FLUOPANC-trial - Intraoperative near-infrared fluorescence imaging in pancreatic- and extrahepatic bile duct tumors using cRGD-ZW800-1 and dedicated imaging systems: A phase II feasibility, dose-ranging and optimal dose-(interval) selection trial

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- To assess the feasibility, safety and tolerability of cRGD-ZW800-1 for visualization of (neoadjuvantly treated) pancreatic carcinomas, perihilar or distal cholangiocarcinomas and if present associated metastatic lymph nodes and their distant...

Ethical review	Approved WMO
Status	Completed
Health condition type	Malignant and unspecified neoplasms gastrointestinal NEC
Study type	Interventional

Summary

ID

NL-OMON54735

Source
ToetsingOnline

Brief title
FLUOPANC-trial

Condition

- Malignant and unspecified neoplasms gastrointestinal NEC
- Gastrointestinal neoplasms malignant and unspecified

Synonym

pancreatic/bile duct cancer, pancreatic/cholangio carcinoma

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: Subsidie A.L. Vahrmeijer. (Vahrmeijer research lab)

Intervention

Keyword: Cholangiocarcinoma, Fluorescence, Imaging, Pancreatic carcinoma

Outcome measures

Primary outcome

Visualization of the primary tumor using cRGD-ZW800-1 and dedicated NIR-Fluorescence imaging system. Visualization is measured using the tumor-to-background ratio (TBR) in in-vivo and ex-vivo setting. A tumor-to-background ratio (TBR) of at least >=1.5 provides sufficient contrast for adequate visualization/delineation and will therefore be used as cut-off value.

Secondary outcome

- Number and grade of treatment-emergent (serious) adverse events ((S)AEs).

- Concordance between clinical assessment, histopathologic examination and NIR-Fluorescence imaging assessment of the resected tumor, lymph nodes and/or metastatic lesions and their histopathologic result.

- Define the optimal dose and dose interval of a single intravenous bolus injection of cRGD-ZW800-1. The optimal dose and ideal time window between administration of the study drug and intra-operative imaging during surgery will be assessed after all consecutive patients have been included, the

endpoint for the combination of optimal dose and dose-interval is a

tumor-to-background ratio of at least >=1.5.

- Tumor positive margins detected with NIR fluorescence imaging using

cRGD-ZW800-1, referenced to histopathology.

- Number of tumor-positive lymph nodes and metastases detected by NIR

fluorescence imaging using cRGD-ZW800-1, referenced to histopathology.

Study description

Background summary

Pancreatic cancer is 4th leading cause of cancer death in the United States. Prognosis is very poor with median survival of < 6 month. Upon diagnosis, the disease is associated with a 1-year and 5-year survival rate of ~25% and < 5%, respectively. Surgical resection is the only curative option with a 5-year survival rate of up to 20-30% depending on the tumor size. However, discriminating between malignant and benign tissue can be challenging, especially after neoadjuvant treatment. Currently, enhancing contrast of structures using near-infrared (NIR) fluorescence is a technique under development. It can provide accurate and real-time visualization of tumors during surgery. Fluorescent agents are intravenously administered and specifically bind to malignant cells or tumor-associated tissue, such as neoangiogenic vessels or stroma, and emit light in the invisible, near-infrared spectrum (i.e. 700-900 nm). Using a dedicated fluorescence imaging system, contrast of tumors relative to their background can be improved, which allows real-time image-guided surgery and improve complete resection rates. cRGD-ZW800-1 is a fluorescent contrast agent that specifically binds to integrins associated with neo-angiogenesis, and has the potential to improve visualization of pancreatic cancer cells during surgery and therefore increasing the R0 resection rate.

Study objective

- To assess the feasibility, safety and tolerability of cRGD-ZW800-1 for visualization of (neoadjuvantly treated) pancreatic carcinomas, perihilar or distal cholangiocarcinomas and if present associated metastatic lymph nodes and their distant metastases using dedicated NIR fluorescence imaging systems.

- To define the optimal dose and dose interval of a single intravenous bolus

injection of cRGD-ZW800-1.

Study design

The study was designed as an open-label, phase II clinical trial with a 2-factorial design: A phase II feasibility test, dose and optimal dose (interval) selection study.

Intervention

Intervention: Single bolus injection of cRGD-ZW800-1 2-24h before surgery. Intra-operative in-vivo assessment of NIR-fluorescence of tumor, lymph nodes, possible distant metastasis and anatomical related structures. After resection ex-vivo assessment of NIR-fluorescence of all resected tissue, on gross-macroscopy, bread loafs and microscopic slides.

Investigational drug: Intravenous single bolus injection of the targeted NIR fluorophore cRGD-ZW800-1. This targeted 800nm zwitterionic fluorophore developed by the Hospital Pharmacy Department of LUMC consists of the fluorophore ZW800-1 conjugated to the cRGD peptide.

Imaging: Intraoperative imaging will be performed with at least one of the following CE-marked near-infrared (NIR) fluorescence imaging systems: Quest Spectrum imaging platform (v2/3.0) for open-procedures, the Olympus or Karl-Storz system for the diagnostic laparoscopy or the Intuitive Surgical Da Vinci Xi (Firefly-mode) for minimally invasive robot-assisted procedures. With a NIR-imaging system a potential fluorescent signal of the tumor can be evaluated. Furthermore, the Quest Spectrum platform will also be used for evaluation of ex-vivo fluorescence of resected tissue on the back table (Back table imaging) and pathology department (ex-vivo imaging), which shall be performed during and after every procedure.

