IMAGE GUIDED SURGERY FOR MARGIN ASSESSMENT OF HEAD & NECK CANCER USING CETUXIMAB-IRDYE800CW CONJUGATE (ICON)

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

Summary

ID

NL-OMON47640

Source
ToetsingOnline

Brief title
ICON

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified
- Skin neoplasms malignant and unspecified

Synonym
squamous cell carcinoma; head & neck cancer

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: KWF Kankerbestrijding RUG-8084

Intervention

Keyword: EGFR, Fluorescence, head & neck cancer, Near Infrared tracer

Outcome measures

Primary outcome

Primary objective Part 1 (dose finding)

To determine the optimal dose of cetuximab-IRDye800CW for intra operative imaging with the SurgVision F2 open air NIRF imaging system of easily accessible anatomical areas in the head & neck region, or with a standard nasopharyngeal endoscope coupled to the SurgVision F2 NIRF imaging system for difficult accessible anatomical areas in the head & neck region.

Primary objective Part 2 (main study)

The main purpose is to establish the intraoperative use of cetuximab-IRDye800CW as a reliable marker for residual tumor in resection margins after surgical removal of HNSCC. The objective is to establish the positive predictive value of cetuximab-IRDye800CW fluorescence as a marker for a tumor positive resection margin.

Secondary outcome

To determine the threshold level in vivo of cetuximab-IRDye800CW fluorescence for reliable intraoperative deep margins assessment with high sensitivity while ensuring an adequate positive predictive value.

To quantify sensitivity and positive predictive value of cetuximab-IRDye800CW fluorescence of HNSCC ex vivo using optical molecular imaging and MDSFR/SFF versus fluorescence microscopy and EGFR immunohistochemistry.

To obtain information on safety aspects of cetuximab-IRDye800CW administration by registration of conjugate blood levels, conjugate integrity, side effects, adverse events (AE), serious adverse events (SAE) and suspected unexpected serious adverse reactions (SUSAR).

Study description

Background summary

Surgery remains a main pillar in the treatment of head and neck squamous cell carcinoma (HNSCC). The margin status is the main prognostic factor of local tumor control in surgically treated HNSCC and will determine the postoperative treatment strategy. A margin of *1 mm of normal tissue is considered a positive margin and requires either a re-operation or postoperative chemoradiation with a combination of cisplatin and 5FU, which substantially increases morbidity. Margins wider than 1 mm require re-operation or, if that is not possible, post-operative radiotherapy without the concomitant use of chemotherapy. Currently, no technology is available in the operating room, which reliably supports tumor excision in terms of margin status. In fact, surgeons can only combine pre- operative imaging data with tactile and visual information during surgery for 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. Tracers are based on antibodies directed against Vascular Endothelial Growth Factor-A, i.e. bevacizumab-IRDye800CW, in patients with breast cancer or against Epidermal Growth Factor Receptor, i.e. cetuximab-IRDye800CW, in patients with HNSCC. First trials have shown that systemic administration of these compounds is safe and tumor specific. These findings prompted us to design this innovative application in a clinical trial for the intraoperative assessment of tumor margins during surgical treatment of HNSCC using cetuximab-IRDye800CW. The study is subsidized by the Dutch Cancer Foundation.

Study objective

The main purpose is to establish the intraoperative use of cetuximab-IRDye800CW as a reliable marker for residual tumor in resection margins after surgical removal of HNSCC. The objective is to establish the positive predictive value of cetuximab-IRDye800CW fluorescence as a marker for a tumor positive resection margin.

Study design

The study is designed as a phase 1-2, single center prospective cross sectional diagnostic study in patients with HNSCC that require surgical excision. First, a dose escalation study will be performed in 9 patients using 10, 25 and 50 mg of cetuximab-IRDye800CW with three patients per dose cohort. Additional, one to three cohorts will receive a *cold* predosing dose cetuximab. Patients will receive one hour prior to cetuximab-IRDye800CW (15 or 25 or 50mg) an unlabeled *cold* unlabeled pre-dose of cetuximab. The dose found to be optimal in the first and only performed study using cetuximab-IRDye800CW in the detection of HNSCC was 25mg/m2. We therefore think that a sufficient dose will be found within this range. The most optimal dose will be used in the second part of the study which will include a cohort of 70 patients. The choice of cetuximab-IRDye800CW dose will be a balance between the lowest dose vs. a clinically usable tumor to background ration (TBR) on the fluorescence images.

