Intraoperative near-infrared fluorescence imaging of colorectal carcinoma with cRGD-ZW800-1 and dedicated imaging systems: A Phase II study

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To assess the feasibility of cRGD-ZW800-1 to visualize tumors in real-time using dedicated NIR fluorescence imaging systems

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Miscellaneous and site unspecified neoplasms malignant and unspecified
Study type	Observational invasive

Summary

ID

NL-OMON50658

Source
ToetsingOnline

Brief title
Phase 2 study with cRGD-ZW800-1

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
Cancer, Malignant tumors

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum

Source(s) of monetary or material Support: LUMC is de sponsor

Intervention

Keyword: cRGD-ZW800-1, Feasibility, Pharmacokinetics, Safety

Outcome measures

Primary outcome

Primary endpoint

To determine the sensitivity of NIR fluorescence imaging with cRGD-ZW800-1

Secondary outcome

Secondary endpoints

To define the optimal dose of cRGD-ZW800-1 for intraoperative near-infrared

fluorescence imaging of tumors.

To assess safety and tolerability of single doses of cRGD-ZW800-1.

Study description

Background summary

Accurate and real-time detection of tumors during surgery remains challenging. Sensitivity of available imaging modalities is often inadequate with respect to margin or metastasis detection. Following SPECT and PET agents, tumor targeted ligands can also be conjugated to NIR (near-infrared, 700-900 nm) fluorophores and being visualized using specific intraoperative near-infrared imaging systems. Traditionally, NIR fluorophores have been developed for a variety of preclinical applications, including labeling to specific ligands, and can be used to understand the fate of intravenously administered anticancer therapeutics, in determining biodistribution, tissue penetration and cellular localization. Currently, NIR fluorescent labeled vehicles are also being used as a diagnostic tool for accurate localization of cancer cells in real-time during surgery.
Here we study cRGD-ZW800-1, a cyclic pentapeptide (cRGD) conjugated to the 800 nm NIR fluorophore ZW800-1. The cyclic 3-amino acid sequence (RGD) is clinically a well-known peptide that binds to

various integrins (αvβ1, αVβ3, αvβ5, αvβ6, αvβ8, α5β1, α8β1 and αIIbβ3), mostly associated with neoangiogenesis. Tumors larger than 1-2 mm depend on the formation of new blood vessels to acquire sufficient amounts of oxygen and nutrients. Some of these integrins are therefore overexpressed on malignant cells and in tumor stroma, for example in breast, colorectal, pancreas and lung cancer. RGD based molecules have already been investigated in various phase I and phase II imaging studies using PET and SPECT and in a phase III study as an anticancer therapy (cilengitide).
Extensive preliminary work on the cRGD-ZW800-1 agent has been performed by our group and showed clear delineation of melanomas and colorectal, liver, pancreatic, lung, and head and neck tumors in xenograft mouse models while due to its renal clearance route also ureters could be recognized.

Study objective

To assess the feasibility of cRGD-ZW800-1 to visualize tumors in real-time using dedicated NIR fluorescence imaging systems

Study design

This is an exploratory study to evaluate the diagnostic value of fluorescent imaging using cRGD-ZW800-1 in patients with primary rectal and sigmoid cancer undergoing a low anterior resection at the Leiden University Medical Center. The study will consist of 18 patients, spread out over 4 cohorts where three different doses of cRGD-ZW800-1 will be explored to select the optimal dose for surgery. The selected doses are based on the pre-clinical and phase I results. cRGD-ZW800-1 will be administered in a bolus injection at least two hours prior to surgery as follows:

Cohort 1 (up to 4 patients): 0.005 mg/kg cRGD-ZW800-1
Cohort 2 (up to 4 patients): 0.015 mg/kg cRGD-ZW800-1
Cohort 3 (up to 4 patients): 0.050 mg/kg cRGD-ZW800-1
Cohort 4 (up to 6 patients): 0.050 mg/kg cRGD-ZW800-1 (optimal dose)

Study burden and risks

The risks to subjects related to cRGD-ZW800-1 are not completly known yet. In the phase 1 study, 11 healthy volunteers were administered cRGD-ZW800-1 without signs of acute or chronic toxicity.

Other risks to subjects mainly relate to the i.v. injection and venous blood sampling. Intravenous injection and the use of cannulas (1 cannula for i.v. injection and 1 cannula for venous blood sampling) are known to carry a small

risk of infection and hematoma. Based on consistent observations in the preclinical efficacy and safety pharmacology studies, it is expected that discoloration of the skin and urine may occur. Based on experience with other fluorescent probes, it cannot be excluded that hypersensitivity reactions may occur, although there are no indications for cRGD-ZW800-1.

There are no expected direct benefits to subjects who participate in this trial. Participants may help others prospectively by contributing to the knowledge base for designing future studies to evaluate the use of cRGD-ZW800-1 administration in patients undergoing oncologic surgery.

Contacts

Public
Leids Universitair Medisch Centrum

Albinusdreef 2
Leiden 2333 ZA
NL
Scientific
Leids Universitair Medisch Centrum

Albinusdreef 2
Leiden 2333 ZA
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1) Patients > 18 years old;
2) Patients scheduled and eligible for resection because of colorectal carcinoma without any other clinically significant co-morbidity that can potentially jeopardize the patient well-being (judged by principal investigator);
3) Patients should be capable and willing to give informed consent before study specific procedures;
4) Screening ECG and clinical laboratory test results are within normal limits, or if any are outside of normal limits they are considered to be clinically insignificant;
5) The patient has a normal or clinically acceptable medical history, physical examination, and vital signs findings at screening;
6) Absence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before registration in the trial.

Exclusion criteria

1) History of a clinically significant allergy or anaphylactic reactions;
2) Patients pregnant or breastfeeding, lack of effective contraception in male or female patients with reproductive potential;
3) Patients with renal insufficiency (eGFR<60)
4) Patients with a previous kidney transplantation in the medical history
5) Immunocompromised patients who do not have the ability to respond normally to an infection due to an impaired on weakened immune system, caused by either a pre-existing disease or concomitant medications.
6) Any condition that the investigator considers to be potentially jeopardizing the patients well-being or the study objectives.

Study design

Design

Study phase:	2
Study type:	Observational invasive
Masking:	Open (masking not used)
Control:	Uncontrolled

Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	24-09-2018
Enrollment:	18
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	cRGD-ZW800-1
Generic name:	n.a.

Ethics review

Approved WMO Date:	09-08-2017
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
Approved WMO Date:	24-01-2018
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
Approved WMO Date:	07-03-2018
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
Approved WMO Date:	11-03-2019
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
Approved WMO Date:	06-05-2019
Application type:	Amendment

Review commission:	METC Leiden-Den Haag-Delft (Leiden)
Approved WMO Date:	10-02-2020
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)

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	EUCTR2017-002772-60-NL
CCMO	NL62508.058.17