Image guided surgery for tumor detection in solid cancers using the pH activated micellar probe ONM-100: The SHINe study

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

Summary

ID

NL-OMON46738

Source
ToetsingOnline

Brief title
The SHINe study

Condition

- Malignant and unspecified neoplasms gastrointestinal NEC
- Miscellaneous and site unspecified neoplasms malignant and unspecified
- Breast disorders

Synonym
multiple cancer types, Solid cancer

Research involving
Human

Sponsors and support

Primary sponsor: OncoNano Medicine's Inc.
Source(s) of monetary or material Support: OncoNano Medicine, Texas, USA ,OncoNano Medicine;Texas;USA

Intervention

Keyword: fluorescence, image-guided surgery, pH-activated, solid cancer

Outcome measures

Primary outcome

- To evaluate safety and pharmacokinetics of a single dose of ONM-100

administered intravenously in patients with solid tumors (HNSCC, breast cancer,

rectal cancer and esophageal cancer)

- To assess the feasibility of using ONM-100 for intra operative imaging of

solid tumors (HNSCC, breast cancer, rectal cancer and esophageal cancer).

Secondary outcome

- To determine a range of safe doses of ONM-100 for intra-operative imaging of

solid tumors and metastatic nodes with an adequate Tumor to Background contrast

(CNR).

- To evaluate usability of commonly used camera systems for intra-operative

imaging with ONM-100 (SurgVision and Novadaq imaging systems (see section 7.1))

Study description

Background summary

Surgery remains a main pillar in the treatment of most solid tumors (e.g. breastcancer, head and neck squamous cell carcinoma (HNSCC), esophageal cancer, rectal cancer etc.). In these cancer, the postopervative margin status is one of the most important prognostic factors of local tumor control and therefore

the chance for recurrent disease or tumor metastasis. Despite the growing options in imaging modalities, such as CT, MRI or ultrasound which are used for intra-operative navigation, these techniques don*t provide *real-time* feedback. In fact, surgeons can only combine pre- operative imaging data with tactile and visual information during surgery for tumor detection and assessing tumor margins with limited accuracy. With the introduction of (molecular) imaging techniques using near infrared (NIR) fluorescent optical contrast agents coupled to targeted compounds, new avenues have opened up for intra-operative assessment of tumor margins. The potential advantages of optical imaging include real-time feedback and the availability of camera systems that provide a wide view of the surgical field. Despite promising results, one of the major limitations is the lack of broad tumor applicability in cancer patients, due to complex oncogenotypes and different histologic phenotypes of cancer.
One strategy to overcome this is to target metabolic vulnerabilities that are more ubiquitous. Aerobic glycolysis, where cancer cells preferentially take up glucose and convert it into lactic acid, has rekindled intense interest for optical imaging. Briefly, compared to blood pH (7.4), most extracellular pH (pHe) of cancer ranges from 6.71-7.01. Recently, a pH-sensitive optical tracer has been developed. This tracer nanotransistor with binary off/on response is sensitive to very small pH changes of the environment. This nanotransistor, coupled to the NIR dye Indocyanine Green (ICG), *enlights* when pHe<6.9 and remains in an *off* state when pHe>6.9. This makes pH transistor nanoprobes a broadly applicable strategy to allow highly sensitive, cancer-specific detection of malignant tumors.

These findings prompted us to design this innovative application for a *first-in-human* clinical trial for the intraoperative detection of tumor during surgical treatment of a varierty of solid cancers using the pH activated micellar nanoprobe ONM-100. First, the optimal dose of ONM-100 will be determined in one tumor type (phase 1a). Next, this dose will be used in multiple solid tumor types (phase 1b). The study is sponsored in collaboration and subsidized by OncoNano Medicine Inc, Texas, USA

Study objective

The main purpose is to investigate the safety, pharmacokinetics and feasibility of ONM-100 as an intra-operative optical tracer to detect tumors and metastatic lymph nodes in solid cancers. Moreover, the study will investigate the optimal dose of ONM-100 for an adequate Tumor to Background Contrast Ratio (CNR) of fluorescence obtained intraoperatively and with ex-vivo specimens using ICG compatible camera and imaging devices.

Study design

The study is designed as a phase 1, single center, safety, pharmacokinetics and

imaging feasibility study in patients with solid cancers that require surgical excision. This study contains two phases (1a and 1b). Phase 1a is set up as a dose-finding study that will be performed in 4-6 cohorts of 3 patients with different solid tumor types. Based on previous studies performed in the UMCG, this number of participants should be enough for an adequate CNR analysis. Phase 1b will verify the optimal in multiple solid tumor types (N=15).

Intervention

Investigational Product administration: Patients will visit the hospital 1 day prior to the planned surgery. ONM-100 will be injected 24 +/-8 hours before surgery by slow intravenous infusion and patients will be monitored for adverse events. The dose levels will be 0.3, 0.5, and 0.8mg/kg. Additional dose levels (0.1, 1.2, 1.6, 2.0mg/kg) will be included up to a maximum of 6 dose levels if needed to obtain the optimal dose range and/or a 2-3x safety coverage above the optimal dose. In GLP toxicology studies, the no observed adverse effect level (NOAEL) was found to be 30mg/kg in dogs and rats (maximum dose studied). The dog is the most sensitive species, so the conversion to human equivalent doses are based on dog data. The acceptable safe starting dose and maximum dose for phase 1, based on the GLP toxicology studies are 0.6mg/kg (1/50 NOAEL) (or a human equivalent dose of 0.3 mg/kg) and 15mg/kg (1/2 the NOAEL) (or a human equivalent dose of 7.5 mg/kg) respectively. The proposed phase 1 starting dose of 0.3mg/kg and maximum dose of 2.0mg/kg are within the acceptable values based on animal data.

