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Testing if the SonoTran Platform can enhance drug delivery in metastatic colorectal cancer

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Recruitment status
No longer recruiting

Registration date
09/09/2021

Overall study status
Completed

Last Edited
08/10/2024

Condition category
Cancer

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

Plain English summary of protocol
https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-study-looking-at-the-sonotran-platform-for-bowel-cancer-that-has-spread-to-the-liver-ceedd

Background and study aims
This study will look at a new intervention in patients with bowel cancer that has spread to the liver (called colorectal cancer liver metastases (CRLM)). This is required because bowel cancer is very common, and despite best efforts, once CRLM are present, the chances of cure are small. The planned intervention combines specialist ultrasound treatment delivered to the body through the skin over the liver area (SonoTran System), and the injection of microscopic cup-shaped ‘particles’ (SonoTran Particles) that are given into the vein. The hope is that when these two are delivered together (termed the SonoTran Platform) they will help ‘push’ standard cancer drugs deeper into the tumours and increase the effectiveness of those drugs (both standard chemotherapy drugs, and newer larger cancer antibody drugs). The study is split into three parts. In the first part (cohort 1) patients who have received all standard drugs for their bowel cancer, or who are having a break off standard drugs, will receive one ‘treatment’ with the specialist ultrasound (called SonoTran System-SS) and one injection of the SonoTran Particles (SP), in order to assess the safety of the new intervention. In Cohort 2, patients who are about to have their CRLMs removed by surgery will, on the day before, receive one low dose each of the anticancer drugs irinotecan and cetuximab and, in addition, half of the patients will receive an injection of SonoTran Particles and a single 'treatment' with SonoTran ultrasound. The tumours (CRLMs) that are removed will be examined to see how much and how deep the drugs get into them. In Cohort 3, patients who have not yet received treatment for their CRLMs will receive repeated cycles of standard chemotherapy drugs (5-fluoruracil, irinotecan and cetuximab) and half of them will also receive SonoTran particles and SonoTran Ultrasound. Tumour responses will be measured and compared.

Who can participate?
Patients diagnosed with colorectal (bowel) cancer that has spread to the liver. Patients must be over 18 years of age and meet the trial’s specific eligibility criteria to participate in the study. For more information, please contact your GP or oncologist

What does the study involve?
For Cohort 1 (Safety), the researchers are looking at the safety of the SonoTran Platform intervention alone (ultrasound and particles), and no anticancer drugs will be given. During the SonoTran 'intervention' phase, patients will receive a long injection (called an infusion) of SonoTran Particles, and an administration of therapeutic SonoTran ultrasound using the SonoTran System. Additional blood samples will be taken for research tests on Day 1; the first sample will be taken immediately before patients receive the SonoTran Particles, and then at set timepoints after the start of the infusion - 15 minutes, 30 minutes, 45 minutes and 60 minutes. Patients will then be asked to return for a follow-up visit on weekly intervals - Day 8, Day 15 and Day 22 after the intervention and receive a physical examination, be asked about symptoms and any other medications, have weight, heart rate, temperature, pulse and blood pressure checked, and have routine blood tests. About 4 weeks after receiving the SonoTran Platform intervention, patients will have an FDG-PET-CT scan, an MRI scan and a CT scan to assess their tumour(s) and the effect of the SonoTran Platform.
In Cohort 2 (Performance), the researchers will investigate whether the SonoTran Platform (the combination of the SonoTran System and SonoTran Particles) can increase the delivery of a couple of routine anticancer drugs to the tumour. To do this the researchers will recruit 6 patients who, the day before their liver operation, will receive two anticancer drugs alone - cetuximab and irinotecan (at lower than standard doses), and another 6 who will receive the same anticancer drugs plus the SonoTran Platform intervention; and the researchers will compare how much of the drugs get into the tumour and how deep they get into the tumour. The researchers will be taking some of the tumour and normal tissue that is taken from the liver at your operation and they will look at the drug levels in the normal and tumour tissue in the liver. Once patients have received the intervention (drugs alone or drugs plus SonoTran Platform intervention), on Day 1, they will return the following day (Day 2) to have their tumour nodule(s) surgically removed from their liver; patients will undergo this procedure as they normally would in standard of care, and taking part in this study will not affect or delay the surgery. Additional blood samples will be taken for research tests on Day 1 and Day 2. Patients will then be asked to return for a follow-up visit on weekly intervals - Day 8, Day 15, Day 22 and on Day 29 (+/- 3 days) after the intervention and receive a physical examination, be asked about symptoms and any other medications, have weight, heart rate, temperature, pulse and blood pressure checked, and have routine blood tests.
Cohort 3 (Efficacy) will make a comparison of response between the two groups of patients; 12 patients will receive the administration of the SonoTran Particles and SonoTran System in addition to the anticancer drugs, and another 12 patients will receive the chemotherapy without the addition of the SonoTran Platform. All patients in Cohort 3 (Efficacy) will receive anticancer drugs that are used routinely in the treatment of metastatic colorectal cancer (mCRC) i.e. cancer that has spread elsewhere outside the bowel. This treatment involves a drug called cetuximab, which is an antibody treatment that blocks a growth factor receptor on tumour cells to help stop them from growing. Patients will also receive two chemotherapy drugs which are called irinotecan and 5-fluorouracil (5FU). The combination of these drugs is called FOLFIRI. During the 'intervention' phase of your study involvement, participants will attend the hospital to receive six cycles of this routine cetuximab and FOLFIRI, which will be given at standard doses, every 2 weeks for a 10-week period (six cycles in all). All patients will have a CT scan, MRI scan and PET-CT scan after three 'cycles' of anticancer treatment, to assess their tumour and the effect of the drugs (+/- the SonoTran Platform). These scans will be repeated after six cycles of anticancer agents, or sooner if the patient has to come off trial treatment for any other reason. For patients who are receiving chemotherapy drugs AND the SonoTran intervention, additional blood samples will be taken for research tests on every visit they receive intervention – Day 1, Day 15, Day 29, Day 43, Day 57 and Day 71 – one sample will be taken each treatment day about