Study burden and risks

Patients participating in this study will undergo intraoperative NIR-fluorescence imaging after injection of a single bolus solution with the cRGD-ZW800-1 NIR-fluorophore. NIR-fluorescence imaging is a clinical technology that requires administration of a fluorescence-imaging agent that can be excited at near-infrared (NIR) wavelengths of ~800*nm. Upon illuminating tissue surfaces with penetrating NIR light to excite the imaging agent within the tissues, the generated fluorescence is collected to form a two-dimensional (2D) image demarking the tissue deposition of the imaging agent. This study drug (cRGD-ZW800-1) and study design have been used previously in colorectal cancer patients (phase II). All study drug administrations will be done in the clinic under medical supervision. The patients receiving any study drug will remain in the clinic after the administration of the study drug and subsequent surgery.

Thus, the patients can be closely monitored for any adverse signs during the different treatments. Therefore, providing the protocol is adhered to, careful observation and medical management will minimize any associated risk in this study. Previous clinical phase I-II studies showed no adverse events related to cRGD-ZW800-1 injection, as well as no significant changes in vital signs, ECG or laboratory analysis were observed. Although, when administrating an investigational product, it is possible that unknown side effects or (hyper)sensitivity reactions occur. Based on experience with other fluorescent tracers, such reactions are generally mild and transient in nature. The risk of damage in this study related to administration of this compound is considered negligible.

The scheduled (partial) pancreatic resection will be carried out according to standardized peri-operative planning, besides white-light visual inspection (WLI) and palpation, NIR-fluorescence imaging will be performed before and after resection to additionally to screen and inspect the target lesion, the vital structures, and four-abdominal quadrants as study procedure. Aiming to identify, visualize and delineate the primary tumor, related vital structures in the surgical field and fluorescent positive, white-light occult suspect tumor(rest) in the surgical bed; in lymph nodes, the peritoneal lining, liver or abdominal fat. NIR-Fluorescence imaging is an addition on the standard practice of clinical assessment with white-light visual inspection and palpation, safety and the clinical assessment will always be leading in the decision of responsible surgeon(s) to deviate from the initial plan. Concrete, when the additional NIR-fluorescence imaging results in identification of suspected (rest-)tumor tissue in the surgical bed (i.e. suspect positive surgical margins), or identification of suspect lymphoid or distant metastatic disease, the surgeon*s final decision to perform an additional resection, will be based on clinical (re)assessment with this additional information. In which the deviation of the resection, e.g. resection of additional tumor-suspect (pancreatic) tissue in the resection bed or around related structures (veins, arteries, lymph tracts) or suspect lymph nodes, is always carefully weighed and only perfumed if considered safe and surgically feasible. Intraoperative freeze-biopsy(-ies) could be performed to prove presence of malignant tissue and support intra-operative decision-making.

Thus, participation in this study could result a more accurate intra-operative assessment of local tumor status, including the identification of suspected incomplete resection margins in the surgical bed, or identification of suspect lymphoid or distant metastatic disease. Which will be based on all available information gained from pre-operative diagnostics, clinical assessment and WLI, complemented by NIR-fluorescence imaging and the option for freeze-biopsy(-ies). Furthermore, if additional (suspect) tumor tissue will be resected, this concerns a minimal amount. In concrete terms, one or a few nano/millimeters of tissue of the surgical margins or additional lymph nodes around the tumor. Given the magnitude of the planned surgery, the likelihood of harm caused by potential tissue removal based on a false positive signal could

be graded nihil. Therefore, the potential harm related to intraoperative NIR-fluorescence imaging is estimated to be minimal compared to the potential benefit of a more accurate assessment of local tumor status and the potential of a more complete (radical) resection of the tumor.

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 >18 years old;
- Patients scheduled and eligible for open/robotic resection because of (histologically proven) pancreatic carcinoma with or without neoadjuvant treatment. As well as patients scheduled and eligible for resection because of (histologically proven) distal or perihilar cholangiocarcinoma with or without neoadjuvant treatment.

- All women of childbearing potential and all males must practice effective contraception during the study and be willing and able to continue contraception for at least 30 days after their last dose of study treatment.
- Patients should be capable and willing to give informed consent before study specific procedures;

Exclusion criteria

- History of a clinically significant allergy or anaphylactic reactions;
- Patients with renal insufficiency (eGFR<60 ml/min/1,73 m2);
- Patients with a previous kidney transplantation in the medical history;
- Pregnant women, or women giving breast feeding;
- Patients who are immunocompromised and do not have the ability to respond normally to an infection due to an impaired or weakened immune system, caused by either a pre-existing disease or concomitant medications (excluding intended neoadjuvant treatment);
- Presence 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;
- 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:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	24-11-2022
Enrollment:	20

Type:	Actual

Medical products/devices used

Generic name:	Intuitive da Vinci Xi - Firefly
Registration:	Yes - CE outside intended use
Product type:	Medicine
Brand name:	cRGD-ZW800-1
Generic name:	cRGD-ZW800-1

Ethics review

Approved WMO Date:	28-07-2022
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	07-11-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	09-11-2022
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	29-08-2023
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

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	EUCTR2019-004217-14-NL
CCMO	NL71219.058.22