A Phase 3, Randomized, Single Dose, Open-Label Study to Investigate the Safety and Efficacy of OTL38 Injection (OTL38) for Intra-operative Imaging of Folate Receptor Positive Ovarian Cancer

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Primary* To confirm the efficacy of OTL38 in combination with fluorescent light to detect additional Folate Receptor-positive (FR+) ovarian cancer lesions not detected by palpation and visualization under normal light in patients with FR+ ovarian...

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

Summary

ID

NL-OMON48066

Source
ToetsingOnline

Brief title
Phase 3 study with OTL38 in ovarian cancer

Condition

- Reproductive neoplasms female malignant and unspecified
- Obstetric and gynaecological therapeutic procedures

Synonym
Ovarian cancer

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: OnTarget laboratories LLC

Intervention

Keyword: Fluorescent probe, Image guided surgery, Ovarian cancer

Outcome measures

Primary outcome

Primary Efficacy:

* Proportion of patients with at least one evaluable FR+ ovarian cancer lesion confirmed by central pathology (Standard of truth) that was detected using the combination of OTL38 and fluorescent light but not under normal light or palpation. All evaluable FR+ ovarian cancer lesions that were identified prior to or after surgery, that were detected using the combination of OTL38 and fluorescent light but not under normal light or palpation, and were removed based on the evaluation under fluorescent light, will be included in the calculation of the proportion of patients with at least one FR+ ovarian cancer lesion confirmed by central pathology. The primary endpoint will be determined based on evaluable lesions as described below.

* Evaluable lesions are defined as follows: lesions that do not appear on an organ or tissue that was intended for removal based on the Pre-Fluorescence Surgical Plan, regardless of the absence or presence of tumor.

Secondary outcome

Secondary Efficacy:

* False Positive Rate at the patient level (FPRp) will be a major secondary

efficacy endpoint and is defined as the proportion of folate positive ovarian cancer patients in whom all lesions, without regard to evaluable lesion status, detected by fluorescent light only, are histologically negative.

* Sensitivity or True Positive Rate (TPR) for OTL38 in combination with fluorescent light, defined as the proportion of fluorescent light positive lesions that are histologically confirmed to be FR+ and ovarian cancer by central pathology relative to the total number of lesions confirmed to be FR+ and ovarian cancer by central pathology without regard to evaluable lesion status. From the classification table below: TP/TP+FN

* 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 lesions removed that are histologically confirmed to be non-cancerous, or if cancerous, not FR+ and ovarian cancer, by central pathology relative to the total number of lesions removed with fluorescent light imaging without regard to evaluable lesion status.

Study description

Background summary

Ovarian cancer is the twelfth leading cause of cancer death in the United States. Based on data from SEER 18 2006-2012, the overall five-year survival rate is 46.2% and for distant and unstaged disease it is only 24-28% (SEER 2016; Kosary 2007). The standard management of primary ovarian cancer is optimal cytoreductive surgery (usually defined as reduction of residual disease to less than 1 to 2 cm) followed by chemotherapy (Al Rawahi 2013). Experts are advocating complete cytoreductive surgery for tumor debulking as it results in better overall survival than optimal cytoreduction (Shih 2010). Although tumor

debulking surgery is the cornerstone of current treatment in patients, the lesions can be diffuse and numerous, of various sizes, and often not readily visible in the surgical field, leading to varying rates of optimal cytoreduction among surgeons (Ibeanu 2010). This is an important factor in the poor prognosis for patients with advanced ovarian cancer. Tumor-specific intraoperative fluorescence imaging may improve staging and debulking efforts in cytoreductive surgery.

Study objective

Primary
* To confirm the efficacy of OTL38 in combination with fluorescent light to detect additional Folate Receptor-positive (FR+) ovarian cancer lesions not detected by palpation and visualization under normal light in patients with FR+ ovarian cancer scheduled to undergo primary surgical cytoreduction, interval debulking, or recurrent ovarian cancer surgery

Secondary
* To estimate the proportion of folate positive ovarian cancer patients in whom all lesions detected by fluorescent light only are histologically negative, the patient level False Positive Rate (FPRp)
* To estimate the Sensitivity and False Positive Rate for OTL38 in combination with fluorescent light with respect to the detection of FR+ ovarian cancer lesions confirmed by central pathology
* To assess the safety of using OTL38 and Visionsense VS3 Imaging System for intraoperative imaging with OTL38

Exploratory
* To estimate the lesion inoperability rate for all lesions identified by fluorescent light only.
* To describe the diagnostic characteristics of OTL38 in combination with fluorescent light for lesions of various histological and pathological cell types
* To assess CA-125 levels before and after surgery
* To estimate the plasma pharmacokinetics (PK) of OTL38 in patients with FR+ ovarian cancer scheduled to undergo primary surgical cytoreduction, interval debulking, or recurrent ovarian cancer surgery

