Chemoradiation with gemcitabine in combination with panitumumab for patients with locally advanced pancreatic cancer.

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Phase I part To determine the recommended safe dosing for the combination of chemoradiation with gemcitabine plus panitumumab in patients with inoperable locally advanced pancreatic cancer.Phase II part 1) To investigate the proportion of patients...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Gastrointestinal neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON36705

Source
ToetsingOnline

Brief title
Vectibix

Condition

- Gastrointestinal neoplasms malignant and unspecified

Synonym
pancreas cancer, Pancreatic cancer

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum

Source(s) of monetary or material Support: Amgen B.V. ,Amgen Inc

Intervention

Keyword: Chemoradiation, Gemcitabine, Pancreatic cancer, Panitumumab

Outcome measures

Primary outcome

Primary objective Phase I

1 To determine the recommended safe dosing for the combination of chemoradiation with gemcitabine plus panitumumab in patients with inoperable locally advanced pancreatic cancer.

Primary objectives Phase II

1) To investigate the proportion of patients with inoperable locally advanced pancreatic cancer receiving chemoradiation with gemcitabine plus panitumumab as first line treatment, that is alive and progression-free at 7 months.

2) To evaluate the safety and tolerability for the combination of chemoradiation with gemcitabine, plus panitumumab in patients with inoperable locally advanced pancreatic cancer.

Secondary outcome

Phase I & II part:

1) To assess early signs of clinical activity of the combination of chemoradiation with gemcitabine plus panitumumab in patients with inoperable locally advanced pancreatic cancer.

2) To assess the clinical response rate of the combination of chemoradiation with gemcitabine plus panitumumab in patients with inoperable locally advanced

pancreatic cancer.

3) To assess time-to-progression (TTP) and overall survival amongst patients

with inoperable locally advanced pancreatic cancer receiving chemoradiation

with gemcitabine plus panitumumab as first line treatment.

Study description

Background summary

Based on the radiotherapy potentiating effects of both gemcitabine and EGFR-inhibitors (independent of K-ras mutation status), and the non-overlapping toxicity profiles of gemcitabine and panitumumab, we aim to evaluate the combination of radiotherapy plus gemcitabine and panitumumab in patients with locally advanced inoperable pancreatic cancer in a phase I-II feasibility study aiming for an increase in the PFS. Based on historical data of patients with locally advanced, inoperable, pancreatic cancer treated with chemoradiation, we aim to increase the number of patients who are cancer progression free at 7 months from the historical value of 50% to 70% with combination treatment of chemoradiation with gemcitabine plus panitumumab. In addition to efficacy, we will evaluate treatment toxicity to determine whether this combination strategy is feasible and safe.

Study objective

Phase I part
To determine the recommended safe dosing for the combination of chemoradiation with gemcitabine plus panitumumab in patients with inoperable locally advanced pancreatic cancer.

Phase II part
1) To investigate the proportion of patients with inoperable locally advanced pancreatic cancer receiving chemoradiation with gemcitabine plus panitumumab as first line treatment, that is progression-free at 7 months.

2) To evaluate the safety and tolerability for the combination of chemoradiation with gemcitabine plus panitumumab in patients with inoperable locally advanced pancreatic cancer.

Secondary Aims
1) To assess early signs of clinical activity of the combination of chemoradiation with gemcitabine plus panitumumab in patients with inoperable

locally advanced pancreatic cancer.*
2) To assess the clinical response rate of the combination of chemoradiation with gemcitabine plus panitumumab in patients with inoperable locally advanced pancreatic cancer.
3) To assess time-to-progression (TTP) and overall survival amongst patients with inoperable locally advanced pancreatic cancer receiving chemoradiation with gemcitabine plus panitumumab as first line treatment.

Exploratory aim
To explore the activity of combination chemoradiation with gemcitabine plus panitumumab in relation to response to therapy and:
a) the prevalence of mutant versus wild-type K-ras and B-raf.
b) pre-treatment kinome tumor profiles and serum proteomic profiles.

Study design

This is a phase I/II, multi-center dose escalation study of panitumumab in combination with gemcitabine and radiotherapy in patients with inoperable locally advanced pancreatic cancer. The phase I study will be performed in the VU medical center in Amsterdam. For the phase II part of the study two additional sites will be involved in the Netherlands.

Phase I part:
Patients will be enrolled in cohorts of 3 per dose level. The first 3 patients enrolled will be assigned to dose level 1. If there are no dose-limiting toxicities (DLTs) experienced by the first 3 patients in a cohort during the first 43 days after the first study treatment, additional patients will be entered in the next dose level. Entry of patients into the expansion cohort will not occur until at least 43 days after the last patient in the escalation phase received his first study treatment. At the final dose level recommended for the phase II study a minimum of 6 patients will be treated.
Intra-individual dose escalation is not permitted in order to allow determination of any possible cumulative effect and to evaluate the inherent toxicity of the regimen at any given dose level and before starting with the next cohort.

