Fluorescence-guided resection Of Colorectal liver metastases Using SGM-101 and Indocyanine GREEN.

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To assess the feasibility of simultaneous use of ICG and SGM-101 for intraoperative imaging of colorectal liver metastases.

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Hepatic and hepatobiliary disorders
Study type	Interventional

Summary

ID

NL-OMON53182

Source
ToetsingOnline

Brief title
SGM-101 and ICG in Colorectal Liver Metastasis

Condition

- Hepatic and hepatobiliary disorders
- Metastases
- Hepatobiliary therapeutic procedures

Synonym
liver cancer, metastases

Research involving
Human

Sponsors and support

Primary sponsor: Chirurgie
Source(s) of monetary or material Support: subsidies A.Vahrmeijer,Surgimab S.A.S.

Intervention

Keyword: Fluorescence, ICG, liver metastases, SGM-101

Outcome measures

Primary outcome

The main endpoint is feasibility of the simultaneous use of ICG and SGM-101. It is deemed feasible when it meets all of the following criteria:

1. A positive score on practical workability measured with survey A *practical workability during surgery*, defined as an average score of at least neutral.

2. A positive score on the patient*s experience measured with survey B *patient experience*, defined as an average score of at least neutral.

3. SGM-101: at least 80% sensitivity, measured as follows:

- For capsular lesions, that are visible in white light are counted positive if TBR >= 1.5 in vivo.

- For subcapsular lesions that are not visible in white light will be counted as positive if:

A: TBR >= 1.5 in vivo, OR

B: TBR >= 1.5 ex vivo on whole specimen or on bread loafs

All the above measurements are performed with the Quest Open Camera System

4. No cross-interference of fluorescent signal of both dyes within the two different excitation and emission channels. Cross-Interference is deemed insignificant if at macroscopic bread loaf imaging with the Quest spectrum System:

A: At the 800nm channel the rim signal (ICG, 800nm) to tumour (possibly due to SGM-101, 700nm) ratio (STR) >= 1.5

B: At the 700nm channel the tumour (SGM, 700nm) to rim signal (ICG, 800nm) ratio (TRR) >= 1.5 in SGM-101 positive tumours (defined in bullet point 3). Feasibility is reached when we get a positive result on all four items.

Secondary outcome

Secondary study parameters/endpoints (if applicable) 1. The accuracy of ICG, SGM-101 or both to demonstrate an irradical resection. The accuracy comprises of the rate of true positives, true negatives, false positives and false negative with accompanied sensitivity, specificity, positive predictive value and negative predictive value. An irradical resection may be demonstrated by: a. A fluorescent hotspot in the wound bed of either ICG, SGM-101 or both. If this results in a reresection of the hotspot in the wound bed this is correlated to the pathology outcome. When the surgeon was not able to perform a reresection of the wound bed then the assumed corresponding site at the ex-vivo specimen will be marked to correlate it to pathology. A margin of <1mm is classified as R1. Additionally, when the surgeon performs a reresection based on white light only (SGM-101 and ICG negative), this will be noted and correlated to pathology. b. A fluorescent hotspot on the ex-vivo specimen of either ICG, SGM-101 or both. This hotspot will be marked with a stitch and correlated to pathology. Likewise, the possible reresection will be correlated to pathology. 2. Concordance rate of ICG, SGM-101, ICG and SGM-101 combined (both fluorescent) or ICG and SGM-101 combined (for which only one is fluorescent), to histopathological result (lesion benign vs malignant). The concordance rate comprises of the rate of true positives, true negatives, false positives and false negative with accompanied sensitivity, specificity,