30 minutes after patients start receiving the SonoTran Particles. Patients will receive a physical examination, be asked about symptoms and any other medications, have their weight, heart rate, temperature, pulse and blood pressure checked, and have routine blood tests at all visits.

What are the possible benefits and risks of participating?
In Cohort 1 (Safety), patients will not receive any routine cancer drugs to treat their cancer. Therefore, there are no expected benefits from taking part in this study.
For Cohort 2 (Performance) there will likely be no benefit to patients from taking part in this study and receiving either the small amount of drugs alone; or the small amount plus the SonoTran Platform intervention. It is hoped that by patients taking part in the study, the researchers will learn about whether the SonoTran Platform intervention helps drugs to get into tumour nodules at greater concentrations, and deeper into the tumours, which will provide evidence that the intervention may increase the effectiveness of the cancer drugs. However, the researchers will not know the answer to this until they have completed the whole of this study.
All patients in Cohort 3 (Efficacy) will receive routine anticancer treatment and half of the patients will in addition receive the SonoTran Platform intervention. For patients who receive the standard anticancer treatments alone, the chances of response should be the same as if they were receiving these treatments outside of the trial. For those patients who also receive the SonoTran intervention, it is hoped that the extra intervention may increase the amount of chemotherapy drug reaching the tumour, and it is hoped that for some individuals, this may then improve the chances of response to the routine anticancer treatment. However, this improvement, compared to standard anticancer treatment alone, cannot be guaranteed as this has not yet been tested in this way in human beings.
By entering this study patients will be making a significant contribution to a study that will provide information to increase our knowledge of the SonoTran Platform, which may help us to improve the future treatment of patients with metastatic colorectal cancer, with metastases to the liver.
As the SonoTran Particles and SonoTran System have never been used on patients before, the risks of both medical devices are unknown, so there is the risk that these interventions may cause side effects that we do not yet know about.
Based on the preclinical (animal) testing of SonoTran Particles the following side effects may occur - mild inflammation of the liver, a reaction or inflammation locally in the vein (where the particles go in). It is also possible that unexpected side effects could occur.
For the standard chemotherapy treatment, potential side effects may include but are not limited to: skin reactions e.g. rash, chills, dizziness, diarrhoea, anaemia (low number of red blood cells), shortness of breath, sore mouth, feeling sick (nausea), hair loss, fever, tiredness (fatigue), dehydration, headache, vomiting, lowered resistance to infection. (This treatment can potentially reduce the production of white blood cells by the bone marrow, making patients more prone to infection. This is potentially life-threatening and needs prompt assessment and treatment)