Phase II part:
Up to approximately 56 patients will be treated at the MTD level of panitumumab as established in the phase I part of the study.
Based on historic data of patients with pancreatic cancer treated with gemcitabine based chemoradiation, we aim to increase the number of patients who are alive and cancer progression free at 7 months from the historical value of 50% to 70% with combination treatment of chemoradiation plus panitumumab. In addition, we consider this increase meaningfull as long as the combination treatment does not increase combination treatment related toxicity grade 3 or 4 in * 30% of patients.

Interim analysisfor 7 months progression free survival and toxicity:
An interim analysis (IA) will be performed after treatment of a total of 24 patients that reached 7 months progression free survival or did progress within the first 7 months. If the number of patients progression free (PF) at 7 months is *12 then the study will terminate due to lack of response. In addition, at the same IA of 24 patients, the number of patients with combination treatment related grade 3/4 toxicity will be analyzed and if this number is 12 or higher patients the study will be terminated because of unacceptable toxicity. Enrolment of new patients (more than 24) up to 30 will continue as long as no IA can be performed due to rapid inclusion of patients within the first 7 months after start of the phase II part.

Intervention

Phase I part:
Cohorts of 3-6 patients will be treated with escalating doses of panitumumab to determine the recommended safe dosing for the combination of chemoradiation with gemcitabine plus panitumumab in patients with inoperable locally advanced pancreatic cancer.

Phase II part:
Up to approximately 56 patients will be treated at the MTD level of panitumumab (in combination with gemcitabine and radiation therapy) as established in the phase I part of the study.

Study burden and risks

Possible side effects of gemcitabine: nausea and vomiting, low lymphocyte and erythrocyte count. Patients can suffer from influenza-like syndroms like fever, headache, backpain, chills, muscle pain and fatigue.

The most common side effects of panitumumab are skin rash and diarrhea (mild), fatigue, nausea, infusion reactions (influenza-like syndroms, allergy), shortness of breath, low magnesium in blood and keratitis.

The possible side effects of radiotherapy are: fatigue, nausea, loss of apetite, weight loss and diarrhea.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Histological or cytological confirmed pancreatic cancer.
2. Not eligible for curative resection.
3. No distant metastases present.
4. Previously untreated with chemotherapy and anti-cancer biologicals for current malignancy.
5. No other current malignant disease.
6. Measurable or evaluable disease as defined by RECIST 1.1 criteria.
7. Performance status 0*2 Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) Scale.
8. Age * 18 years.
9. Adequate haematological and biological functions:
* Bone marrow function:
a. Neutrophils * 1.5 x 10E9/L
b. Platelets * 100 x 10E9/L
c. Hb * 10 g/dL (<= 6 mmol/L)
* Hepatic function:
a. AST/ALT and alkaline phosphatase (ALP) * 2.5 x institutional upper limit of normal (ULN)
b. Bilirubin * 1.5 times institutional ULN
* Renal function:

Serum creatinine * 1.5 times institutional ULN.
* Metabolic Function:
a. Magnesium * lower limit of normal
b. Calcium * lower limit of normal.
10. No imminent bowel obstruction.
11. No active bleeding.
12. No uncontrolled infection.
13. Patients with reproductive potential must use effective contraception. Female patients must have a negative pregnancy test.
14. Signed informed consent.

Exclusion criteria

1. Participation in another therapeutic clinical study within 30 days of enrollment or during this clinical study.
2. No adequate radiation therapy possible: based on the opinion of the radiation oncologist when radiation therapy cannot be performed because radiation field is too large (PTV volume too large or OAR too high)
3. History of allergic reactions to gemcitabine or antibody treatment.
4. Presence of any serious concomitant systemic disorders incompatible with the clinical study (e.g. uncontrolled inter-current illness including ongoing or active infection, uncontrolled hypertension).
5. Clinically significant cardiovascular disease (including myocardial infarction, unstable angina, symptomatic congestive heart failure, serious uncontrolled cardiac arrhythmia) within 1 year before enrolment/randomization
6. History of interstitial lung disease e.g. pneumonitis or pulmonary fibrosis or evidence of interstitial lung disease on baseline chest CT scan.
7. Presence of any significant central nervous system or psychiatric disorder(s) that would hamper the patient*s compliance.
8. Pregnant or breastfeeding women.
9. Absence of adequate contraception for both male and female fertile patients for the duration of the study; and also for six months after last treatment.
10. Known positive status for HIV and/or hepatitis B or C.
11. Any reason why, in the investigator*s opinion, the patient should not participate in the study.
12. Drug or alcohol abuse.

Study design

Design

Study phase: 2

Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	14-07-2010
Enrollment:	63
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Gemzar
Generic name:	Gemcitabine
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Vectibix
Generic name:	Panitumumab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	22-02-2010
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-06-2010
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-02-2011
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-03-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-05-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	31-05-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-06-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-10-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-12-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-03-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-02-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	31-07-2014
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	30-10-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2010-018327-26-NL
CCMO	NL30918.029.10