The (cost)effectiveness of neoadjuvant FOLFIRINOX versus neoadjuvant gemcitabine based chemoradiotherapy and adjuvant gemcitabine for (borderline) resectable pancreatic cancer.

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This study has been transitioned to CTIS with ID 2024-516260-29-00 check the CTIS register for the current data. To determine whether neoadjuvant FOLFIRINOX followed by surgery improves overall survival and quality of life compared to neoadjuvant...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Exocrine pancreas conditions
Study type	Interventional

Summary

ID

NL-OMON55463

Source
ToetsingOnline

Brief title
PREOPANC-2

Condition

- Exocrine pancreas conditions
- Gastrointestinal neoplasms malignant and unspecified

Synonym
(borderline) resectable pancreatic cancer, pancreatic cancer

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: ZonMw,KWF

Intervention

Keyword: FOLFIRINOX, neo-adjuvant treatment, pancreatic cancer, Quality of life

Outcome measures

Primary outcome

The main endpoint is overall survival (OS).

Secondary outcome

• Chemotherapy rate, defined as the percentage of eligible randomized patients who received at least one cycle of chemotherapy.

• Chemotherapy completion rate, defined as the percentage of eligible randomized patients who completed all cycles of scheduled chemotherapy.

• Staging laparoscopy rate, defined as the percentage of eligible randomized patients that actually underwent a staging laparoscopy, regardless whether a laparotomy or resection was performed.

• Laparoscopy yield, defined as the percentage of patients that underwent staging laparoscopy and were diagnosed with metastatic disease during this procedure.

• Exploratory laparotomy rate, defined as the percentage of eligible randomized patients who actually underwent an exploratory laparotomy, regardless whether a resection was performed.

• Resection rate, defined as the percentage of eligible randomized patients

that underwent a curative-intent resection.

• R0 resection rate, defined as the percentage of eligible randomized patients that underwent a microscopically complete (R0) resection. The resection is considered R0 if the inked margin is more than 1 mm away from tumor cells.

• Progression-free survival, defined as survival without progressive or recurrent pancreatic cancer from the date of randomization. Death from any cause is also considered an event for this endpoint.

• Locoregional recurrence free interval (LRFI), defined as the period of time without locoregional recurrence after randomization. A locoregional failure is any persistent or recurrent pancreatic cancer in the original tumor location, or the N1 lymph node areas.

• Distant metastases free interval (DMFI), defined as the period of time without distant metastases after randomization.

• Disease free survival (DFS), defined as the period of time between randomization and locoregional recurrence, occurrence of distant metastases or second pancreatic cancer, or death (all causes).

• Locoregional recurrence free interval (LRFI), defined as the time interval between the day of randomization and the date of locoregional recurrence, including the N1 lymph node areas.

• Postoperative complications, defined according to the Clavien-Dindo classification and definitions of post-pancreatic surgery complications (pancreatic fistula, delayed gastric emptying, and bleeding) by the International Study Group on Pancreatic Surgery.

• Toxicity, gastro-intestinal and hematologic, according to CTCAE version

4.0.3, until 90 days after the last dose of chemotherapy.

• Quality of life years (QALYs) from randomization until last follow-up.

• Indirect and direct medical and nonmedical costs.

• Incremental cost-effectiveness ratio (ICER). Is calculated as the ratio between the difference in QALYs and the difference in total costs per patient.

• Predictive value of biomarkers in serum and resected tumors.

• Clinical response rate defined according to RECIST criteria version 1.1 comparing pre-randomization and restaging imaging after preoperative chemoradiotherapy and after 4 and 8 cycles of FOLFIRINOX.

• Serum Cancer Antigen 19-9 (CA 19.9) and Carcino-Embryonal-Antigen (CEA) response, defined as the change in CA 19-9 and CEA after preoperative chemoradiotherapy and after 4 and 8 cycles of FOLFIRINOX compared to baseline.

• Pathologic response, 3-tier histologic tumor regression grading (HTRG) scheme; HTRG 0, no viable tumor; HTRG 1, <5% viable tumor cells; HTRG 2, >=5% viable tumor cells.

Study description

Background summary

The annual incidence of pancreatic cancer in the Netherlands is approximately 3500 patients. In 2030, pancreatic cancer is expected to be the second leading cause of cancer death. The 1-year overall survival (OS) for pancreatic cancer in the Netherlands is 20%; the 5-year OS is only 3%.

Upfront resection with adjuvant gemcitabine has been the standard of care for patients with (borderline) resectable pancreatic cancer in the Netherlands as stated in the Dutch national guideline. However, the recent Dutch multicenter PREOPANC-1 trial, found that neoadjuvant gemcitabine based chemoradiotherapy followed by resection and adjuvant gemcitabine confers superior overall

survival (median 17 vs 13 months, p<0.05). These results confirm the results of a systematic review and a smaller Korean trial. Since FOLFIRINOX (a combination of 5-fluorouracil, irinotecan, oxaliplatin, and leucovorin) is more potent chemotherapy compared to gemcitabine, this treatment may further improve survival. Moreover, it is already the standard of care in patients with locally advanced and metastatic pancreatic cancer. A patient-level meta-analysis of FOLFIRINOX for patients with (borderline) resectable pancreatic cancer found a median overall survival of 24 months.

