Phase I clinical study of the feasibility of pretargeted radioimmunotherapy of an anti-CEA bispecific antibody and Lu-177 labeled peptide in patients with advanced colorectal cancer

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To determine the feasibility, toxicity and safety of anti-CEA x anti hapten bispecific antibodies (TF2) and Lu-177-labelled di-HSG-DOTA peptide (IMP-288) in patients with advanced colorectal carcinoma.

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

Summary

ID

NL-OMON32192

Source
ToetsingOnline

Brief title
PRIT

Condition

- Gastrointestinal neoplasms malignant and unspecified

Synonym
colorectal neoplasms, large bowel cancer

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Sint Radboud
Source(s) of monetary or material Support: KWF-subsidie: KUN 2008-4038

Intervention

Keyword: antibodies, bispecific, clinical trial, colorectal neoplasms, phase I, radioimmunotherapy

Outcome measures

Primary outcome

Toxicity, as defined in NCI Common Terminology Criteria for Adverse Events

(CTCAE v 3.0)

Secondary outcome

Pharmacokinetics and biodistribution of bispecific antibody TF2 and

Lu-177-labeled IMP-288 peptide;

Tumor response using RECIST criteria

Study description

Background summary

Radioimmunotherpay is an effective therapy for hematologic malignicies. Two radiolabeled anti-CD20 antibodies are registered for Non-Hodgkin*s Lymphoma. The treatment of solid tumors with the same technique is suboptimal, with a low percentage of the injected dose that will reach the tumor, and signicifant bone marrow toxicity. One of the methods to improve the efficacy is pretargeting with bispecific antibodies, that are anti-tumor as well as anti-hapten. First the antibody will be (intravenously) administered, and after its clearance from the circulation the radiolabeled hapten will be given. For colorectal tumors the humanized anti-CEA x anti-HSG bispecific antibody, TF2, and the di-HSG-DOTA peptide, IMP-288 are developed. In preclinical studies it is shown that the pretargeting system can bring higher activity doses to the tumor. A therapeutic study in mice has shown superior therapeutic effects compared to (non-pretargeted) radioimmunotherapy. No clinical studies have been performed

with TF2 and/or IMP-288.

Study objective

To determine the feasibility, toxicity and safety of anti-CEA x anti hapten bispecific antibodies (TF2) and Lu-177-labelled di-HSG-DOTA peptide (IMP-288) in patients with advanced colorectal carcinoma.

Study design

Phase I clinical trial

Intervention

All patients receive intravenously TF2 and radiolabeled IMP-288. The dose of IMP-288 will be the same for each patient. Variation in the TF2 dose and the interval between TF2 and IMP-288 will be executed in four cohorts. Cohort 1 will receive 150 mg TF2, and five days later IMP-288. Cohort 2: 300 mg, 5-days interval; cohort 3: 300 mg, 3-days interval; cohort 4: 600 mg, 5-days interval. Two weeks prior to administration of Lu-177-IMP288, for each individual patient dosimetric calculations will be performed with a low diagnostic dose of In-111-IMP288. Patients receive TF2 and IMP288 according to the dosing schedule of their cohort. With gamma camera imaging the Lu-177-IMP288 dose will be calculated that will result in a safe radiation dose: 15 Gy for the kidneys and 125 cGy for the bone marrow. In previous clinical trials, with much higher radiation doses that did not exceed 27 Gy for the kidneys and 125 cGy for the bone marrow, rarely long term renal failure or irreversible bone marrow toxicity was observed.
This individual total activity dose Lu-177 will be administered in four successive cycles, each with a quarter of the total dose. The maximal Lu-177 dose per cycle is 3.7 GBq in cohort 1, and 7.4 GBq in the next cohorts.
After each therapeutic cycle of Lu, the cumulative radiation dose to the bone marrow and kidneys will be calculated, to evaluate if this does not exceed the maximum radiation dose.
The minimal period of time for recovery and before to start with the next cycle is eight weeks.

Study burden and risks

Potential risks of this therapy are: reversible bone marrow toxicity, renal toxicity or allergic/infusion reaction on TF2.
The burden for the participating patients consists of frequent visits to the hospital, for venapuncture and gamma camera imaging. These are performed for farmacokinetics, biodistribution and monitoring of potential toxicity. A short admission in an isolated room after the infusion of IMP-288-Lu-177 will prevent radiation to the surroundings. During and till 6-8 hours after TF2 infusion,

patients will be guarded by medical and nursing staff, their vital signs will be checked and they will be observed for adverse reactions or infusion reactions.

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

•Patients with CEA expressing advanced colorectal tumors for which no standard treatment is available
•WHO performance status: 0 or 1
•Having normal hematological funtion:
• Neutrophils > 1.5 x 109/l
• Platelet count > 150 x 109/l, without transfusion
• Hemoglobin > 6 mmol/l

• Total bilirubin < 2 x upper limit of normal (ULN)
• ASAT, ALAT < 3 x ULN
• Serum creatinine < 2 x ULN
•Cockcroft clearance > 50 ml/min
•Negative pregnancy test for women of child¬bearing potential (urine or serum)
•Age over 18 years
•Ability to provide written informed consent

Exclusion criteria

•Known metastases to the brain
•Chemotherapy, external beam radiation or immunotherapy within 4 weeks prior to study. Limited field external beam radiotherapy to prevent pathological fractures is allowed, when unirradiated, evaluable lesions elsewhere are present.
•Prior angiogenesis inhibitors within 4 weeks; bevacizumab within 8 weeks
•Cardiac disease with New York Heart Association classification of III or IV
•Patients who are pregnant, nursing or of reproductive potential and are not practicing an effective method of contraception
•Any unrelated illness, e.g. active infection, inflammation, medical condition or laboratory abnormalities, which in the judgement of the investigator will significantly affect patients* clinical status
•Life expectancy shorter than 6 months.

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-10-2008
Enrollment:	20
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Generic name:	Lu-177-IMP288
Product type:	Medicine
Brand name:	-
Generic name:	IMP288
Product type:	Medicine
Brand name:	-
Generic name:	TF2

Ethics review

Approved WMO Date:	08-09-2008
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	EUCTR2008-004003-55-NL
CCMO	NL23625.091.08