A phase I/ II, non-randomized, feasibility/ safety and efficacy study of the combination of everolimus, cetuximab and capecitabine in patients with metastatic pancreatic cancer

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In this study we want to determine the activity and safety of concurrent interruption of the MAPK and PI3K pathways by EGFR and mTOR inhibition in patients with metatastatic pancreatic cancer

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

Summary

ID

NL-OMON32581

Source
ToetsingOnline

Brief title
CEC-study

Condition

- Gastrointestinal neoplasms malignant and unspecified

Synonym
metastatic 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: EGFR inhibition, mTOR inhibition, pancreatic cancer, Pharmacodynamics

Outcome measures

Primary outcome

For the phase I part: Assessment of the dose limiting toxicity (DLT) and the maximal tolerated dose (MTD) of the combination of everolimus, cetuximab and capecitabine.

For the phase II part: Determination of the efficacy and feasibility of the combination of everolimus, cetuximab and capecitabine. Primary endpoint of the study will be response rate.

Secondary outcome

- Time to progression (TTP)

- Response duration

- Toxicity profile

- Pharmacodynamics

Study description

Background summary

Pancreatic cancer patients have one of the worst prognoses among all cancer types with a 5 year survival rate of less than 5%. Despite significant changes during the last decade in our molecular knowledge on this disease, the prognosis and management of pancreatic cancer have remained unchanged. Although epidermal growth factor receptor (EGFR) mutation is rare in pancreatic

cancer (2-4%), overexpression of EGFR occurs in at least one-half of all pancreatic cancers and correlates with a poor prognosis. Recently several studies explored the activity of epidermal growth factor receptor (EGFR) inhibitors in patients with pancreatic cancer. But, in spite of its biological background, EGFR inhibitors have no or only modest clinical activity in pancreatic cancer. One of the mechanisms responsible for this observation will be the presence of other activated pathways. Therefore, the best change of success will be realized when using a combination of agents that inhibit separate pathways known to be critical to the survival of the tumour. Combining a monoclonal antibody against the EGFR and inhibition of the phosphoinositide 3-kinase (PI3K) pathway account for potential candidates of the above combinatorial approaches since they inhibit both the upstream and downstream mediators of the same signal transduction pathways. Indeed, pre-clinical data suggest that combined inhibition of the PI3K pathway (via its downstream effector protein mTOR) and EGFR is synergistic in anti-cancer activity, can prevent upregulation of the PI3K pathway and restore EGFR resistance to EFGR inhibitors.
There is a strong rationale to combine targeted therapy with classical cytotoxic drugs. For pancreatic cancer gemcitabine would be the drug of choice, but a phase I study demonstrated severe bone marrow toxicity by the combined mTOR inhibition and gemcitabine (already at the gemcitabine dose level of 600 mg /m2). Therefore in our study we will add the chemotherapeutic agent capecitabine. In addition to the rationale combining targeted with cytotoxic therapy, there is another argument to choose this cytotoxic agent. Thymidine phosphorylase (TP) is the key enzyme in the metabolic conversion of 5-FU to its active cytotoxic form, thereby enhancing 5-FU cytotoxicity. On the other hand TP promotes tumour angiogenesis by enzymatic conversion of thymidine into dRib. Since it has been demonstrated that mTOR inhibition can block dRib, combining the mTOR inhibitor everolimus and capecitabine can therefore counteract this TP-based escape mechanism under 5-FU treatment.

Study objective

In this study we want to determine the activity and safety of concurrent interruption of the MAPK and PI3K pathways by EGFR and mTOR inhibition in patients with metatastatic pancreatic cancer

Study design

This phase I/II non randomized single center study will be performed as a two step design. Part I is dose finding, whereby dose escalations will be performed for everolimus and capeciatbine. Part II is the efficacy study. At the MTD doses in part II biomarker studies will be performed in blood and tumor tissue.

Study design phase I part:
The first week patients will be treated with everolimus alone. Capecitabine

will be administered for 14 days in a 3 weekly cycle, starting on day 8.
Cetuximab will be administered weekly, starting at day 8. The dose is fixed for cetuximab during study treatment, whereas the doses of everolimus and capecitabine will differ per dose level.

