Image guided treatment optimalization with cetuximab for patients with metastatic colorectal cancer: IMPACT - CRC

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PART I: 1) to demonstrate 89Zr-cetuximab uptake in non-hepatic tumor lesions at standard dose or at cohort wise increased cetuximab doses (dose escalation). 2) to determine the association between 89Zr-cetuximab uptake in non-hepatic tumor lesions...

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

Summary

ID

NL-OMON50209

Source
ToetsingOnline

Brief title
IMPACT-CRC

Condition

- Gastrointestinal neoplasms malignant and unspecified

Synonym
metastatic colorectal cancer; advanced intestinal cancer

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum

Source(s) of monetary or material Support: KWF-Alpe d□Huzes

Intervention

Keyword: cetuximab, colorectal cancer, panitumumab, PET imaging

Outcome measures

Primary outcome

Part 1A:

89Zr-cetuximab uptake in non-hepatic tumor lesions (corrected VOIs);

Clinical benefit rate

Part 1B:

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

Part 2:

Association between CBR and early response evaluation using 18F-FDG PET.

CBR is defined as the sum of CR, PR and SD according to RECIST 1.1 at 3 months after treatment start.

Corrected VOIs are defined as measurements in VOI corrected for background levels.

Secondary outcome

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

2) 18F FDG-PET uptake before and after 2 weeks of cetuximab/ panitumumab

treatment.

3) Grade of skin toxicity as measured by predefined criteria in a skin biopsy

(collected untill july 2020).

Study description

Background summary

Currently, third line systemic treatment for advanced, wild type K-RAS, N-RAS and B-RAF 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 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 and N-RAS wild type 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 tumor lesions 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 K-RAS, N-RAS and B-RAF.

Study objective

PART I:
1) to demonstrate 89Zr-cetuximab uptake in non-hepatic tumor lesions at standard dose or at cohort wise increased cetuximab doses (dose escalation).
2) to determine the association between 89Zr-cetuximab uptake in non-hepatic tumor lesions and treatment response.
3) to determine the association between metabolic change (evaluated with 18F-FDG PET after 2 weeks of treatment) and treatment response.

PART II
1)Validate early response evaluation with 18F-FDG PET and the association with treatment benefit.
2) Evaluate optimal quantification methods for 18F-FDG PET images

Study design

In the first part we will perform an exploratory PET study in patients with metastasized, K-RAS, N-RAS and B-RAF wild type CRC who will be treated with cetuximab. We hypothesize that uptake of 89Zr-cetuximab in tumor lesions is required for response to cetuximab. We will analyze targeting of 89Zr-cetuximab to tumor lesions and the association between 89Zr-cetuximab tumor uptake and tumor response. Early response evaluation will be done with 18F-FDG PET and tumor lesion perfusion will be measured with H215O PET scans. In addition, we will investigate the hypothesis that increasing the cetuximab dose results in uptake in patients without uptake in tumor lesions 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 (with patients included untill july 2020, after this skin biopsies will no longer be collected). In addition, the relation of microRNA (miRNA) and peptide profiles as well as circulating tumor DNA in relation to response to therapy will be studied.

Intervention

Part I: two-weekly cetuximab infusion in dosis escalataion/extension protocol

Part I: observational two-weekly cetuximab/ panitumumab infusion protocol

Study burden and risks

Upon enrolment in this study, patients will be asked to undergo two tumor biopsies and (optional) skin biopsies, one before and one during treatment. During therapy, follow-up will include standard laboratory analysis, collection of blood for expermental purposes, immuno-PET and 18F-FDG PET on regular visits to the outpatient clinic. Side effects of the medication and adverse events as a consequence of the tumor- and skin biopsies (skin biopsies collected up to july 2020) may occur. The radiation exposure is acceptable and requires no shielding after injection of 89Zr-labeled cetuximab. Patients may benefit from disease regression or stabilization as cetuximab has proven clinical benefit in this patient population.

Contacts

Public
Vrije Universiteit Medisch Centrum

De Boelelaan 1117
Amsterdam 1081HV
NL
Scientific
Vrije Universiteit Medisch Centrum

De Boelelaan 1117
Amsterdam 1081HV
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Subjects are eligible if they meet the following criteria:
* Advanced colorectal adenocarcinoma
* 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.
* Age * 18 years.
* Histological or cytological documentation of cancer is required.
* Tumor material must be tested wild type for the K-RAS, N-RAS and B-RAF genes.
* Tumor lesions:
- Part 1: 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).
- Parts 2: Subjects have at least one measurable tumor lesion * 1 cm, including liver tumor lesion. 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
* Signed informed consent must be obtained prior to any study specific

procedures.
* Life expectancy * 12 wk

Exclusion criteria

Subjects who meet the following criteria at the time of screening will be excluded:
* 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 2 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 phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	23-05-2014
Enrollment:	151
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Erbitux
Generic name:	cetuximab
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Vectibix
Generic name:	panitumumab
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	30-08-2013
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-10-2013
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-03-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-04-2014
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-08-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-05-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-09-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-10-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-11-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-01-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-02-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-07-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-07-2017
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-01-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-03-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-06-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-07-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	31-07-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-03-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-05-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-11-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-08-2020
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	EUCTR2013-002023-41-NL
ClinicalTrials.gov	NCT01691391
CCMO	NL45039.029.13