Optical PD-L1 imaging using Quantitative Fluorescence Endoscopy in locally advanced esophageal cancer using durvalumab-680LT: a phase I multicenter feasibility and safety study

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This study has been transitioned to CTIS with ID 2024-517258-85-00 check the CTIS register for the current data. The primary objective of this study is to determine the feasibility and safety of quantitative fluorescence endoscopy using the...

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

Summary

ID

NL-OMON51996

Source
ToetsingOnline

Brief title
Fluorescence endoscopy in esophageal cancer

Condition

- Malignant and unspecified neoplasms gastrointestinal NEC

Synonym
Locally advanced esophageal cancer

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: Horizon 2020

Intervention

Keyword: Endoscopy, Fluorescence, Locally advanced esophageal cancer, Programmed death-ligand 1

Outcome measures

Primary outcome

To determine the safety and feasibility of quantitative fluorescence endoscopy using the fluorescent tracer durvalumab-680LT to get more insight in the heterogeneity of programmed death-1 ligand (PD-L1) expression before and after neoadjuvant therapy in patients with locally advanced EC.

Secondary outcome

- To quantify optical properties and fluorescence signals in vivo and ex vivo using multi-diameter single-fiber reflectance, single-fiber fluorescence (MDSFR/SFF) spectroscopy measurements;

- To compare the fluorescence intensity and tumor-to-background (TBR) of the fluorescent tracer durvalumab-680LT before and after neoadjuvant therapy;

- To correlate and validate fluorescence signals detected in vivo with ex vivo histopathology, immunohistochemistry;

- To compare PD-L1 expression detected during study-specific procedures with the standard biopsies to assess spatial heterogeneity;

- To assess the (sub)-cellular location and distribution of durvalumab-680LT by ex vivo fluorescence microscopy;

- To determine the most optimal dose of durvalumab-680LT for fluorescence

molecular endoscopy if the lowest dose proves to be insufficient;

- To evaluate the feasibility of molecular fluorescence endoscopy for in vivo

detection of fluorescence;

- To validate single fiber reflection / single fiber fluorescence (SFR/SFF)

spectroscopy measurements to identify submucosal residual tumor expression, and

to distinguish between positive and negative lymph nodes and to correlate to

cytology results;

Study description

Background summary

Treatment of patients with locally advanced esophageal cancer (EC) is multidisciplinary and consists of neoadjuvant therapy followed by surgical removal of the esophageal tumor and potentially tumor positive lymph nodes. The beneficial effect of the addition of immunotherapy to improve response rates to current treatment strategies has been investigated response to, since only 16 to 43% of EC patients achieve a pathological complete response (pCR) after neoadjuvant therapy and a pCR is associated with better long-term outcomes. Unfortunately, not all patients respond to immunotherapy and the knowledge about biomarkers that predict response to therapy are required. A promising novel parameter is tumor programmed death-ligand 1 (PD-L1) expression, one of the immune checkpoints targeted by cancer immunotherapy. Studies performed in patients with various solid tumors demonstrate improved response to immunotherapy and survival benefit in patients with higher PD-L1 expression. Nonetheless, not all patients with high PD-L1 expression show benefit and some without expression do. Moreover, mostly biopsy-based tests are used to assess PD-L1 status, although these tests are prone to errors, partly due to heterogeneity in tissue expression. Novel methods are needed to gain more insight in the PD-L1 expression in order to better select patients who are likely to benefit from immunotherapy. We hypothesize that quantitative fluorescence endoscopy using the tracer durvalumab-680LT targeting PD-L1 is a promising technique to investigate the heterogeneity of PD-L1 expression.

Study objective

This study has been transitioned to CTIS with ID 2024-517258-85-00 check the CTIS register for the current data.

The primary objective of this study is to determine the feasibility and safety of quantitative fluorescence endoscopy using the fluorescent tracer durvalumab-680LT to get insight in the PD-L1 expression before and after neoadjuvant therapy in patients with locally advanced EC.

Study design

The study design is similar to the previously approved study for molecular fluorescence endoscopy of patients with EC using bevacizumab-800CW as a tracer (NL65856.042.18). The current study is a non-randomized, non-blinded, prospective, multicenter feasibility, safety study in patients with locally advanced EC. Thirty-one patients with non-metastatic locally advanced EC will be included in this study. Patients will undergo two fluorescence endoscopy procedures for in vivo analysis, that are scheduled before and after neoadjuvant therapy, after receiving a single intravenous dose of 4.5 mg durvalumab-680LT. After the fluorescence endoscopy, extensive ex vivo analyses will be performed to correlate fluorescence signals with histology, and to gain more insight in tissue distribution of the tracer. An interim analysis will be conducted when study procedures have been performed in 5 patients before neoadjuvant therapy. In case of insufficient fluorescent signal, the tracer dose will be increased. Additionally, a maximum of 5 *blanco* control patients will be included who will not receive durvalumab-680LT.