positive predictive value and negative predictive value. a. In-vivo: An in-vivo SBR (ICG)/TBR (SGM-101) of >=1,5 is determined as positive for both SGM-101 as ICG. b. ex-vivo: this will be performed with the Quest open imaging system. An ex-vivo SBR/TBR of >=1,5 is noted as positive for both SGM-101 as ICG. c. Ex-vivo bread loafs: This will be performed with both the ex-vivo Quest open imaging system as with the Pearl imaging system. A TBR/SBR of >=1,5 is noted as positive for both SGM-101 as ICG. 3. For every lesion a TBR (SGM-101) /SBR (ICG) will be calculated in vivo (Quest open camera), ex vivo whole specimen (Quest open camera, Pearl system) and ex vivo bread loafs (Quest open camera, Pearl system). 4. Modification of operative plan due to imaging (e.g. extension of resection margins, additional resection, preservation of tissue) and the correlation to histopathology. 5. Survey C *surgeon*s satisfaction and judged potency* questionnaire (see section 8.1.4) will be handed to all the surgeons at the end of the trial that have at minimum operated 3 times within this trial. Outcomes will be analysed. 6. To assess the correlation between lesion CEA expression, performed using immunohistochemistry staining, to bread loaf TBR (SGM-101) measured with the Pearl system. Hereby also correlating the effect of: a. Immunohistochemical score for CEA to bread loaf TBR. The amount of CEA expression is determined by immunohistochemistry and quantified using the immunoreactive score (IRS). b. Percentage of tumour comprising of vital tumour cells to bread loaf TBR 7. Effect of tumour depth on fluorescent status of ICG/SGM-101 will be calculated in three ways a. Distance between tumour to liver surface assessed by pre-operative CT or MRI b. Distance between tumour to liver surface as assessed by post-operative pathology c. Distance between

tumour to closest resection margin as assessed by post-operative pathology

Exploratory endpoints 1. To evaluate the feasibility of minimally invasive diagnostic approach for the early detection of colorectal cancer through circulating tumor cells and extracellular vesicles. 2. To evaluate the feasibility of using CTCs and EVs in the blood of CRC patients as biomarkers for early detection of recurrence/metastasis. 3. To evaluate the feasibility of using CTCs and EVs from peripheral blood for disease monitoring and early cancer detection.

Study description

Background summary

25-30% of patients with colorectal cancer develop colorectal liver metastases (CRLM). Cornerstone for optimal survival is achieving radical surgical resections of all metastases . To asisst the surgeon in achieving this, the use of intra-operative ICG for fluorescent tumour delineation has widely been adopted as standard of care. Multiple international trials have demonstrated that the use of ICG increases the rate of radical resections and result in the detection of additional malignant lesions invisible to the naked eye. However, the rate of false positives is still high and although it has increased the number of radical resections, even in a minimal invasive cohort the unintended R1 rate is still as much as 8%. Therefore, we are in need of an additional real-time intra-operative tool to detect R1 resections, especially in patients with a priori high risk for R1. To illustrate, in a large shared database of the Erasmus University Medical Center we found that patients that either received neoadjuvant chemotherapy, underwent a resection for >3 CRLM or patients that had a locally recurrent liver metastasis were independently associated with high R1 rates, ranging between 23-29%. Therefore, we propose the addition of SGM-101, a tumour targeted (carcinoembryonic antigen, CEA) NIR-fluorescence probe to ICG in patients scheduled for a resection with high risk of R1, ultimately to reduce the R1 ratio. This is the first trial testing the feasibility of working simultaneously with the two fluorescent dyes. If feasibility is met in this trial, this is a step-up towards a powered trial with primary objective to reduce the rate of R1 resections. An additional exploratory objective of this study is to investigate the feasibility of SGM-101*s potential to isolate circulating tumour cells (CTCs) and

tumour-derived extracellular vesicles (EVs) as biomarkers for CRC. The load of CTCs and EVs in the circulation is strongly associated with poor clinical outcomes. Studies have shown that they contain information about the molecular profile of the tumour. The administration of SGM-101 may enable the detection of CEA positive CTCs and EVs.

Study objective

To assess the feasibility of simultaneous use of ICG and SGM-101 for intraoperative imaging of colorectal liver metastases.

Study design

This is an open-label, single dose, exploratory study in the Leiden University Medical Center (LUMC).

Intervention

Administration of SGM-101: 4 (+/-1) days prior to surgery, the patient will be hospitalized. Written informed consent will be obtained prior to any study-related procedure. SGM-101 administration takes 30 minutes. After the injection, patients will remain in the hospital for at least 2 hours for observation. They will complete survey B "patient experience.

