A phase 1a/1b/2 study to assess the safety, tolerability and pharmacokinetics of OTL78, a PSMA-targeted fluorescent agent, for the intraoperative imaging of prostate cancer

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Part A: healthy volunteers (n=up to 15)Primary/safety objective: - To assess the safety, tolerability and pharmacokinetics of a single IV dosage of OTL78 Secondary objective: - To assess the pharmacodynamics of OTL78 by measuring the temporal...

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

Summary

ID

NL-OMON49366

Source
ToetsingOnline

Brief title
Study for intraoperative imaging of prostate cancer using OTL78

Condition

- Reproductive neoplasms male malignant and unspecified

Synonym
Prostate cancer

Research involving
Human

Sponsors and support

Primary sponsor: OnTarget Laboratories
Source(s) of monetary or material Support: OnTarget Laboratories

Intervention

Keyword: Fluorescence imaging, OTL78, Prostate cancer

Outcome measures

Primary outcome

Part A: healthy volunteers (n= up to 15)

Primary/safety objective:

- To assess the safety, tolerability and pharmacokinetics of a single IV

dose of OTL78

Part B/part C: patients (n=24)

Primary/safety objective:

- To assess the safety, tolerability and pharmacokinetics of a single IV dose

of OTL78

Secondary outcome

Part A: healthy volunteers (n= up to 15)

Secondary objective:

- To assess the pharmacodynamics of OTL78 by measuring the temporal

relationship of fluorescence of superficial tissues (skin/veins and mucosa).

Part B/Part C: patients (n=24)

Secondary objectives:

- To estimate the Sensitivity (or True Positive rate, TP/(TP+FN)) of OTL78 for detection of tissues expressing PSMA or prostate cancer during near infrared imaging (NIR)

- To estimate the Specificity (or True Negative rate, TN/(TN+FP)) of OTL78 for detection of PSMA+ tissue and prostate cancer cells during near infrared imaging (NIR)

- To estimate the False Positive rate (FP/(FP+TN)) of OTL78 for detection of tissues expressing PSMA or prostate cancer during near infrared imaging (NIR)

- To estimate the False Negative rate (FN/(FN+TP)) of OTL78 for detection of PSMA+ tissues prostate cancer cells during near infrared imaging (NIR)

- To evaluate the tumor to background ratio (TBR)

Exploratory Objective:

- To evaluate the surgeons* rating for the utility of OTL78 IV injection and imaging system in visualizing prostate cancer and/or lymph nodes during surgery

Study description

Background summary

Surgery is the mainstay in the initial treatment of many solid tumors. Complete resection has shown to be an important prognostic indicator for survival. However, this can be challenging when the surgical field is observed with the naked eye only. Therefore, agents that improve tumor identification and the likelihood of complete resection are being developed. These agents are directed towards tumor-specific targets and emit light at non-visible wavelengths. By using near-infrared (NIR) camera systems, they may enable detection of malignant tissues and distinguish them from normal tissue. OTL78 is an imaging agent that specifically binds to the PSMA (prostate specific membrane antigen) which is expressed on prostate cells, particularly cancer and possibly involved

lymph nodes. Intra-operative identification of cancer tissue using real-time imaging modalities that could improve tumor identification and demarcation would provide a very useful tool to reduce the frequency of positive resection margins and increase complete removal of locally spread tumor and involved lymph nodes. Complete removal of cancer and metastases may in turn reduce rates of re- interventions and therefore morbidity to help improve patient outcomes. As there is no clinical experience with OTL78, the study drug will first be studied in healthy volunteers and subsequently in patients to assess the safety, tolerability and pharmacokinetics The performance of OTL78 in intraoperative imaging of prostate cancer will be assessed in (Part B/part C, proof of concept).

Study objective

Part A: healthy volunteers (n=up to 15)
Primary/safety objective:
- To assess the safety, tolerability and pharmacokinetics of a single IV dosage of OTL78

Secondary objective:
- To assess the pharmacodynamics of OTL78 by measuring the temporal relationship of fluorescence of superficial tissues (skin/veins and mucosa).