Study design

This is a phase 3, randomized, multi-center, single dose, open label, pivotal study in patients diagnosed with, or with high clinical suspicion of, ovarian cancer scheduled to undergo primary surgical cytoreduction, interval debulking, or recurrent ovarian cancer surgery.
All patients participating in the study are expected to receive OTL38 and undergo normal light evaluation; however, to guard against the possible *under-

calling* of lesions during the normal light assessment, a small number of patients will be randomized to a no fluorescent imaging group. All patients will first undergo evaluation by normal light and all suspicious lesions identified under normal white light will be recorded as such. Following normal light assessment, but prior to any surgical removal of lesions or the use of fluorescent light imaging, patients will be randomized to either undergo fluorescent imaging or not. Patients randomized to the no fluorescent imaging group receive the usual standard of care and surgery based on normal light assessment only. Patients randomized to the fluorescent imaging group will undergo assessment with fluorescent light imaging prior to and after surgery. The randomized allocation ratio of normal light and fluorescent imaging patients to normal light only patients will remain blinded to the Investigators and their staff. Please see Section 5.7.1.2. for details regarding surgical procedures and imaging data collection.
Prior to the surgery, the clinician will develop an initial Pre-Fluorescence Surgical Plan for the patient based on medical history, physical examination and laboratory evaluation, including imaging studies such as CT, PET and/or MRI. The clinician will confirm and record this Pre-Fluorescence Surgical Plan at the time of surgery based on their evaluation of the patient under normal white light only, and prior to fluorescent imaging. Any changes to the Pre-Fluorescence Surgical Plan based on fluorescent light imaging, both prior to initiation of the surgical procedure and upon reimaging of the surgical field after the surgical procedure immediately prior to surgical closure, will be recorded in the case report forms.
Efficacy will be assessed for patients undergoing both normal light and fluorescent light imaging. All patients exposed to OTL38, regardless of randomized group assignment, will be followed for safety. The study will consist of a screening period of up to 28 days prior to the scheduled surgery, a diagnosis and treatment period (day of surgery; Day 1), and safety assessment visits on Day 7 (+/-4) and Day 28 (+/-4) after surgery. The study database will be frozen when the last patient completes the Day 28 assessment (which will be considered the study completion date); AEs will not be monitored after the study completion date. Long-term follow-up data on CA-125 levels will be collected 6 months after surgery from available patients

Intervention

Administration of OTL38 and use of a fluorescent imaging system during surgery.

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. Female patients 18 years of age and older
2. Have a primary diagnosis, or at high clinical suspicion, of primary ovarian cancer (of epithelial type), planned for primary surgical cytoreduction, interval debulking, or have recurrent ovarian cancer surgery, and:
o Who are scheduled to undergo laparotomy for the debulking surgery OR
o Who are scheduled to undergo laparoscopy and pre-authorized to undergo laparotomy for the debulking surgery if cancer is detected on the laparoscopy
3. 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
4. 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
5. Ability to understand the requirements of the study, provide written informed consent for participation in the study and authorization of use and disclosure of protected health information, and agree to

Exclusion criteria

1. Previous exposure to OTL38
2. Known FR-negative ovarian cancer
3. Planned surgical debulking via laparoscopy or robotic surgery, with no intent of laparotomy.
4. Patients with known ovarian cancer miliary disease prior to surgery
5. Any medical condition that, in the opinion of the investigators, could potentially jeopardize the safety of the patient
6. History of anaphylactic reactions
7. History of allergy to any of the components of OTL38, including folic acid
8. Pregnancy or positive pregnancy test
9. Clinically significant abnormalities on electrocardiogram (ECG)
10.Presence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule
11.Impaired renal function defined as eGFR< 50 mL/min/1.73m2
12.Impaired liver function defined as values > 3x the upper limit of normal (ULN) for alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), or total bilirubin.
13.Known Stage IV ovarian cancer with brain metastases
14.Received an investigational agent in another clinical trial within 30 days prior to surgery
15.Known sensitivity to fluorescent light

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Diagnostic

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	26-02-2019
Enrollment:	10
Type:	Actual

Medical products/devices used

Generic name:	Visionsense and Quest
Registration:	Yes - CE outside intended use

Ethics review

Approved WMO Date:	06-12-2018
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	26-02-2019
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO	

Date:	22-07-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	20-05-2020
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: 27574
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
EudraCT	EUCTR2018-004255-20-NL
CCMO	NL68086.056.18
OMON	NL-OMON27574