Optimalisatie van de behandeling met cetuximab voor patienten met uitgezaaide dikkedarm kanker door de opname van 89-zirconium gelabeld cetuximab te beoordelen middels PET-scan

No registrations found.

Ethical review	Positive opinion
Status	Recruiting
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON26385

Source
Nationaal Trial Register

Brief title
IMPACT-CRC

Health condition

Metastatic colorecal adenocarcinoma, K-RAS and N-RAS wild type.

Sponsors and support

Primary sponsor: VU University Medical Center (central site)
UMC Groningen
Radboud UMC
Source(s) of monetary or material Support: Alpe d'HuZes (KWF)

Intervention

Outcome measures

Primary outcome

89Zr-cetuximab uptake in non-hepatic metastases (corrected VOIs) and the correlation with clinical benefit rate.

89Zr-cetuximab uptake in non-hepatic metastases with increased dosing of cetuximab (corrected VOIs).

The clinical benefit rate (CR, PR and SD) based upon 89Zr-cetuximab image adjusted dosing

Secondary outcome

1. The % uptake (of total injected) 89Zr-cetuximab in non-tumor liver tissue and hepatic metastases (corrected VOIs).

2. 18F FDG-PET uptake before and after 2 weeks of cetuximab treatment.

3. Tumor perfusion measured with 15O-H2O-PET before and after 2 weeks of cetuximab treatment.

4. Grade of skin toxicity as measured by predefined criteria.

5. Serum magnesium levels before and during treatment.

6. EGFR expression and saturation with cetuximab in tumor and skin biopsies.

7. (Phospho)proteomic and peptide profiles in tumor, blood and skin biopsies before and during treatment with cetuximab.

8. Mutation analysis of K-RAS, N-RAS, B-RAF and other genes potentially involved in response to therapy before, during therapy with cetuximab and at progression in circulating tumor DNA.

9. Mutation analysis of B-RAF and other genes potentially involved in response to therapy before and during therapy with cetuximab in tumor biopsies.

10. PFS and OS in the standard treatment group, in the dose escalation group and in the dose extension group.

11. miRNA in blood and tumor biopsies before and during treatment with cetuximab

12. Effects of skin toxicity due to (escalating doses of) cetuximab monotherapy on health related QoL.

13. Utility and health technology assessment of the intervention and the gain of quality-adjusted life years (QALY).

Study description

Background summary

Currently, third line systemic treatment for patients with advanced, wild type K-RAS and as has recently been demonstrated with wild type N-RAS (thereafter referred to as wild type RAS) colorectal cancer (CRC) includes EGFR inhibition with the anti-EGFR antibody cetuximab. This type of treatment has a modest but significant beneficial activity in this patient group with improved progression-free and overall survival. Although it is known that patients with advanced wild type RAS CRC will not respond to anti-EGFR treatment, it is not understood why patients with wild type RAS CRC do not all benefit from this type of therapy. Apart from other potential gene mutations involved in response to treatment, differences in the variability of pharmacokinetics may play a crucial role in the response to anti-EGFR treatment. In non-responders insufficient drug accumulation may occur in the tumor due to pharmacokinetic processes, such as cetuximab sequestration in the liver which expresses high levels of EGFR, or due to low levels of EGFR expression in tumor lesions. Our main hypothesis is that uptake of cetuximab in metastases is required for response and that achieving cetuximab uptake by increasing its dose will result in improved clinical benefit in patients with advanced CRC with wild type RAS.

Objectives:

PART I:

1) to demonstrate 89Zr-cetuximab uptake in non-hepatic metastases at standard dose or at cohort wise increased cetuximab doses (dose escalation).

2) to determine the association between 89Zr-cetuximab uptake in non-hepatic metastases and treatment response.

PART II

To determine the response rate with an optimized dose of cetuximab as has been selected in part 1 in patients without 89Zr-cetuximab tumor uptake at standard dose of cetuximab (dose extension).

Study design: This is a multicentre non-randomized intervention study; phase I-II dose escalation/extension study.

Study population: Patients with histopathologically confirmed advanced CRC with wild type RAS, without local treatment options, aged ≥ 18 years, with a life expectancy of at least 12 weeks, who are candidates for anti-EGFR antibody monotherapy (3rd line palliative treatment).

Intervention: In the first part we will perform an exploratory PET study in patients with metastasized, RAS wild type CRC without local treatment options, who will be treated with cetuximab. We hypothesize that uptake of 89Zr-cetuximab in metastases is required for response to cetuximab. We will analyze targeting of 89Zr-cetuximab to metastases and the association between 89Zr-cetuximab tumor uptake and tumor response. Early response evaluation will be done with 18F-FDG PET. In a subgroup of 20 patients with metastasis within the field of view (18 cm) including the heart, tumor perfusion will be measured with 15O-water PET scans. In addition, we will investigate the hypothesis that increasing the cetuximab dose results in uptake in patients without uptake in metastases of 89Zr-cetuximab when cetuximab is given at the standard dose regimen. In the second part we will study whether dose adjustments based on 89Zr-cetuximab targeting results in an improved response and clinical benefit rate. In addition, EGFR expression and saturation with cetuximab is studied in tumor biopsies obtained during treatment. Molecular pathways activated by EGFR and kinase activities as well as phosphoproteomics will be studied in tumor biopsies and skin biopsies before and after start of treatment. In addition, the relation of microRNA (miRNA) and peptide profiles in relation to response to therapy will be studied.