Part B: patients (n=24)
Primary/safety objective:
- To assess the safety, tolerability and pharmacokinetics of a single IV dose of OTL78

Secondary objectives:
- To estimate the Sensitivity (or True Positive rate, TP/(TP+FN)) of OTL78 for detection of tissues expressing PSMA during near infrared imaging (NIR)
- To estimate the Specificity (or True Negative rate, TN/(TN+FP)) of OTL78 for detection of prostate cancer cells during near infrared imaging (NIR)
- To estimate the False Positive rate (FP/(FP+TN)) of OTL78 for detection of tissues expressing PSMA during near infrared imaging (NIR)
- To estimate the False Negative rate (FN/(FN+TP)) of OTL78 for detection of prostate cancer cells during near infrared imaging (NIR)
- To evaluate the tumor to background ratio (TBR)

Exploratory Objective:
- To evaluate the surgeons* rating for the utility of OTL78 IV injection and imaging system in visualizing prostate cancer and/or lymph nodes during surgery

Study design

Part A (healthy volunteers)
This is a single ascending dose, double-blind, randomized, placebo-controlled design in 10 healthy volunteers. Two ascending dose levels of OTL78 (0.03mg/kg and 0.06mg/kg) will be investigated in two consecutive cohorts. Placebo will consist of 5% dextrose. To ensure blinding, 5% dextrose fluid bags containing active drug or placebo will be wrapped in foil.

Part B (patients)
This is a single dose, open label, exploratory (proof of concept) study in up to 6 patients with prostate cancer who have been scheduled to undergo a pelvic lymph node dissection for (primairy or recurrent) prostate cancer. Each surgical procedure will be performed with the DaVinci Xi according to standard of care. The dose of OTL78, determined and approved as the highest tolerated dose in Part A (0.06 mg/kg), will be administered. Surgery will take place at least 1 hour after the end of the infusion.
If there is too much background signal in the first 3 patients, the dose is de-escalated from 0.06 mg/kg to 0.03 mg / kg for the following 3 patients. If the fluorescent signal is adequate, the 0.06 mg / kg dose is maintained.
If insufficient fluorescent signal is measured, part B is paused and part A is expanded with a third dose cohort with healthy volunteers (0.12 mg / kg), following the same approach as previous dose cohorts. If this dose is found to be safe and has been approved by the BEBO, part B will be restarted with this dose.
A systematic approach is also designed for use of the different near-infrared cameraystems.
Follow-up phone call will take place +/- 2 weeks after OTL78- administration.

Part C:
This is a single dose, open label, exploratory (proof of concept) study in up to 18 patients with prostate cancer who have been scheduled to undergo a prostatectomy (Gleason score 7+). Each surgical procedure will be performed with the DaVinci Xi according to standard of care. The dose of OTL78, determined and approved as the highest tolerated dose in Part A (0.06 mg/kg), will be administered. Surgery will take place at least 1 hour after the end of the infusion.
if there is too much background signal in the first 3 patients, the dose is de-escalated from 0.06 mg/kg to 0.03 mg / kg for the following patients. If the fluorescent signal is adequate, the 0.06 mg / kg dose is maintained. If insufficient fluorescent signal is measured, part C is paused and part A is expanded with a third dose cohort with healthy volunteers (0.12 mg / kg), following the same approach as previous dose cohorts. If this dose is found to be safe and has been approved by the BEBO, part C will be restarted with this dose.
A systematic approach is also designed for use of the different near-infrared cameraystems.
Follow-up phone call will take place +/- 2 weeks after OTL78- administration.

Intervention

OTL78

Study burden and risks

There are no expected direct benefits to the healthy volunteers (part A) or patients (part B/part C) who participate in the study. However, the participants may help others prospectively by contributing to the knowledge base for designing future studies with OTL78 in patients with prostate cancer. The risks to participants related to OTL78 are currently unknown. Although DUPA and the fluorescent dye OTL have clinical data with no safety signals to date, the risk of hypersensitivity reactions for OTL78 is unknown. During the administration of OTL0078, interruption of the infusion and/or treatment with an anti-histamine may be required in subjects who experience symptoms suggestive of hypersensitivity, followed by an observational period until the symptoms resolve. Symptoms to be aware of may include but are not limited to flushing, nausea, vomiting, abdominal pain and pruritis/urticaria. Other risks to subjects may include injection site adverse reactions (infusion and venous blood sampling), such as infection and hematoma. The use of a near-infrared fluorescence camera system during surgery (part B/part C) may result in, but not limited to, contamination of the sterile field or injury due to disengagement of the imaging device component coming in contact with the patient and/or surgical team.

