Peripheral polyneuropathy > grade 1
- Known dihydropyrimidine dehydrogenase (DPD) deficiency
- Medical history of interstitial lung disease (ILD) or pulmonary fibrosis
- Hypersensitivity against any of the study drugs (nab-paclitaxel, gemcitabine, oxaliplatin, irinotecan, 5-fluorouracil, folinic acid), or the ingredients of these drugs
- Active or uncontrolled bacterial, viral, or fungal infection that requires systemic treatment
- Known HIV- infection or active Hepatitis B virus (HBV)- or Hepatitis C virus (HCV) infection
- Convulsion disorder that requires anticonvulsive treatment
- Clinically significant cardiovascular or vascular disease or disorder ≤ 6 months before study enrolment (e.g. myocardial infarction, unstable angina pectoris, chronic heart failure New York Heart Association (NYHA) ≥ grade 2, uncontrolled arrhythmia, cerebral infarction)
- Any other severe concomitant disease or disorder, which could influence patient's ability to participate in the study and his/her safety during the study or interfere with interpretation of study results e.g. severe hepatic, renal, pulmonary, metabolic, or psychiatric disorders
- Requirement for concomitant antiviral treatment with sorivudine or brivudine
- Requirement of immunosuppressive treatment
- Continuing anticoagulant therapy with coumarin derivatives (treatment with low-molecular weight heparin allowed)
- Continuing abuse of alcohol, drugs, or medical drugs
- Pregnant or breast feeding females
- Participation in any other clinical trial or treatment with any experimental drug within 28 days before enrolment to the study or during study participation until the end of treatment visit.

- Previous or concurrent malignant tumor disease other than underlying tumor disease w ith the exception of cervical cancer in situ, adequately treated basal cell carcinoma or squamous cell carcinoma of the skin, superficial bladder tumors (Ta,Tis, and T1) or any curatively treated tumors > 5 years prior to enrolment

Contacts and Locations

Choosing to participate in a study is an important personal decision. Talk w ith your doctor and family members or friends about deciding to join a study. To learn more about this study, you or your doctor may contact the study research staff using the Contacts provided below. For general information, see Learn About Clinical Studies.

Please refer to this study by its ClinicalTrials.gov identifier: NCT02125136

Contacts

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Locations

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Principal Investigator: Volker Kunzmann, Prof. Dr.

Sponsors and Collaborators

AIO-Studien-gGmbH

Celgene Corporation

ClinAssess GmbH

Investigators

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More Information

Additional Information:

Working Group for Medical Oncology (AIO) from the German Cancer Society (DKG) EXIT

No publications provided

Responsible Party:	AIO-Studien-gGmbH
ClinicalTrials.gov Identifier:	NCT02125136 History of Changes
Other Study ID Numbers:	AIO-PAK-0113, AX-CL-PANC-PI-003324, 2013-004796-12
Study First Received:	April 11, 2014
Last Updated:	July 9, 2015
Health Authority:	Germany: Federal Institute for Drugs and Medical Devices

Keyw ords provided by AIO-Studien-gGmbH:
unresectable
borderline resectable

Additional relevant MeSH terms:

Adenocarcinoma	Endocrine Gland Neoplasms
Carcinoma, Ductal, Breast	Endocrine System Diseases
Pancreatic Neoplasms	Neoplasms
Breast Diseases	Neoplasms by Histologic Type
Breast Neoplasms	Neoplasms by Site
Carcinoma	Neoplasms, Ductal, Lobular, and Medullary
Carcinoma, Ductal	Neoplasms, Glandular and Epithelial
Digestive System Diseases	Pancreatic Diseases
Digestive System Neoplasms	Skin Diseases

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