Study objective

About half of the patients with advanced CRC, RAS wild type, will respond to anti-EGFR treatment, it is unknown why not all patients benefit from this type of therapy. Although other mutations in downstream signaling molecules (e.g. B-RAF) may play a role, this does not explain it completely. We hypothesize that differences in response to cetuximab treatment is primarily due to variability in the pharmacokinetics and -dynamics of the antibody, for instance more sequestration of cetuximab in the liver resulting in a reduced amount of cetuximab available for tumor tissue.

Using PET-scan we will evaluate the 89Zr-cetuximab uptake in extra-hepatic metastases. If no uptake is present we hypothesize that these patients will not respond to the treatment. By

selecting these patients and preform a dose escalation/extention we hope to improve the clinical benefit of the cetuximab treatment.

Study design

The first treatment with cetuximab will be done at day 1, at day 6 the PET-scan is made. On day 15 the second cetuximab treatment will be given, the dose depends on the first PET-scan. If dose escalation/extension takes place a second PET-scan will be done on day 21.

Hereafter a biweekly infusion of cetuximab will be given. Every 2 months a CT-scan will be performed for response evaluation (according to RECIST 1.1). The patient continues with the treatment until progressive disease, unacceptable toxicity or upon patient's request.

Intervention

89Zr-cetuximab PET scan: After a therapeutic dose of cetuximab, 10mg of 89Zr-cetuximab is injected. Six days after injection a PET-scan will be made. If this scan is considerd positive, meaning uptake in extra-hepatic metastases is present, the normal dose of cetuximab will be continued.

If the first PET-scan is negative, we will increase the dose of cetuximab (3 by 3 cohort design) and repeat the PET-scan. The patient will continue the higher dose biweekly.

Furthermore we will preform a 18F-FDG PET scan and 15O-H2O PET scan, on baseline and after 2 weeks of treatment, to evaluate early changes in respectively metabolic changes and changes in tumor perfusion.

At baseline and after 3-4 week of treatment a skin biopsy and tumor biopsy will be done. We will preform oncogenic mutation analysis, we will determine EGFR expression and saturation.

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Eligibility criteria

Inclusion criteria

• Advanced colorectal adenocarcinoma

• Subjects must have been treated according to standard care with palliative chemotherapy including a fluoropyrimidine (e.g. fluorouracil or capecitabine), irinotecan, and oxaliplatin or had contra-indications to treatment with these drugs.

• No local treatment options

• Life expectancy of at least 12 weeks.

• Age >= 18 years.

• Histological or cytological documentation of cancer is required.

• Tumor material must be tested wild type for the K-RAS (codon 12, 13, 61, 117, 146) and N-RAS (codon 12, 13, 61, 117, 146) genes.

• Subjects have at least one measurable lesion ≥ 2 cm outside the liver. Lesions must be evaluable by CT or MRI according to Response Evaluation Criteria in Solid Tumors (RECIST 1.1).

• ECOG Performance Status of 0, 1 or 2

• Adequate liver and renal functions as assessed by the following laboratory requirements to be conducted within 7 days prior to start of treatment:

o Total bilirubin ≤ 1.5 times the upper limit of normal

o ALT and AST ≤ 2.5 times upper limit of normal (≤ 5 times upper limit of normal for subjects with liver involvement of their cancer)

o Serum creatinin ≤ 1.5 times upper limit of normal or a calculated creatinin clearance >= 50 ml/min

• Signed informed consent must be obtained prior to any study specific procedures.

Exclusion criteria

• Previous exposure to an anti-EGFR therapy

• Significant skin condition interfering with treatment

• Pregnant or breast-feeding subjects. Women of childbearing potential must have a negative pregnancy test performed within 7 days of the start of treatment. Both men and women enrolled in this trial must agree to use adequate barrier birth control measures (e.g., cervical cap, condom, and diaphragm) during the course of the trial. Oral birth control methods alone will not be considered adequate on this study, because of the potential pharmacokinetic interaction between study drug and oral contraceptives. Concomitant use of oral and barrier contraceptives is advised. Contraception is necessary for at least 6 months after receiving study drug.

• Concurrent anticancer chemotherapy, immunotherapy or investigational drug therapy during the study or within 4 weeks of the start of study drug.

• Radiotherapy to the target lesions during study or within 4 weeks of the start of study drug. Palliative radiotherapy will be allowed.

• Major surgery within 28 days of start of study drug.

• Substance abuse, medical, psychological or social conditions that may interfere with the subject’s participation in the study or evaluation of the study results.

• Any condition that is unstable or could jeopardize the safety of the subject and their compliance in the study.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	N/A , unknown

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	01-05-2014
Enrollment:	85
Type:	Anticipated

Ethics review

Positive opinion

Date:	06-05-2014
Application type:	First submission

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
NTR-new	NL4460
NTR-old	NTR4583
Other	: 2013.265 METc VUmc

Study results