Multispectral and bimodal fluorescent guided surgery (FGS) of high-grade glioma for refining margin assessment: A phase 1 dose finding study using Cetuximab-IRDye800CW- combined with 5-ALA. (*MIRROR study*)

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This study has been transitioned to CTIS with ID 2024-513392-40-01 check the CTIS register for the current data. The design will be a prospective, single center phase I feasibility and dose finding study in patients with high-grade glioma, to...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Nervous system neoplasms malignant and unspecified NEC
Study type	Interventional

Summary

ID

NL-OMON53583

Source
ToetsingOnline

Brief title
MIRROR-study

Condition

- Nervous system neoplasms malignant and unspecified NEC

Synonym
High-grade glioma

Research involving

Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: 5-ALA., Cetuximab-IRDye800CW, Fluorescent guided surgery (FGS), High-grade glioma

Outcome measures

Primary outcome

The main study parameters are to establish the safety, feasibility, and optimal

dosage of Cetuximab-IRDye800CW for fluorescence guided surgery, in comparison

to the standard of care (SOC), 5-ALA fluorescent imaging agent.

Secondary outcome

The identification of DSC MR imaging biomarkers predictive for EGFR

amplification

Study description

Background summary

High-grade glioma is a high-grade astrocytoma (grade 4) and the most common primary malignant central nervous system tumor, accounting for 14.7% of the primary brain tumors each year, with an annual incidence rate of 3.21/100.000. High-grade glioma is associated with a low overall survival rate of around 15 months, with a 5-year survival rate of 5.6% post diagnosis.

Because of the (intrinsic) invasive nature of high-grade glioma in the brain, complete surgical resection will almost never be achieved. Nonetheless, surgical treatment still plays an important role in the treatment of high-grade glioma, as extensive surgical resection is a key prognostic factor of better outcomes. The downside of extensive surgical treatment however, is the potential increase in surgery related morbidity and a decrease in postoperative

quality of life. Underlying all of this and constraining extensive surgical resection, is the neurosurgeon*s visual inability to delineate tumorous tissue from healthy tissue because of a lack of contrast.

Currently, 5-aminolevulinic acid (5-ALA) is used for real-life intraoperative fluorescent imaging in patients with a high-grade glioma. 5-ALA supports the neurosurgeon intraoperatively to distinguish tumorous tissue from healthy tissue. The use of 5-ALA for High Grade Glioma surgery is described to lead to a longer progression free survival (PFS) and overall survival (OS) after surgery. However, 5-ALA has intrinsic properties that makes its use undesirable and unpractical. For example, when using 5-ALA fluorescent signals can be observed outside tumor margins, possibly leading to higher percentages of post-operative and surgery- related neurological complications.

There is a clear need for tumor specific agents that can be used during surgery for HGG to improve tumor delineation, and by that establish a refinement of margin control and achieve the most complete but non- incapacitating resection. Several studies have described the use of near infrared (NIR) fluorescent labeled antibodies for sensitive and specific cancer detection during surgical oncological resections to guide margin assessment. Optical imaging has several advantages over current methods for visualizing tumor characteristics: it does not use ionizing radiation, it provides real-time molecular information, and it is relatively cheap. Due to the inherent optical properties of NIR fluorescent dyes, improved tissue penetration is achieved by less absorption of NIR emitted light by hemoglobin, whereas less autofluorescence and scattering in the NIR region results in less non-specific fluorescence leading to false-positive signals. These properties often lead to higher signal-to-background ratios, improving contrast between healthy and non-healthy tissue.

The Epidermal Growth Factor Receptor (EGFR) gene is a proto-oncogene involved in cancer pathogenesis and EGFR-gene amplification is known to be present in 40% of high-grade gliomas. Because of the low EGFR expression in surrounding healthy brain tissue, it has the potential to be used for better tumor delineation and therefore refinement of the margin assessment compared to 5-ALA. The therapeutic antibody which targets EGFR is cetuximab. In this study, GMP fluorescent labelled Cetuximab (cetuximab-IRDye800CW) will be investigated for tumor delineation in high-grade glioma surgery.

Study objective

This study has been transitioned to CTIS with ID 2024-513392-40-01 check the CTIS register for the current data.

The design will be a prospective, single center phase I feasibility and dose finding study in patients with high-grade glioma, to establish the safety, feasibility, and optimal dosage of Cetuximab-IRDye800CW for fluorescence guided surgery, in comparison to the standard of care (SOC), 5-ALA fluorescent imaging

agent.

Study design

The first cohort, receiving a predose of 75 mg Cetuximab followed by 25 mg of Cetuximab-IRDye800CW, will be expanded until 5 patients have been included in whom a fluorescent signal is observed intraoperatively or until 10 patients have been imaged in total. After inclusion of the first cohort is finalized, an interim analysis will be performed to determine if a TBR of >2 is obtained. If an adequate TBR is found (TBR of >2), the dose of Cetuximab-IRDye800CW will be deescalated to 15 mg. If an inadequate TBR (TBR of <2) is found, the study will be terminated. During the interim analysis, DSC biomarkers obtained from the patients included in the first cohort will be correlated with EGFR-gene amplification status. If a clinically relevant predictive imaging marker is found, this marker will be validated and used for the stratification of patients with a HGG that are included after the interim analysis.