Study burden and risks

Burden - Time investment: For most surgeries, patients are usually admitted one day prior to the planned surgery. Dependent on tumor type, patients will be discharged between 1-10 days after surgery. Therefore, some patients (usually breast cancer) are asked to visit the UMCG postoperative on day 3 and 10 post dosing . For other surgeries (HNSCC, Esophageal Cancer and Colorectal), patients usually stay admitted after surgery for longer periods. Therefore, post-operative follow-up is not necessarily prolonged for these patients. Participants will be followed-up 17 days post dosing.
Burden-extra procedures: 1) Intravenous administration of ONM-100. 2) The estimated time for taking fluorescence images is approximately 45-60min. Therefore, the time under general anesthesia will be prolonged. The usual time for surgical procedures for removal of solid tumors varies between 2-10 hours (see Table 1, end of summary) 3) If the surgeon considers it safe, study related biopsies are taken from clinical non-suspicious spots when fluorescent (maximum of 10). Biopsies will be taken in the ongoing general anesthesia. 4) Bloodsamples will be drawn at different timepoints to evaluate pharmacokinetics and safety aspects. 5) ECG will be performed.
Risks: Side effects of ONM-100 are possible, but this is considered as a low risk based on the safety margin observed in preclinical studies. The potential

extra risk of the biopsies is considered as (very) low.

Benefit: Patients will have no benefit from this study directly. Surgery will be planned as usual. During surgery, no decisions will be made based on the fluorescence imaging. The benefit of this study will be the establishment of usefulness of ONM-100 during surgery to identify tumor and margins containing tumor and metastatic lymph nodes. The results of these types of study will be at least beneficial for other patients with cancer in the future. Clinical experience will be obtained with a *non-cancer-type specific* optical tracer for the safety and feasibility of intraoperative tumor detection and margin assessment using ONM-100 during surgery (HNSCC, Breast Cancer, Colorectal Cancer and Esophageal Cancer)

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

1) Biopsy confirmed diagnosis of primary or recurrent respective tumor type (see section 3.1) and scheduled to undergo surgical resection as decided by the respective Multi-Disciplinary Tumor Boards.
o Breast cancer, HNSCC, Esophageal Cancer, Colorectal cancer
2) Age * 18 years
3) Written informed consent
4) Adequate potential for follow-up
5) Acceptable hematologic status, kidney function, and liver function, as respective standard surgery protocol requires, as determined by the Investigator.
6) Patients must agree to abstain from alcohol consumption from 24 hours before ONM-100 administration through end of study (Study Day 17)
7) Patients should not be taking, nor take concomitantly, any medication that has, in the opinion of the investigator, a substantial risk of hepatotoxicity

Exclusion criteria

1) Medical or psychiatric conditions that compromise the patient*s ability to give informed consent.
2) Concurrent uncontrolled medical conditions.
3) Received an investigational drug within 30 days prior to the dose of ONM-100.
4) Tumors at sites of which the surgeon would assess that in vivo imaging would not be feasible.
5) Had within 6 months prior to enrolment: myocardial infarction, cerebrovascular accident, uncontrolled cardiac heart failure, significant liver disease (ALT >3X ULN* or increased total bilirubin), unstable angina.
6) Received prior to surgery neoadjuvant therapies (chemotherapy, radiation, target therapies) on respective tumor (Only applicable for phase 1a)
7) Inadequately controlled hypertension with or without current antihypertensive medications.
8) History of allergic reaction or infusion reactions to iodine, iodine based contrast or shellfish, indocyanine green (ICG) or any other components of ONM-100.
9) Receiving medication with high chance of hepatotoxicity, as judged by the PI based on standard protocols within the UMCG and Dutch database (in Dutch: Farmacotherapeutisch Kompas)
10) Pregnant or lactating women. Documentation of a negative pregnancy test must be available for women of childbearing potential. Moreover, the need to be willing to ensure that she or her partner uses effective contraception during the trial and for 6 months thereafter. Woman of childbearing potential are premenopausal women with intact reproductive organs and women less than two years after menopause.
11) Lab values that in the opinion of the primary surgeon would prevent surgical resection.
12) Magnesium, potassium and calcium lower than the lower limit of normal range.
13) Life expectancy < 12 weeks

14) Karnofsky performance status < 70%.

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	28-02-2018
Enrollment:	33
Type:	Actual

Medical products/devices used

Generic name:	Novadaq Spy fluorescentie camera's / SurgVision Fluorescentie camera's
Registration:	No

Ethics review

Approved WMO Date:	06-12-2017
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	26-01-2018
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	15-03-2018

Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	08-05-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	17-05-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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 - 003543--NL
CCMO	NL63129.042.17
Other	NTR - aanvraag gedaan