Study objective

This study has been transitioned to CTIS with ID 2024-516260-29-00 check the CTIS register for the current data.

To determine whether neoadjuvant FOLFIRINOX followed by surgery improves overall survival and quality of life compared to neoadjuvant chemoradiotherapy followed by surgery and adjuvant gemcitabine in patients with (borderline) resectable pancreatic cancer in an intention-to-treat setting.

Study design

Prospective multicenter randomized phase III clinical superiority trial.

Intervention

8 cycles of neoadjuvant FOLFIRINOX chemotherapy followed by surgery.

Study burden and risks

All patients (standard of care)
Patients will undergo a triphasic CT scan of the chest and abdomen to rule out metastatic disease and determine resectability. Endoscopic Ultrasonography with Fine Needle Aspiration (EUS/FNA) is performed to obtain a pathological diagnosis. Patients with hyperbilirubinemia may be randomized, but biliary drainage should be performed before start of neoadjuvant therapy if bilirubin is higher than 1.5 times upper limit of normal.
After treatment, patients will go into routine follow-up for 5 years. Follow up includes regular outpatient clinic visits, CT scans when indicated, and blood collection. All patients are asked to complete questionnaires during follow-up.

Patients in the intervention arm
The treatment starts with 4 cycles of chemotherapy with FOLFIRINOX. If a CT scan shows no disease progression after 4 cycles, the patient will receive an additional 4 cycles of chemotherapy. If a CT scan shows (borderline) resectable disease after chemotherapy, the patient will undergo curative-intent surgery. Surgery will start with a staging laparoscopy (i.e. in the same operation) to

rule out occult metastatic disease. A resection is performed in the absence of metastatic or locally advanced (i.e. unresectable) disease. No adjuvant chemotherapy is given. Patients with metastatic or locally advanced disease at restaging or surgery continue with palliative treatment or receive best supportive care; these patients forgo a resection. Patients who discontinue chemotherapy because of toxicity proceed to surgery without completing all scheduled cycles of chemotherapy.
Toxicity of the FOLFIRINOX regimen is well described, because it is the standard of care in the metastatic and locally advanced setting. Severe toxicity is more common with FOLFIRINOX than with gemcitabine. However, in two large studies no death was attributed to FOLFIRINOX.

Patients in the comparator arm
Treatment in the standard arm starts with a schedule based on three cycles of full-dose gemcitabine, adding hypofractionated radiotherapy (36 Gy in 15 fractions) during the second cycle. This chemoradiotherapy is followed by surgery within 4-6 weeks after completion of chemotherapy, followed within 12 weeks by 4 cycles of adjuvant gemcitabine.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

• Histologically or cytologically confirmed pancreatic cancer (i.e. pancreatic ductal adenocarcinoma)
• (Borderline) resectable tumor without metastatic disease
• WHO performance status 0 or 1
• Ability to undergo surgery, chemoradiotherapy and chemotherapy
• Leucocytes (WBC) >= 3.0 X 109/l (should be assesed within 4 weeks prior to randomization)
• Platelets >= 100X 109 /l (should be assesed within 4 weeks prior to randomization)
• Hemoglobin >= 6 mmol/l (should be assesed within 4 weeks prior to randomization)
• Renal function: E-GFR >= 50 ml/min (should be assesed within 4 weeks prior to randomization)
• Age >= 18 years
• Written informed consent

Exclusion criteria

• Prior radiotherapy, chemotherapy, or resection for pancreatic cancer.
• Prior radiotherapy or chemotherapy precluding chemoradiotherapy or FOLFIRINOX.
• Previous malignancy (excluding non-melanoma skin cancer, pancreatic neuroendocrine tumor (pNET) <2cm, and gastrointestinal stromal tumor (GIST) <2cm), unless no evidence of disease and diagnosed more than 3 years before diagnosis of pancreatic cancer, or with a life expectancy of more than 5 years from date of inclusion.
• Pregnancy.
• Serious concomitant systemic disorders that would compromise the safety of the patient or his/her ability to complete the study, at the discretion of the investigator.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	05-06-2018
Enrollment:	368
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Fluorouracil
Generic name:	5-Fluorouracil
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Gemcitabine
Generic name:	Gemzar
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Irinotecan
Generic name:	Irinotecan HCL-trihydraat
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Leucovorin calcium
Generic name:	Folinic acid
Registration:	Yes - NL outside intended use
Product type:	Medicine

Brand name:	Oxaliplatin
Generic name:	Oxaliplatin
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	22-01-2018
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	06-03-2018
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-05-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-09-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-10-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	30-11-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO	

Date:	20-12-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-10-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-10-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	01-02-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-09-2024
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	18-09-2024
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

ID: 28312
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
EU-CTR	CTIS2024-516260-29-00
EudraCT	EUCTR2017-002036-17-NL
CCMO	NL61961.078.17