In the second cohort, receiving a predose of 75 mg Cetuximab followed by 15 mg of Cetuximab-IRDye800CW, the inclusion will be continued until 5 patients have been included in whom a fluorescent signal is observed intraoperatively or when 10 patients have been included in cohort 2. An interim analysis will then be performed to determine if a TBR of >2 is obtained by either intraoperative fluorescence imaging. If a TBR of >2 found, expansion of the cohort with the best TBR, either cohort 1 (25 mg) or cohort 2 (15 mg), will take place until 15 fluorescence positive patients have been included or the total number of 21 patients is reached. If no adequate TBR is found (TBR of <2), expansion cohort 1 (25 mg) will take place until 15 fluorescence positive patients have been included or the total number of 21 patients is reached.

Intervention

Patients will - after written informed consent -receive an intravenous injection of the predose unlabeled cetuximab and one hour later the fluorescent tracer cetuximab-IRDye800CW. The injection of cetuximab and cetuximab-IRDye800CW will be preceded by injection of clemastine 2 mg, to reduce the chance of allergic reactions. Two to four days later, fluorescence imaging is performed during surgery and after surgery, at the department of Pathology. A detailed description of the imaging procedures can be found in section 8.3. Furthermore, patients can voluntarily participate in the development of a radiomics tool, for which they will undergo approximately 30 minutes of additional MRI scanning, focused on DSC biomarkers. Additional informed consent will be obtained for this study aspect.

Study burden and risks

Burden: The burden associated with participation consists of a longer admission

visit because of the tracer administration. Also, the surgical procedure will be prolonged with approximately 15-30 minutes for taking fluorescence images.

When the participant decides that he/she wants to participate in the voluntary aspect of the study, i.e. the development of a radiomics model, his/her regular clinical MRI scanning time will be extended by approximately 30 minutes.

Risks: Risks to study participants are mainly related to the, already present, risks of the surgical procedure and to the administration of the tracer. No preclinical or clinical study reported higher than grade 2 adverse events, moreover, these studies used significant higher doses of the investigational product. Previous studies with cetuximab-IRDye800CW reported no tracer related serious events.

Benefit: Patients will have no direct benefit from this study. Surgery will be planned as usual. During surgery, no decisions will be made based on the fluorescence imaging with Cetuximab-IRDye800CW.

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

- Willing to adhere to the prohibitions and restrictions specified in this protocol.
- Capable of giving signed informed consent (voluntarily), indicating that the patient understands the purpose and procedures required for the study and is willing to comply with the requirements and restrictions listed in the informed consent form and in this protocol.
- Patients aged >= 18 years inclusive at moment signing informed consent form.
- Established High-grade glioma (astrocytoma grade 4 according to the WHO classification) and scheduled for surgical intervention.
- Life expectancy of > 12 weeks.
- Karnofsky performance status of at least 70%.
- No clinically significant laboratory abnormalities as determined by the investigator
o Note: one retest of lab tests is allowed within the screening window
- Female patients should fulfil one of the following criteria:
o At least 1 year post-menopausal (amenorrhea >12 months) at screening
o Surgically sterile (bilateral oophorectomy, hysterectomy, or tubal ligation)
o Women >18 years of age who are fertile, need to agree to use an adequate form of contraceptives during and till 3 months after the study. Before study enrollment, a pregnancy test in blood or urine will be performed to rule out a pregnancy. In the case of an unlikely pregnancy during the study, they accept the possible maternal/ fetal risk of participation in the study.

Exclusion criteria

General:
- Behavioral or cognitive impairment or psychiatric disease that in the opinion of the investigator affects the ability of the patient to understand and cooperate with the study protocol
- Deprived of freedom by an administrative or court order or in an emergency setting.
- Insufficient venous access for the study procedures.
- Close affiliation with the investigator; e.g. a close relative of the investigator,
dependent person (e.g. employee or student), employee of the department of Neurosurgery of the UMCG, or affiliates

- Any finding in the medical examinations or medical history giving, that in the opinion of the investigator, leads to a reasonable suspicion of a disease or condition that makes treatment with the investigational drug unadvisable, or that might affect interpretation of the results of the study or render the patient at high risk for treatment complications
- Participation in an interventional clinical study within 30 days prior to tracer administration that involved treatment with any drug (excluding vitamins and minerals) or medical device
Medical conditions
- Concomitant malignancies, including metastasized colon-, rectal-, breast carcinoma, non-small cellular lung carcinoma (NSCLC); primary epithelial ovarian-, fallopian tube-, primary peritoneal- or cervical carcinoma.
- Any abnormalities in the vital signs of the patient, as judged by the investigator, as a result of which the patient cannot participate
- eGFR (based on plasma-creatinine) outside of normal range at screening or known renal impairment (<=40 mL/min).
- Current evidence or history of bacterial, viral or fungal infections within 7 days before Cetuximab-IRDye800CW administration, as judged by the Investigator. o T > = 38.0°C or lab confirmed viral/bacterial/fungal infection (PCR)) or symptoms suggestive of an infection)
- Any laboratory test which is abnormal, and which is deemed by the Investigator(s) to be clinically significant
- A history of anaphylaxis, history of allergic reaction(s), known allergy to one of the drugs or excipients administered as part of this study. Mild allergies without angio-edema or treatment need can be acceptable if deemed not to be of clinical significance (including but not limited to allergy to animals or mild seasonal hay fever)

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	10-04-2023

Enrollment:	21
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Cetuximab-IRDye800CW
Generic name:	Cetuximab-IRDye800CW

Ethics review

Approved WMO Date:	09-02-2023
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	07-03-2023
Application type:	First submission
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
EU-CTR	CTIS2024-513392-40-01

Register	ID
EudraCT	EUCTR2022-002666-32-NL
CCMO	NL83364.056.22