A Phase 2, Single dose, Open-Label, Exploratory Study to Investigate the Safety and Efficacy of OTL38 Injection for Intraoperative Imaging of Folate Receptor Positive Lung Nodules

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4.1 Primary• To estimate the Sensitivity and False Positive rate of OTL38 for malignancy detection during Near Infrared Imaging (NIR).• To assess the safety and tolerability of single intravenous doses of OTL384.2 Secondary• To assess the safety of...

Ethical review	Approved WMO
Status	Completed
Health condition type	Respiratory and mediastinal neoplasms malignant and unspecified
Study type	Observational invasive

Summary

ID

NL-OMON44263

Source
ToetsingOnline

Brief title
Folate imaging in lung cancer

Condition

- Respiratory and mediastinal neoplasms malignant and unspecified
- Respiratory tract therapeutic procedures

Synonym
adenocarcinoma lung cancer / lung cancer

Research involving
Human

Sponsors and support

Primary sponsor: On Target Labs, LLC
Source(s) of monetary or material Support: On Target Laboratories;LLC

Intervention

Keyword: Fluorescent probe, Image guided surgery, Lungcancer

Outcome measures

Primary outcome

Primary

The primary efficacy endpoints are the Sensitivity and False Positive rate of OTL38 for malignancy detection during Near Infrared Imaging (NIR).

• Sensitivity or True Positive Rate (TPR) for OTL38 in combination with fluorescent light, defined as the proportion of fluorescent light positive tissue samples (nodule, synchronous lesion, and margin but excluding lymph nodes) that are histologically confirmed to be FR+ and lung cancer by central pathology relative to the total number of tissue samples confirmed to be FR+ and lung cancer by central pathology. Sensitivity = (True Positive)/(True Positive +False Negative).

• False positive rate (FPR) for OTL38 in combination with fluorescent light, for the purpose of this protocol, will be calculated as 1 - the Positive Predictive Value (PPV) and is defined as the proportion of fluorescent light positive tissue samples removed (nodule, synchronous lesion, and margin but excluding lymph nodes) that are histologically confirmed to be non-cancerous, or if cancerous, not FR+ and lung cancer, by central pathology relative to the total number of tissue samples removed with fluorescent light imaging. False

Positive Rate = (False Positives) / (True Positives + False Positives).

Secondary outcome

Secondary

The secondary efficacy endpoint is proportion of patients with at least one CSE as a result of utilizing OTL-38 and Near Infrared Imaging. These include:

1. Identification of at least one pulmonary nodule identified with OTL-38 and Near Infrared Imaging (NIR) that was not identified by white light and finger palpation, OR

2. Identification of at least one synchronous lesion identified with OTL38 and NIR that was not identified by white light, OR

3. Identification of at least one positive cancer margin identified with OTL38 and NIR (in situ or back table) OR

4. Demonstration of at least one Intraoperative Challenge that could be resolved only by OTL-38 and NIR

• Up/Down-Staging of a patient*s diagnosis

• Operation scaling - increasing or decreasing scope of surgery.

• Back table orientation - localization of a nodule or aspect of a nodule suspicious for cancer.

Exploratory

1. The difference in detection rates of adenocarcinoma tissue samples (excluding lymph nodes) between OTL38 fluorescence at time of surgery vs. frozen section assessment as determined by final local pathology report.

2. To compare the proportion of all fluorescing lesions vs. the proportion of lesions expressing FRα+ and/or FRβ+ as determined by immunohistochemical

analysis, excluding lymph nodes

3. Sensitivity and false positive rate estimated as described above for lymph nodes alone.

4. Proportion of subjects with at least one event for each of the separate CSE components when calculated excluding lymph nodes:

a. Primary nodules (open-thoracotomy, endoscopic procedures, and post-operative procedures)

b. Synchronous Lesions (open and endoscopic procedures)

c. Positive Margin Identification (in situ and back table)

d. Intraoperative Challenge (aggregate and individual components)

Safety

1. Incidence rates of all treatment-emergent AEs (TEAEs), adverse device effects (ADEs), and SAEs, from the time of OTL38 administration through follow-up Visit 4.

2. Laboratory parameters (chemistry and hematology) and vital signs collected at: screening, during day of surgery and 7-day follow-up

3. Electrocardiograms (ECG) and physical examinations will be collected at screening, day of infusion, and within 24 hours prior to discharge.