During surgery, fluorescence will be imaged with the Quest spectum camera system.

Study burden and risks

NIR fluorescence imaging using ICG results in improved detection of CRLM, although improvements could still be made. By using a tumour-specific fluorophore, SGM-101, which could be visualized on another wavelength channel, we aim to improve the intraoperative detection of CRLM and thus the rate of R0 resections. This is directly correlated with an improved overall survival. As ICG currently standard of care during oncologic liver surgery, participation in this study only requires an additional visit 4 days before surgery. SGM-101 has already shown great potential in phase I/II studies and proven to be safe and effective. No DLT have occurred. An extensive risk analysis is described in Chapter 13. The potential benefits and risks of intra-operative NIR-Fluorescence imaging during curative-intent surgical resection of CRLM using SGM-101: Potential benefits: - Potential improved intra-operative visualization of local tumor status and extent, and surgical plane, potentially resulting in: * Lesion removal with greater precision; higher chance of achieving an R0 resection. Patients participating in this study will undergo intraoperative NIR-fluorescence imaging after injection of a single dose of ICG, which is standard-of-care in the LUMC, and SGM-101. NIR-Fluorescence

imaging is a clinical technology that requires administration of a fluorescence-imaging agent that can be excited at near-infrared (NIR) wavelengths of ~700-800*nm. Upon illuminating tissue surfaces with penetrating NIR light to excite the imaging agent within the tissues, the generated fluorescence is collected to form a two-dimensional (2D) image demarking the tissue deposition of the imaging agent. Intraoperative NIR-fluorescence imaging is an additional intra-operative tool for surgeons which could provide them with real-time visual enhancement and guidance during open and minimally invasive (laparoscopic/robotic) interventions. NIR-fluorescence imaging with SGM-101 is used in conjunction with and as addition to standard white-light visual inspection (WLI), IOUS inspection and NIR-fluorescence ICG inspection and will not substitute standardized perioperative clinical. The potential benefits of NIR-Fluorescence imaging with SGM-101 on top of ICG during resection of CRLM need to be sought within the additional visual information it generates for the surgeon. The scheduled resection will be carried out according to standardized principles, besides white-light visual inspection (WLI), palpation, IOUS and NIR-fluorescence ICG imaging, NIR-fluorescence SGM-101 imaging will be used to inspect the target lesion(s), infiltration, radicality and to screen for new (liver) lesions as described in section 8.3.1. In the recent SGM-101 phase 2 trial, comprising of patients with locally advanced rectal cancer or locally recurrent rectal cancer, it was found that in 19% of patients, SGM-101 led to more complete tumour tissue removal by highlighting tumour tissue that was not detected by the naked eye, and thereby reduced the R0 rate (12). It is therefore that we suspect that the addition of SGM-101 to ICG in patients with CRLM has the potential to increase the R0 rate. Therefore, in the case NIR fluorescence imaging shows: 1) additional extent of the lesion in the surgical plane, or 2) a fluorescent hotspot in the wound bed suggesting incomplete tumor removal or 3) a fluorescent hotspot on the back table - suggesting limited marges or incomplete tumor removal- the surgeon could decide to resect this additional tissue when it is safe and surgically feasible. All lesions that are suspect on standard of care assessment will be resected (WL, ICG, IOUS, pre-operative imaging), independent of fluorescent status of SGM-101. When a lesion is not suspect/visible with standard of care but SGM-101 positive then an excision biopsy will be performed. A lesion that is not suspect in WL, ICG and SGM-101 will not be resected. During the standard follow-up of 6 months this lesion will be monitored and issued as malignant when it turns out to be malignant at the follow-up. Lastly, in case of doubt, the surgeon is able to perform a small fresh frozen biopsy (FFS) and send this to pathology for real-time analysis. Depending on the pathological result on this FFS the surgeon can decide how to judge the fluorescence. Post-operative, additionally to the standard histopathological analyses, the pathologist will evaluate the additional (FLI+, WLI-) biopsies/tissue that have been resected separately for presence of malignant tissue. In case, pathological examination shows that the additionally (FLI+, WLI-) resected tissue is 'true positive' i.e. tumor+, this could result in an (oncological) benefit for the patient. In case pathological examination shows that the additionally (FLI+, WLI-) resected tissue is 'false positive', there will be no (oncological) benefit. The