Where is the study run from?
University of Oxford (UK)

When is the study starting and how long is it expected to run for?
April 2021 to December 2024

Who is funding the study?
1. National Institute for Health Research (NIHR) (UK)
2. OxSonics Ltd (UK)

Who is the main contact?
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Study website
https://www.oncology.ox.ac.uk/clinical-trials/oncology-clinical-trials-office-octo/current-trials/ceedd

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Scientific

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
CPMS 49873, IRAS 289760

Study information

Scientific Title
CEeDD: a first-in-human clinical investigation of cavitation-enhanced drug delivery to solid tumours by co-administration of sonosensitive particles and application of extracorporeal ultrasound in patients with colorectal metastases to the liver

Acronym

CEeDD

Study objectives
The trial is split into three cohorts of patients and each has been designated their own primary and secondary endpoints. However, the overarching aim of the study is to assess the safety, feasibility, and early efficacy of the intervention described. The intervention is a combination of SonoTran particles (SP) which are microscopic polymer particles that are cup-shaped and which carry a 'bubble' within their 'cups' when they are in a liquid such as blood. When they are travelling through the bloodstream and tissues of the body, and then the SonoTran Ultrasound (SonoTran System or SS) is applied to a specific area through the skin, then the 'bubbles' in the particles expand and collapse (called inertial cavitation) and the theory is that this activity has the capability of pushing anti-cancer drugs that are co-administered, deeper and in higher concentration, into tumours. This is important because our current inability to get high concentrations of drugs into tumours (especially large molecules like antibodies) limits the efficacy of these drugs and reduces the impact on tumour shrinkage and cancer survival. So, as mentioned in the study there will be three cohorts. Cohort 1 will run and complete first. Once the safety of the SonoTran Platform (which is the combination of the SonoTran Particles and SonoTran ultrasound System) is established in this group, and the researchers have decided on a dose of particles to take forward, then Cohort 2 and 3 will commence and will run in parallel with each other, as they will recruit different populations of bowel cancer patients with CRLMs. The principal objectives of each cohort are outlined below:

Cohort 1 (termed the SAFETY cohort): To assess the safety of a single intervention with the SonoTran Platform (including administration of SonoTran Particles and SonoTran System ultrasound exposure) in the absence of any anticancer drug.

Cohort 2 (termed the PERFORMANCE cohort): To assess the extent to which the SonoTran Platform enhances the delivery of anticancer chemotherapy and antibodies (irinotecan and cetuximab) to colorectal cancer liver metastases (CRLM).

Cohort 3 (termed the EFFICACY cohort): To assess in a preliminary fashion, any increase in effectiveness of anticancer drugs (cetuximab and 5FU/irinotecan) brought about by the addition of the SonoTran Platform, when delivered alongside those drugs in the management of colorectal cancer liver metastases (CRLM).

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 23/08/2021, North of Scotland Research Ethics Committee (1) (Summerfield House, 2 Eday Road, Aberdeen, AB15 6RE, UK; +44 (0)1224558458; gram.nosres@nhs.scot), REC ref: 21/NS/0090

Study design
Randomized; Interventional; Design type: Treatment, Device

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details to request a participant information sheet

Health condition(s) or problem(s) studied
Colorectal cancer liver metastases (CRLM)

Interventions
The randomisation for patients into Cohort 3 will be on a 1:1 basis, using a validated computer randomisation program called Registration / Randomisation and Management of Product (RRAMP) managed through a secure (encrypted) web-based service by the Oxford Clinical Trials Research Unit (OCTRU) using a permuted block randomisation method.

Overall, the design of all cohorts in the study is based on assessing feasibility and it is important to note that specifically cohorts 2 and 3 are not designed to give adequate statistical power to give definitive evidence of the effectiveness of this novel intervention.