Intervention

Tracer administration: The PD-L1-targeted fluorescent tracer durvalumab-680LT will be administered intravenously 2-4 days prior to the endoscopy at the UMCG. Afterwards, patients will be monitored for one hour by measurements of vital parameters (i.e. heartrate, blood pressure and temperature) for potential side-effects, such as infusion-related reactions. In addition, blood will be drawn before, 1 hour after and 2-4 days after tracer administration.
Endoscopy procedure: Patients will undergo two endoscopies, before and after neoadjuvant therapy. Two to four days before each gastroscopy/endoscopic ultrasound, tracer injection takes place. Both endoscopies will be performed by a dedicated ultrasound endoscopists. First, routine high-definition white-light (HD-WL) inspection is used. Quantification of fluorescence using multi-diameter single fiber reflectance/single fiber fluorescence (MDSFR/SFF) spectroscopy will be performed both in vivo and ex vivo. Subsequently, fluorescence molecular endoscopy (FME) and endoscopic ultrasound (EUS) will be performed. FME allows in vivo fluorescence inspection and during EUS the depth of tissue invasion and regional lymph nodes involvement can be visualized. Furthermore, EUS enables single fiber reflectance/single fiber fluorescence (SFR/SFF) spectroscopy measurements via fine needle aspiration (FNA) to gain insight in the drug distribution throughout the tumor. Additionally, biopsies will be obtained: from the tumor (max. 6), from non-cancerous tissue (max. 2) and from additional suspected lesions when present (max. 2). In addition, cytology will

be obtained through FNA: from the tumor area (max. 3) and from (suspected) lymph nodes (max. 2).

Study burden and risks

Time investment: Three extra visits to the UMCG on the day of tracer administration which takes about two hours are needed for patients involved in this study. The first fluorescent procedures are performed during the diagnostic endoscopy before initiation of neoadjuvant treatment, which is part of normal clinical practice. The second endoscopy will be planned 2-4 weeks after neoadjuvant therapy, since this would be the optimal window to initiate immunotherapy in the future. To minimize the time investment required to attend the appointments associated with the study, when possible, said appointments will be combined with regular hospital care visits.
Risks:
The intravenous injection and the use of a cannula are known to carry a small risk of infection and hematoma. Theoretically, a possible SAE for injection of durvalumab-680LT could be an allergic or anaphylactic reaction. Therefore, anti-histamines, adrenalin and prednisone will always be present at the site of the injection. However, this is considered a very low risk and was not seen in previously injected patients. Although there is no clinical experience with durvalumab-680LT in vivo, our research group has extensive clinical experience with bevacizumab-800CW, cetuximab-800CW and vedoluzimab-800CW. We administered these tracers in more than 250 patients. In addition, the toxicity of the unlabeled antibodies is known. Since the durvalumab tracer will be administered in the clinical trials at a microdose level of 4.5 mg, the risk of adverse events is estimated as negligible. Furthermore, there is extensive clinical experience with durvalumab since it has been used as a therapeutic agent for several years.
The study procedures will prolong a standard endoscopy with approximately 15 minutes, due to spectroscopy, fluorescence imaging and biopsies. The risks of the investigational endoscopy procedures are comparable to the minimal risks of a standard clinical endoscopy as the fibers used for imaging can be inserted through the working channel of the HD-WL endoscope. The superficial biopsies that will be taken pose a very small risk of bleeding which often can be treated by the gastroenterologist. Performing FNA in combination with SFR/SFF spectroscopy poses a remote chance of loss of sterility of the SFR/SFF spectroscopy fiber and breaking of the fiber. To prevent measurements be taken in a non-sterile environment or in case of contamination, a new fiber will be attached to the system.

Benefit: Patients will not benefit from this study directly. Surgery will be planned and performed according to standard clinical care. No decisions will be made based on the fluorescence analysis. The benefit of this study will be the establishment of usefulness of durvalumab-680LT during endoscopy.

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

- Lesion suspected for locally advanced EC (cT1b-4a N0-3 M0)
- Indication for neoadjuvant therapy
- Age >= 18 years;
- Written informed consent.

Exclusion criteria

- Medical or psychiatric conditions that compromise the patient*s ability to give informed consent according to treating medical physician;
- Concurrent uncontrolled medical conditions according to treating medical physician;

- Medical history of auto-immune disease
- Pregnancy or breast feeding. A negative pregnancy test must be available for women of childbearing potential (i.e. premenopausal women with intact reproductive organs and women less than two years after menopause);
- Irradical endoscopic mucosal resection (EMR) or endoscopic submucosal dissection
(ESD) of the primary tumor prior to start of neoadjuvant chemoradiotherapy according to the patient*s medical history;
- Received a different investigational drug within 30 days prior to the dose of durvalumab-IRDye680LT according to the patient*s medical history;
- History of infusion reactions to durvalumab or other monoclonal antibodies according to the patient*s medical history;

Study design

Design

Study type:	Interventional
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	05-04-2023
Enrollment:	20
Type:	Actual

Medical products/devices used

Generic name:	A clinical therapeutic endoscope;a fiber bundle to perform fluorescence endoscopy;a MDSFR/SFF spectr
Registration:	No
Product type:	Medicine
Brand name:	nvt

Generic name:	Durvalumab-680LT, a fluorescent tracer

Ethics review

Approved WMO Date:	11-08-2022
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	14-11-2022
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	02-10-2024
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
EU-CTR	CTIS2024-517258-85-00
EudraCT	EUCTR2020-004714-35-NL
ClinicalTrials.gov	NCT05450484
CCMO	NL75480.042.22