During the second phase of the study tumor margins will be studied in a cohort of 70 patients to determine the positive predictive value of optical imaging to identify positive margins. Based on historical data retrieved from our HNSCC database at UMCG we anticipate in a cohort of 70 patients at least 14 (20%) margin-positive patients and a 90% EGFR overexpression rate. We anticipate a sensitivity of 90% of the cetuximab-IRDye800CW conjugate based on the EGFR overexpression rate, which we will be able to measure with sufficient precision (95%CI of 60-96%).

Intervention

Tracer administration: patients will visit the hospital four days prior to the planned surgery of their HNSCC. The cetuximab-IRDye800CW will be injected by slow infusion and patients will be monitored for potential side effects. The dose will be either 10, 25 or 50 mg of cetuximab-IRDye800CW which is less or equal to10% of the dose of cetuximab when used for curative treatment of HNSCC (usually 400mg/m2 loading dose and 250mg/m2 maintenance dose). In the *cold* predosing group, patients will receive one hour prior to cetuximab-IRDye800CW (15 or 25 or 50mg) an unlabeled *cold* unlabeled pre-dose of cetuximab. Prior to cold-dosing, 2mg clemastine will be given. From these doses one will be chosen based on the study parameters. The second part of the study will be performed with one dose of cetuximab-IRDye800CW.

Study burden and risks

Burden - Time investment: Patients need to make one extra visit to the UMCG four days before their planned surgery that will take approximately 2 hours. Usually patients are admitted one day prior to the planned surgery. Therefore the measurements one day before surgery will not require extra time investment

Burden-extra procedures: 1) Intravenous administration of cetuximab-IRDye800CW and in some cases cetuximab 2) The estimated time for taking fluorescence images and spectroscopy measurements is approximately 30min. Therefore the time under general anesthesia will be prolonged. The usual time of surgical procedures for removal of head & neck squamous cell carcinoma ranges from 2 hrs to 15 hrs, depending on complexity of the surgical procedure. 3) If fluorescence is visible in the surgical cavity of at the resection area at the excised specimen after initial resection, a direct re-resection might be executed if deemed safe by the attending head and neck surgeon.

Risks: Allergic reactions to cetuximab have been reported but this is considered a low risk. No preclinical or clinical study reported higher than grade 2 adverse events. the first study with cetuximab-IRDye800CW no serious events were reported in six patients.

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 cetuximab-IRDye800CW during surgery to identify margins containing tumors. 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 fluorescent labeled antibody in intra operative margin assessment during surgery of HNSCC.

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 HNSCC and scheduled to undergo surgical resection as decided by the Multi-Disciplinary Head & Neck Tumor Board of the UMCG.
2) Age * 18 years
3) Written informed consent
4) Adequate potential for follow up
5) Acceptable hematologic status, kidney function, and liver function, as standard surgery protocol requires.

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 cetuximab-IRDye800CW
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 enrollment: myocardial infarction, cerebrovascular accident, uncontrolled cardiac heart failure, significant liver disease, unstable angina
6) Inadequately controlled hypertension with or without current antihypertensive medications.
7) History of infusion reactions to cetuximab or other monoclonal antibody therapies
8) Pregnant or lactating women. Documentation of a negative pregnancy test must be available for women of childbearing potential. Woman of childbearing potential are premenopausal women with intact reproductive organs and women less than two years after menopause.
9) Evidence of QT prolongation on pretreatment ECG (greater than 440 ms in males or greater than 450 ms in females)
10) Lab values that in the opinion of the primary surgeon would prevent surgical resection
11) Patients receiving Class IA (quinidine, procainamide) or Class III (dofetilide, amiodarone, sotalol) antiarrhythmic agents.
12) Magnesium, potassium and calcium deviations that might lead to cardiac rhythm (grade II or higher deviations by CTCAE).
13) Life expectancy < 12 weeks
14) Karnofsky performance status < 70%

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-12-2017
Enrollment:	88
Type:	Actual

Medical products/devices used

Generic name:	clinical intra operative fluorescence camera/ spectroscoop
Registration:	No

Ethics review

Approved WMO Date:	28-11-2016
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	06-03-2017
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	11-04-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	15-06-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	16-06-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	06-07-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Approved WMO Date:	01-08-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	18-09-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	28-09-2020
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	EUCTR2016-002726-37-NL
ClinicalTrials.gov	NCT03134846
CCMO	NL58585.042.16