Study description

Background summary

According to the World Health Organization, lung cancer is the leading cause of cancer-related deaths in men and women, and is responsible for 1.6 million deaths worldwide annually as of 2012 (Stewart 2014). Surgery remains the preferred method of treatment and the only potentially curative modality for

patients presenting with operable Stage I or II lung cancers; however, the 5-year survival rates for these candidates remain at 55.2% and 28.0% for Stages I and II lung cancer, respectively (SEER 2016). These high rates of local recurrence may be due to the inability to completely detect and remove primary tumor nodules, and lingering metastases in synchronous nodules (tumors located within proximal parenchyma) in a satisfactory manner. Eliminating positive tumor margins through imaging during surgery could facilitate improved rates of recurrent-free patients and thus overall survival (Okusanya 2014, Keating 2015).

Study objective

4.1 Primary
• To estimate the Sensitivity and False Positive rate of OTL38 for malignancy detection during Near Infrared Imaging (NIR).
• To assess the safety and tolerability of single intravenous doses of OTL38

4.2 Secondary
• To assess the safety of the Fluorescence Imaging Systems for intraoperative imaging when used with OTL38.
• To estimate the efficacy of OTL38 and Near Infrared Imaging (NIR) with respect to the identification of Clinically Significant Events (CSEs)

4.3 Exploratory
• To compare the difference in detection rates of adenocarcinoma between positive OTL38 fluorescence imaging vs positive frozen section assessment as determined by final pathology report.
• To assess the Tumor to Background Ratios (TBR) in NIR systems capable of calculating TBR and their correlation to histological subtypes and clinical parameters.

Study design

• This is a phase 2, multi-center, single dose, open-label, exploratory study in suspected lung cancer patients scheduled to undergo endoscopic or thoracic surgery per CT/PET imaging based on standard of care.
• Each patient will be dosed with 0.025 mg/kg OTL38.
• The tumor to background ratio (TBR) for the fluorescence (see Section 5.1.2 for details) will be determined for each patient assessed with systems capable of calculating TBR.

Study burden and risks

Risks:
Hypersensitivity reactions
Risks of taking blood samples: pain, bruising, infection

Presence of a camera system in the operating room

Burden:

Extra time investment

The risks of participation for the subjects in the trial include hypersensitivity reactions. These risks are deemed minimal. Nevertheless precautionary measures (supervised administration by qualified staff and availability of medical treatment to treat hypersensitivity reactions) are in place and these effects are generally well manageable. The burden of the trial is minimal, the research will for the largest part coincide with routine care and the proposed procedures are minimally invasive. We therefore believe this research that, could possibly provide a useful tool to reduce positive resection margins hence reducing rates of re-interventions increase the identification rate of otherwise occult malignant lesions and possibly improves patient outcome and may be used in staging procedures, is justified.

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. Male and Female patients 18 years of age and older
2. Confirmed diagnosis of adenocarcinoma lung cancer
OR,
3. Have a primary diagnosis, or at high clinical suspicion, of lung nodule(s) warranting surgery based on CT and/or PET imaging
4. Who are scheduled to undergo endoscopic or thoracic surgery
5. A negative serum pregnancy test at Screening followed by a negative urine pregnancy test on the day of surgery or day of admission for female patients of childbearing potential
6. Female patients of childbearing potential or less than 2 years postmenopausal agree to use an acceptable form of contraception from the time of signing informed consent until 30 days after study completion
7. Ability to understand the requirements of the study, provide written informed consent and authorization of use and disclosure of protected health information, and agree to abide by the study restrictions and to return for the required assessments

Exclusion criteria

1. Previous exposure to OTL38
2. Known FR-negative lung nodules
3. Any medical condition that in the opinion of the investigators could potentially jeopardize the safety of the patient
4. History of anaphylactic reactions
5. History of allergy to any of the components of OTL38, including folic acid
6. Pregnancy, or positive pregnancy test
7. Clinically significant abnormalities on electrocardiogram (ECG) at screening.
8. Presence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule
9. Impaired renal function defined as eGFR< 50 mL/min/1.73m2
10. Impaired liver function defined as values > 3x the upper limit of normal (ULN) for alanine aminotransferase (ALT) or aspartate aminotransferase (AST), alkaline phosphatase (ALP), or total bilirubin.
11. Received an investigational agent in another investigational drug or vaccine trial within 30 days prior to surgery
12. Known sensitivity to fluorescent light

Study design

Design

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

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	27-03-2018
Enrollment:	10
Type:	Actual

Medical products/devices used

Generic name:	Artemis Handheld Camera System
Registration:	Yes - CE intended use
Product type:	Medicine
Brand name:	OTL-038
Generic name:	n.a.

Ethics review

Approved WMO Date:	09-10-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-10-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek

	(Assen)
Approved WMO Date:	20-09-2018
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

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2017-003560-13-NL
CCMO	NL63166.056.17