Cohort 1 - 'Safety': Dose escalation design
Up to 12 participants will be recruited to the 'Safety' Cohort. Each patient will receive one dose of SonoTran particles and one SonoTran US System intervention at the same time on the same visit. The whole visit (including preparation time etc) will likely take most of one day. This will be in the Early Phase Trials Unit. The patients will then be followed up for 4 weeks after the day of the interventions, with weekly visits for blood tests and examinations; plus scans (CT/MRI PET) at baseline and after 4 weeks (to assess any radiological changes). The follow-up visits are likely to take approximately 2 hours maximum. On Day 1 (intervention day) baseline blood samples will be taken for routine and research tests (15-50ml in all = 3-4 teaspoons) taken just before the SonoTran intervention. Subsequently, at set timepoints after the start of the Particle administration - 15 minutes, 30 minutes, 45 minutes and 60 minutes a further 5 ml of blood (1 teaspoon) will be taken (for particle concentration measurement. Follow up bloods on subsequent visits will total 3 vials of blood (approx. 3 teaspoons of blood).

The researchers will initially test (in the first 3 patients) the lowest dose of SonoTran Particles and this starting dose has been selected based on information from animal studies. The researchers have defined three dose levels they will test and they are calling them dose level (-1), dose level (0) and dose level (+1). If the dose of (-1) is well tolerated in 3 patients, they will increase the dose of SonoTran Particles up to (0) for the next set of 3 patients, and then perhaps up to dose level (+1) depending on what they see in terms of side effects and the information they get back from the ultrasound machine to see how the SonoTran System is working in terms of causing the 'inertial cavitation' (expanding and collapsing), of the bubbles associated with the particles.

Cohort 2 - 'Performance': Parallel group allocated (non-randomised) design
The researchers will recruit 12 patients who, as part of their standard cancer pathway, are listed to have their CRLMs removed by surgery and they will investigate whether the SonoTran Platform (SonoTran US and Particles) can increase the delivery of routine anticancer drugs

(irinotecan and cetuximab) to the tumours in the liver. In this part of the study, the day before planned surgery to remove the CRLMs, 6 patients will receive one dose each of the anticancer drugs (irinotecan and cetuximab, but NO SONOTRAN intervention; and another 6 will receive the same drugs plus the SonoTran intervention; and the researchers will be comparing how much of the drugs in the two groups of patients, get into the tumour; and how deeply they penetrate the tumour. The researchers will be taking some of the tumour and the surrounding normal liver tissue that is taken from patients at the operation and they will look at the drug levels in the normal and tumour tissue. They will not be taking any extra tissue at the operation compared to what the surgeons would normally be taking, and it will not affect the way in which the pathologist assesses the tumour. The drugs (irinotecan and cetuximab) are drugs that are frequently used for colorectal cancer liver metastases and are licensed for use in these patients. As patients are having these before surgery and because the researchers are not trying to see whether these will shrink the tumours, they will be giving them at lower than maximum doses to ensure their safety.

Additional blood samples (above those taken for routine practice) will be taken for research tests on Day 1 and Day 2:

In terms of extra blood samples, for the half of the patients that will be undergoing the SonoTran Platform intervention as well as receiving the drugs, then on Day 1, two vials of blood (10ml - 2 teaspoons) will be taken 30 minutes after the start of the SonoTran Particles infusion, and on Day 2 vials of blood (10ml - 2 teaspoons) will be taken within 4 hours prior to surgery. For patients not receiving the SonoTran Platform intervention, then on Day 1, one vial of blood (5 ml - 1 teaspoon) will be taken 60 minutes after they have finished the irinotecan infusion, and on Day 2, one vial of blood (5 ml - 1 teaspoon) will be taken within 4 hours prior to surgery.

On Day 2 of the study, patients will attend to have their planned operation to remove their CRLMs and they will undergo this procedure as they normally would within their standard of care pathway, and no extra tissue will be taken. The study will take research samples from the tumour in addition to taking healthy liver samples from the surrounding tissue (again all taken as part of the routine operation) in order to analyse and compare the effect of the intervention and to check for any signs of damage due to the intervention in the healthy liver tissue surrounding the tumour nodules.

Cohort 3 - 'Efficacy': Randomised early phase 2 design
This cohort will recruit 24 patients to assess (in a preliminary fashion) whether applying the SonoTran platform (Particles and US) alongside standard of care (SOC) anticancer drugs (cetuximab plus 5FU and irinotecan (together known as the FOLFIRI/cetuximab regime)) potentially increases the response rates and response depths to the anticancer drugs; and whether potentially it also increases the chance that the individual patient will eventually get to curative liver resection for their CRLMs.

