TIming of start of systemIc treatment for asymptomatic MEtastasized PANcreatic cancer (TIMEPAN): a prospective multicenter patient preference cohort.

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Primary objective:To assess the effect of immediate versus delayed start of chemotherapy on quality adjusted survival in patients with metastatic pancreatic cancer. Secondary Objectives:To determine time to disease progression after randomizationTo...

Ethical review	Approved WMO
Status	Pending
Health condition type	Malignant and unspecified neoplasms gastrointestinal NEC
Study type	Observational invasive

Summary

ID

NL-OMON52527

Source
ToetsingOnline

Brief title
TIMEPAN

Condition

- Malignant and unspecified neoplasms gastrointestinal NEC

Synonym
Pancreatic cancer

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: carcinoma, chemotherapy, pancreas

Outcome measures

Primary outcome

Quality Adjusted Survival.

Secondary outcome

Time to disease progression after randomization.

Adverse events according to NCI CTC version 5.0.

Study description

Background summary

Pancreatic ductal adenocarcinoma (PDAC) is one of the most deadliest forms of cancer with a 5-year survival of less than 5% for patients with metastatic disease. Since the introduction of gemcitabine several decades ago, advances in therapy of metastatic disease have been slow. Numerous phase III studies have evaluated different gemcitabine-based regimens as first-line treatment, but in most cases, observed benefits have been small and restricted to patients with a good performance status. A significant breakthrough for patients with metastatic disease was achieved with the FOLFIRINOX regimen (5-fluorouracil, folinic acid, oxaliplatin and irinotecan) and the combination of nab-paclitaxel and gemcitabine. Both chemotherapy combination schedules demonstrated a significant survival improvement compared to gemcitabine alone. However, despite these improvements, the vast majority of patients will have disease recurrence or progression within 6 months. Moreover, chemotherapy is at the cost of substantial toxicity.

Not every patient diagnosed with pancreatic cancer has disease-related symptoms at initial presentation. Metastatic disease could be diagnosed incidentally or during routine follow-up visits after a previous diagnosis and resection of resectable pancreatic cancer. If it turns out that patients with asymptomatic

metastatic pancreatic cancer are incurable, the start of palliative systemic treatment could be at initial presentation, or could be delayed until disease-related symptoms occur. Whether starting palliative systemic therapy immediately after diagnosis has survival benefit and weighs up against the potential side effects is currently under debate, and will be investigated in this trial.

Rationale
Prolonging life and improving or maintaining quality of life are the main goals of palliative systemic treatment in patients with metastatic pancreatic cancer. It has yet to be determined as to when to commence chemotherapy during the disease course in patients with asymptomatic metastatic disease. Since patients with metastatic pancreatic cancer have a limited life expectancy, it is important to determine the timing of start of chemotherapy in order to optimise the benefits of chemotherapy relative to the side effects. Typically, patients who start with systemic therapy experience an initial decrease in quality of life. Especially in patients without symptoms there is little to gain. So, one could argue to start chemotherapy only in case of symptoms. In this way, quality of life may improve again if treatment proves effective. On the other hand, starting chemotherapy immediately after diagnosis could maximize survival benefit since disease control may be more difficult to achieve once tumor burden has increased over time.

Study objective

Primary objective:
To assess the effect of immediate versus delayed start of chemotherapy on quality adjusted survival in patients with metastatic pancreatic cancer.

Secondary Objectives:
To determine time to disease progression after randomization
To determine the adverse events according to NCI CTC version 5.0

Exploratory Objectives:
To determine change in CA 19.9

Study design

This is a prospective multicenter patient preference cohort study to compare immediate treatment (to begin within 3 weeks of date of diagnosis) or treatment delayed until development of symptoms in patients with metastatic pancreatic cancer.

The treatment schedule will be either FOLFIRINOX or nab paclitaxel in combination with gemcitabine per investigator*s choice, or delayed treatment with FOLFIRINOX or nab paclitaxel in combination with gemcitabine per

investigator*s choice.