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

Healthy volunteers (part A)
1) Male and 18-65 years old at screening.
2) Able and willing to comply with study procedures, with signed and dated informed consent obtained before any study-related procedures are performed.
3) Agree to use an effective method of contraception for 90 days after administration.
4) A body mass index is *30 kg/m2.
5) The subject is healthy with no acute or chronic medical illnesses, has a normal physical examination, and normal vital signs findings at screening.
6) The subject*s screening 12-lead ECG and clinical laboratory test results are within normal limits, or if any are outside of normal limits they are considered clinically insignificant at the discretion of the investigator.
7) Negative screening test results for hepatitis B, hepatitis C, and human immunodeficiency virus.
8) Negative test results for drug and alcohol screening.
9) Absence of any psychological, familial, sociological or geographical condition that at the discretion of the investigator could potentially hamper compliance with the study protocol and follow-up schedule; such conditions should be discussed with the patient during the prescreening period.

Patients (part B)
1) Male patients > 18 years of age and older at screening.
2) Able and willing to comply with study procedures, and signed and dated informed consent obtained before any study-related procedures are performed.
3) Known or high clinical suspicion of (primary or recurrent) prostate cancer scheduled to undergo a pelvic lymph node dissection for salvage or staging at the LUMC.
4) The 12-lead ECG and clinical laboratory test results are within normal limits, or if any are outside of normal limits they are considered clinically insignificant at the discretion of the investigator
5) Chronic or acute medical illness that in the discretion of the investigator may confound or complicate the findings in this study

6) Patients are clinically fit for surgery
7) Agree to use an effective method of contraception for 90 days after administration
8) Absence of psychological familial, sociological or geographical condition that at the discretion of the investigator could potentially hamper compliance with the study protocol and follow- up schedule; such conditions should be discussed with the patient during the prescreening period.

Patients (part C)
1) Male patients > 18 years of age and older at screening.
2) Able and willing to comply with study procedures, and signed and dated informed consent obtained before any study-related procedures are performed.
3) Known or high clinical suspicion of prostate cancer (Gleason score 7+) planned for a prostatectomy at the NKI.
4) The 12-lead ECG and clinical laboratory test results are within normal limits, or if any are outside of normal limits they are considered clinically insignificant at the discretion of the investigator
5) Chronic or acute medical illness that in the discretion of the investigator may confound or complicate the findings in this study
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6) Patients are clinically fit for surgery
7) Agree to use an effective method of contraception for 90 days after administration
8) Absence of psychological familial, sociological or geographical condition that at the discretion of the investigator could potentially hamper compliance with the study protocol and follow- up schedule; such conditions should be discussed with the patient during the prescreening period.

Exclusion criteria

Healthy volunteers (part A)
1) Female subjects
2) Known acute or chronic disease, abnormal physical examination or blood tests of clinical significance.
3) The subject has previously been included in an OTL study.
4) Use of prescription drugs within 30 days of screening and during study participation
5) Participation in a clinical trial within 90 days of screening or more than 4 times in the previous year.
6) History of clinically significant allergies or anaphylactic reactions.
7) History of allergy to any of the components of OTL78 or excipients (see Investigator*s Brochure).

Patients (part B)
1) Any condition that in the opinion of the investigators could potentially

jeopardize the health status of the patient
2) History of clinically significant allergies or anaphylactic reactions
3) History of allergy to any of the components of OTL78 or excipients (see Investigator*s Brochure)
4) Impaired renal function defined as eGFR<50 ml/min/1.73m2
5) Impaired liver function defined as values greater than 3x the upper limit of normal (ULN) for ALT, AST, or 2x the upper limit of normal for total bilirubin (excl. Gilbert*s syndrome)
6) Previous participation in an OTL study

Patients (part C)
1) Any condition that in the opinion of the investigators could potentially jeopardize the health status of the patient
2) History of clinically significant allergies or anaphylactic reactions
3) History of allergy to any of the components of OTL78 or excipients (see Investigator*s Brochure)
4) Impaired renal function defined as eGFR<50 ml/min/1.73m2
5) Impaired liver function defined as values greater than 3x the upper limit of normal (ULN) for ALT, AST, or 2x the upper limit of normal for total bilirubin (excl. Gilbert*s syndrome)
6) Previous participation in an OTL study

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	19-07-2019
Enrollment:	39
Type:	Actual

Medical products/devices used

Generic name:	Quest;Visionsense and DaVinci
Registration:	Yes - CE outside intended use
Product type:	Medicine
Brand name:	OTL78
Generic name:	na

Ethics review

Approved WMO Date:	25-06-2019
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	19-07-2019
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	15-11-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	02-12-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	17-02-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	09-04-2020

Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-12-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	28-12-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

ID: 21822
Source: NTR
Title:

In other registers

Register	ID
EudraCT	EUCTR2019-002393-31-NL
CCMO	NL70379.056.19
OMON	NL-OMON21822