The investigation will make a comparison of response between the two groups of patients; The control group will be 12 patients who receive the SOC anticancer agents alone in the standard FOLFIRI regime. The intervention group will be 12 patients who receive the same FOLFIRI regime plus the SonoTran Particles and SonoTran System, The FOLFIRI/cetuximab regime +/- SonoTran platform will be administered six times at 2-weekly intervals within the study. Comparison of response will be made by measuring the tumour size on CT and MRI and SUV on PET-CT, with all scans carried out at baseline prior to starting treatment, then after 3 and 6 cycles of treatment/ intervention (so about 7 and 13 weeks after initial intervention).

It is important to reiterate that all patients in this Cohort will receive standard anticancer medications (FOLFIRI/cetuximab regime) that are used in the routine treatment of metastatic colorectal cancer (mCRC) and at standard doses, with a plan to receive 6 cycles plus or minus the SonoTran Platform intervention with each cycle.

For patients receiving chemotherapy drugs AND the SonoTran intervention, an additional blood sample will be taken for research tests on each visit during which they receive the drugs and SonoTran intervention: Day 1, Day 15, Day 29, Day 43, Day 57 and Day 71. This will be one vial of blood each time, taken approximately 30 minutes after they start receiving the SonoTran Particles. If patients are not receiving the SonoTran intervention then they will not have these additional blood samples taken.

In addition to the SOC CT scan, PET-CT scan & MRI scan that the patients would receive before and after their six cycles of FOLFIRI/cetuximab treatment, additional scans will be performed at Day 36 to assess early response to treatment. However, it is important to note that even within SOC, many centres do repeat their monitoring scans at 6-8 week intervals, so this frequency is not unusual.

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Irinotecan, cetuximab, fluorouracil

Primary outcome measure
Cohort 1: Safety assessed using:
1. Immediate ill effects e.g. pain, fever
2. Full blood count (FBC), urea and electrolytes (U&E), creatinine and liver function tests (LFTs) (ALT/AST/alkaline phosphatase/albumin)
3. Acute radiological changes
In terms of all of the above the researchers will be looking at the presence of grade 3 /4 Common Terminology Criteria for Adverse Events (CTCAE) events that are not expected within the context of the disease state for that patient
Timepoint(s): Cohort 1 - Cumulative up to 28 days post-intervention, measured weekly for 4 weeks post-intervention. All grades will be recorded. The worst grade reached will define the maximum toxicity for that event.

Cohort 2: Drug delivery assessed using the intratumoural concentration of cetuximab, irinotecan, SN38 and SN38G in resected tumour tissues in the SonoTran Platform group compared to the group receiving drug treatment alone (2B versus 2A)
The timepoint is the time of resection of the surgical specimen as this is the point at which no further drugs will reach the tumour tissue. Tumour will be carried immediately to the pathology lab where the pathologist will dissect appropriate tissue for fresh frozen allocation for future assays. The remainder of the tissue will be embedded and some used for standard path data; slices will subsequently be taken for formalin-fixed, paraffin-embedded (FFPE) analysis of cetuximab distribution.

Cohort 3: Efficacy, comparing Arm 3B (drugs plus SonoTran intervention) versus Arm 3A (drugs alone) by:
1. Response on CT (response evaluation criteria in solid tumors (RECIST)/immune-related RECIST (irRECIST)/Choi)
2. Response on PET-CT (SUV Max and glycolytic volume)
3. Response on MRI
The timepoints are pre-treatment and post cycle 3 and post cycle 6, for each modality.