For patients that will start with delayed treatment based on symptoms, chemotherapy will start as soon as one of the following criteria is met:
- Decline in performance status to ECOG < 1 or Karnofsky < 80%
- Weight loss more than 5% of the total body weight from the time of study entry
- Persistent nausea requiring medication
- Pain requiring regular narcotic analgesics
- Development of clinically significant third-space fluid collections
- Liver function deterioration in the presence of progressive liver metastases

The regimen of FOLFIRINOX consists of oxaliplatin at a dose of 85 mg/m2, given as a 2-hour i.v. infusion, immediately followed by leucovorin at a dose of 400 mg/m2, given as a 2-hour i.v. infusion, with the addition, after 30 minutes, of irinotecan at a dose of 180 mg/m2, given as a 90-minute i.v. infusion. This treatment will immediately be followed by fluorouracil at a dose of 400 mg/m2, administered by i.v. bolus, followed by a continuous i.v. infusion of 2400 mg/m2 over a 46-hour period. This regimen will be repeated every 2 weeks
The combination of nab-paclitaxel and gemcitabine consist of nab paclitaxel at a dose of 125 mg/m2, given as a 30 minute infusion, followed by gemcitabine at a dose of 1000 mg/m2, given as a 30 minute infusion. Both chemotherapeutic agents will be administered on days 1, 8 and 15 of a 4 week cycle.
Tumor response and progression will be assessed using RECIST version 1.1 criteria. Imaging assessments will be conducted by computed tomography [CT] scans and/or Magnetic Resonance Imaging [MRI]. Tumor assessment will be performed every 2 months.
Toxicities will be graded by the Investigator using the National Cancer Institute (NCI) Common CTCAE Version 5.0 (appendix 2).
The end of the study is defined by the final QoL analysis.

Intervention

- FOLFIRINOX; a combination of oxaliplatin, leucovorin, irinotecan and fluorouracil every 2 weeks

or

- Gemcitabine + nab paclitaxel weekly for 3 weeks, every 4 weeks

Study burden and risks

Postponing chemotherapy can have a negative effect on disease control and tumor burden. In addition to treatment patients have to fill out questionnaires to gain insight in the quality of life.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

1. Signed, written Institutional Review Board/Ethics Committee-approved Informed Consent Form (ICF).
2. Patients with histologically/cytological confirmed diagnosis of metastatic pancreatic ductal adenocarcinoma.
3. Measurable disease on computed tomography (CT) scan per RECIST version 1.1 criteria.
4. Eastern Cooperative Oncology Group Performance Status of 0-1.
5. Life expectancy >= 3 months.
6. Age >= 18 years.
7. No symptoms related to advanced disease.

Exclusion criteria

1. Known central nervous system involvement or brain metastases.
2. New York Heart Association Class III or IV cardiac disease or myocardial infarction within the past 12 months.
3. Any other disease, active, uncontrolled bacterial, viral or fungal infection requiring systemic therapy, metabolic dysfunction, physical examination finding or clinical laboratory finding that leads to reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug, that may affect the interpretation of the results, or that may render the subject at high risk for treatment complications.
4. Inability to comply with study and follow-up procedures as judged by the Investigator.
5. Women currently pregnant or breastfeeding.

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-04-2021
Enrollment:	184
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Fluorouracil
Generic name:	Fluorouracil

Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Irinotecan
Generic name:	Irinotecan
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Leucovorin
Generic name:	Leucovorin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Oxaliplatin
Generic name:	Oxaliplatin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Paclitaxel
Generic name:	Paclitaxel
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	29-01-2021
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-03-2021
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-04-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-07-2021
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-07-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-08-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-10-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-01-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-01-2023
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660 1100 DD Amsterdam 020 566 7389 mecamc@amsterdamumc.nl
Approved WMO Date:	30-03-2023
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660

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Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

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

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2019-004582-40-NL
CCMO	NL72253.018.19