additional resected tissue is minimal compared to the magnitude of the planned surgery, the likelihood of harm caused by potential tissue removal based on a false positive signal could be graded minimal. Therefore, the potential harm for the patient is estimated to be negligible compared to the potential benefit of a more complete removal of the CRLM. This study drug (SGM-101) and study design have been used previously in colorectal and pancreatic cancer patients (phase II), without significant drug-related events, as well as no significant changes in vital signs, ECG or laboratory analysis were observed. Although, when administrating an investigational product, it is possible that unknown side effects or (hyper)sensitivity reactions occur. Based on experience with other fluorescent tracers, such reactions are generally mild and transient in nature. The risk of damage in this study related to administration of this compound is considered negligible. Currently several clinical studies (Phase II and III) are enrolling patients with colorectal cancer for evaluation of SGM-101. The multicenter national phase II trial on locally advanced rectal cancer and recurrent rectal cancer (L19-069, NL69838.056.19), still open for inclusion aims to reduce the R1 rate, similar as in the proposed study. The international multicentric phase 3 trial in colorectal cancer is currently in progress in 10 clinical centers and aims for FDA approval (P19.004 and EudraCT 2018-000151-40). In over >300 patients so far, SGM-101 has proven to be well tolerated and safe. All study drug administrations will be done in the clinic under medical supervision. The patients receiving any study drug will remain in the clinic after the administration of the study drug. Thus, the patients can be closely monitored for any adverse signs during the treatment. Therefore, providing the protocol is adhered to, careful observation and medical management will minimize any associated risk in this study. Issues of possible concern with the use of the SGM-101 and accompanying imaging system are: • Adverse reactions to SGM-101. • Presence and functioning of a Near-Infrared-Fluoresence camerasystem in the operating room; • Nonspecificity of localization; • Phototoxicity from the light source; • Fading of the chromophore (photobleaching); • Inability to excite SGM-101 or to record emission; As proven with extensive knowledge of the Leiden University Medical Center, the presence of a camera system in the operating room is not novel and should create little problem with maintaining a sterile field. The Quest Spectrum Platform Camera will be used initially prior to surgical excision to record the localization of tumors and post-excision to document the status. As such, it needs not be intrusive during the procedure. Standard hospital procedures to ensure sterilization or masking of the equipment will be employed. There is limited potential for phototoxicity from any light source

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

In total 10 patients will be included who are scheduled for resection of colorectal liver metastases and meet at least one of the following criteria: 1. Scheduled for resection of >3 CRLM or, 2. Completed neo-adjuvant chemotherapy, of which the last course was completed within 3 months before surgery or, 3. Scheduled for surgery because of a locally recurrent liver metastasis.

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:
1. Patients with contraindications for SGM-101
a. History of any anaphylactic shock;
b. Patients pregnant or breastfeeding (pregnancy should be ruled out by a pregnancy test within two weeks prior to administration of the conjugate);
c. Known positive test for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAG) or hepatitis C virus (HCV) antibody or patients with

untreated serious infections;
d. Previous administration of SGM-101
2. Patients with contraindications for Indocyanine green:
a. Allergy for shells and/or clamps
b. Hyperthyroidism
c. Known allergy for ICG
3. Any condition that the investigator considers to be potentially jeopardizing the patient*s well-being or the study objectives

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	22-02-2024
Enrollment:	10
Type:	Actual

Medical products/devices used

Generic name:	Quest Spectrum Platform imaging system v2/3.0
Registration:	Yes - CE outside intended use

Ethics review

Approved WMO

Date:	14-08-2023
Application type:	First submission

Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

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
CCMO	NL84605.058.23