First dose level:
Everolimus 5 mg daily continuously, Capecitabine 600 mg/m2 bid for 2 weeks every 3 weeks, Cetuximab 400mg/m2 (120 min infusion) first dose, thereafter 250 mg/m2 (60 min infusion) weekly.
Second dose level:
Everolimus 10 mg daily continuously, Capecitabine 600 mg/m2 bid for 2 weeks every 3 weeks, Cetuximab 400mg/m2 (120 min infusion) first dose, thereafter 250 mg/m2 (60 min infusion) weekly.
Third dose level:
Everolimus 10 mg daily continuously, Capecitabine 800 mg/m2 bid for 2 weeks every 3 weeks, Cetuximab 400mg/m2 (120 min infusion) first dose, thereafter 250 mg/m2 (60 min infusion) weekly.

Study design phase II part

At the MTD 14-25 patients with pancreatic cancer will be included.
In the phase II part, everolimus will be administered during one week before start of cetuximab. At day 8 the first dose of cetuximab will be administered. Capecitabine will be started one week thereafter. This enables us to perform pharmacodynamic studies to assess biomarker changes during the different phases of treatment.

Everolimus will be administered continuously in a dose of 5 or 10 mg orally once daily (dependent on MTD from part 1).
Capecitabine will be administered orally in a dose of 400 - 800 mg/m2 twice daily for 14 days followed by one week rest (dependent on MTD from part 1).
Patients will receive cetuximab infusions via an infusion pump, with an initial dose of 400 mg/m² (over 120 min) and subsequent weekly infusions of 250 mg/m² (over 60 min), starting day 8.

Intervention

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Study burden and risks

Each cycle contains 3 weeks, in which the patients take everolimus daily and capecitabine the first 2 weeks, followed by one week rest. Cetuximab will be administred via an infusion pump weekly. At various days during treatment the patient will come to the hospital for blood investigations and evaluation of the toxicity profile. After 3 cycles (9 weeks) during the treatment fase a CTscan will be performed to establish response.
The expected adverse events of everolimus are nausea, vomiting, rash, fatigue, anorexia, hyperlipidemia, hyperglycaemia, diarrhoea, elevation of transaminases, bone marrow suppression, lung toxicity, headache and stomatitis. The most common reported side effects of capecitabine are: diarrhoea, nausea and vomiting, stomatitis, anorexia, hand-foot syndrome, fatigue and bone marrow suppression. Adverse events of cetuximab are skin reaction and infusion related reactions.

Contacts

Public
Academisch Medisch Centrum

Meibergdreef 9
1105 AZ
Nederland
Scientific
Academisch Medisch Centrum

Meibergdreef 9
1105 AZ
Nederland

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age

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

Inclusion criteria

*Cytological or histological confirmed adenocarcinoma of the pancreas
*Metastatic pancreatic cancer
*ECOG/ WHO performance 0-2
*Age > 18 years
*Life expectancy > 3 months
*Adequate renal function (creatinine < 150 µmol/L)
*Adequate liver function (bilirubin < 2.5 times upper limit of normal, ALAT or ASAT < 5.0 times upper limit of normal in case of liver metastases and < 2.5 the upper limit of normal in absence of liver metastases
*Adequate bone marrow function (WBC > 3.0 x 10 9/L, platelets > 100 x 10 9/L)
*Mentally, physically, and geographically able to undergo treatment and follow up

Exclusion criteria

*Clinical or radiological evidence of CNS metastases
*Pregnancy (positive serum pregnancy test) or patients (male/female with reproductive potential (without effective contraception) or lactation
*Concomitent treatment with other experimental drugs or any other anticancer therapy
*Previous treatment with cetuximab
*Other malignancy within the last 5 years, except adequately treated basocellular skin carcinoma or cervical carcinoma
*Medical or physiological conditions that would not permit the subject to complete the study or sign informed consent
*Serious concomitant systemic disorder that would compromise the safety of the patient, at the discretion of the investigator

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-01-2009
Enrollment:	35
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	certican
Generic name:	everolimus
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	erbitux
Generic name:	cetuximab
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	xeloda
Generic name:	capecitabine
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	06-02-2009
Application type:	First submission
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	EUCTR2008-007686-24-NL
CCMO	NL25955.018.08