Optimalisatie van de behandeling van uitgezaaide darmkanker met cetuximab middels opname metingen van 89Zr gelabeld cetuximab mbv PET.

No registrations found.

Ethical review	Positive opinion
Status	Recruitment stopped
Health condition type	-
Study type	Observational non invasive

Summary

ID

NL-OMON25781

Source
Nationaal Trial Register

Health condition

metastatic colorectal cancer,

Sponsors and support

Primary sponsor: VU Univeristy Medical Center
Source(s) of monetary or material Support: fund = initiator = sponsor

Intervention

Outcome measures

Primary outcome

To demonstrate uptake of 89Zr-cetuximab in non-hepatic tumor lesions using immuno-PET when administered during the loading dose of cetuximab.

Part two - Primary objective:

To investigate whether there is an association between uptake of cetuximab in non-hepatic tumor lesions and response according to RECIST 1.1 criteria.

Secondary outcome

1. To investigate whether there is an association between levels of uptake of 89Zr-cetuximab in the liver compared to levels of uptake in non-hepatic tumor lesions;

2. To explore whether the response observed on [18F]-FDG-PET can serve as an early response marker for future response to targeted therapy according to RECIST 1.1;

3. To explore whether there is an association between 89Zr-cetuximab uptake in non-hepatic tumor lesions, grade of skin toxicity and response according to RECIST 1.1.

Study description

Background summary

3rd line standard treatment of patients with metastatic colorectal cancer (CRC) harboring K-ras wild type consists of anti-EGFR treatment with either cetuximab or panitumumab. 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 well known that patients with advanced CRC harboring a K-Ras mutation will not respond to anti-EGFR treatment, it is not understood why patients with K-Ras wild type CRC do not all benefit from this type of therapy. In order to optimize treatment of these patients as well as health care costs, it is extremely important to identify those patients who will respond to treatment with an EGFR inhibitor at an early stage.

We hypothesize that the differences in response to treatment with cetuximab are due to variability in the pharmacokinetics and -dynamics of the antibody. Thus, we hypothesize that patients who do not respond to anti-EGFR treatment, have insufficient drug levels in tumor tissue. We hypothesize that this is due to pharmacodynamic processes such as sequestration of cetuximab in the liver which expresses high levels of EGF receptor.

With the introduction of immuno-positron emission tomography (PET), an attractive novel option to visualize molecular interactions has been developed using the combination of PET with labeled mAbs. Cetuximab labeled with zirconium-89 (89Zr) has been successfully generated (GMP) and is available for this study. Previous studies have shown excellent stability of this compound and 89Zr is shown to be safe in humans. We will use 89Zr-cetuximab to demonstrate tumor targeting by imaging and explore the relation of uptake with treatment response. With this approach we hope to achieve a better understanding of the mechanisms of action of this therapeutic mAb in metastasized CRC and eventually

develop strategies that may improve efficacy of cetuximab treatment.

Study objective

N/A

Study design

The detection of 89Zr-cetuximab uptake in non-hepatic tumor lesions (present/absent; present being defined as levels measured in ROI's > standard deviation of background +1).

Part two – Primary endpoint:

The % uptake (of total injected) 89Zr-cetuximab in non-hepatic tumor lesions as measured in ROI's corrected for background levels.

Part two - Secondary endpoints:

1. The % uptake (of total injected) 89Zr-cetuximab in liver lesions as measured in ROI's corrected for background levels;

2. [18F-]FDG PET measurements (SUVmax) before and after 4 weeks of treatment with cetuximab;

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

Intervention

Patients will be treated with cetuximab. For pharmacodynamic purposes PET-imaging with 89Zr-labelled cetuximab will be performed. In addition, two [18F-]-FDG PET-CT will be performed to explore early response. Patients will undergo blood sampling and two skin biopsies for pharmacodynamic purposes of 89Zr-labelled cetuximab and kinase activity profiles, respectively.

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Eligibility criteria

Inclusion criteria

1. Advanced colorectal adenocarcinoma;

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

3. Age ≥ 18 years;

4. Histological or cytological documentation of cancer is required;

5. Tumor material must be tested wild type for the K-Ras gene;

6. Subjects have at least one measurable lesion outside the liver. Lesions must be evaluated by CT-scan or MRI according to Response Evaluation Criteria in Solid Tumors (RECIST 1.1);

7. ECOG Performance Status of 0, 1 or 2;

8. Adequate liver and renal functions as assessed by the following laboratory requirements to be conducted within 7 days prior to screening:

A. Total bilirubin ≤ 1.5 times the upper limit of normal;

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

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

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

Exclusion criteria

1. Previous exposure to an anti-EGFR therapy;

2. Significant skin condition interfering with treatment;

3. Insulin dependency;

4. 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;

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

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

7. Major surgery within 28 days of start of study drug;

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

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

Study design

Design

Study type:	Observational non invasive
Intervention model:	Parallel
Allocation:	Non controlled trial
Masking:	Open (masking not used)

Control:	N/A , unknown

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	30-12-2011
Enrollment:	25
Type:	Actual

Ethics review

Positive opinion

Date:	15-05-2012
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	NL3287
NTR-old	NTR3433
Other	METC VUmc : 2010/323
ISRCTN	ISRCTN wordt niet meer aangevraagd.

Study results

Summary results
N/A