Secondary outcome measures
Cohort 1 Safety:
The detection of acoustic emissions in the target tumour by Passive Acoustic Mapping (PAM) at the time of the single intervention on day 1

Cohort 2 Performance:
Adverse events (symptoms and haematological/liver function tests (LFTs) (ALT/AST/alkaline phosphatase/albumin)) weekly up to 28 days post-intervention in Arm 2B versus 2A control

Cohort 3 Efficacy:
1. Adverse events (symptoms and haematological/liver function tests - ALT/AST/alkaline phosphatase/albumin) pre-each cycle of drugs (+/- SonoTran) and at the exit from the study
2. Radiological read-outs of damage to normal liver as measured by CT and MRI after 3 and 6 cycles of intervention and compared with baseline
3. Downstream liver metastatic resectability as measured by local MTD at the patient's exit point from the clinical investigation after completing drug (+/- SonoTran) intervention

Overall study start date
01/04/2021

Completion date
31/12/2024

Eligibility

Key inclusion criteria
Current inclusion criteria as of 12/06/2023:
Current participant inclusion criteria as of 12/06/2023:
Cohort 1 (safety):
1. At least 1 confirmed CRC liver metastasis >1cm in diameter that is geographically accessible to SonoTran intervention
2. ≥ 18 years of age.
3. Written (signed and dated) informed consent and be capable of cooperating with treatment and follow-up.
4. Haematological and biochemical indices within the ranges shown below within 14 days prior to enrolment:
4.1. Haemoglobin (Hb) ≥9.0 g/dl (can be transfused to this value)
4.2. Absolute neutrophil count ≥1.5 x 10e9/l
4.3. Platelet count ≥100 x 10e9/l
4.4. Serum bilirubin ≤1.5 x upper limit of normal (ULN)
4.5. Alanine aminotransferase (ALT) ≤5 x ULN
4.6. Aspartate aminotransferase (AST) ≤5 x ULN

4.7. Serum creatinine ≤1.5 x ULN
4.8. PT and APTT ≤1.25 x ULN
4.9 Albumin ≥28 g/l
5. Female subjects of childbearing potential must have negative pregnancy test within 14 days prior to SonoTran intervention.
6. Patients with a diagnosis of mCRC, who are either not eligible to receive the standard of care chemotherapy or who have exhausted all lines of standard of care; or who are presently on a planned break from SOC chemotherapy.
7. ECOG performance status of 0, 1 or 2.

Cohort 2 (performance):
1. At least 1 confirmed CRC liver metastasis >1cm in diameter, and metastatic disease that is planned to be IMMEDIATELY resected is without formal neo-adjuvant chemotherapy.
2. The metastasis(es) can be geographically inaccessible to SonoTran intervention as long as there are still spaces in Cohort 2A of the study (i.e. drugs alone prior to surgical resection). If there are no spaces on Arm 2A and spaces still remain on Arm 2B, the patients will require to have at least one geographically-accessible lesion amenable to SonoTran intervention.
3. Chemotherapy-naïve in terms of chemotherapy for metastatic CRC (patients can have received adjuvant chemotherapy as long as this has been completed at least 3 months prior to planned intervention within the study)
4. If there is disease outside of the liver, there must be a plan to eradicate this e.g. by surgery, ablation or SABR treatment as part of the curative strategy.
5. ≥ 18 years of age.
6. Written (signed and dated) informed consent and be capable of cooperating with treatment and follow-up.
7. Haematological and biochemical indices within the ranges shown below within 14 days prior to enrolment:
7.1. Haemoglobin (Hb) ≥9.0 g/dL (can be transfused to this value)
7.2. Absolute neutrophil count ≥1.5 x 10e9/l
7.3. Platelet count ≥100 x 10e9/L
7.4. Serum bilirubin ≤1.5 x upper limit of normal (ULN)
7.5. Alanine aminotransferase (ALT) ≤5 x ULN
7.6. Aspartate aminotransferase (AST) ≤5 x ULN
7.7. Serum creatinine ≤1.5 x ULN
7.8. PT and APTT ≤1.25 x ULN
7.9. Albumin ≥28g/l
8. Female subjects of childbearing potential must have negative pregnancy test within 14 days prior to SonoTran intervention.
9. ECOG performance status of 0 or 1.
10. Female subjects of childbearing potential and male subjects whose sexual partners are of childbearing potential must agree to abstain from sexual intercourse or to use an effective method of contraception during the study and up to 6 months after the end of study. Examples of effective methods of contraception include oral or injected contraceptives or double barrier methods such as condom plus spermicide or condom plus diaphragm.

Cohort 3 (efficacy):
1. At least 1 confirmed CRC liver metastasis >1cm in diameter, and metastatic disease that is NOT planned to be IMMEDIATELY resected or ablated.
2. Patients will require to have at least one geographically-accessible lesion amenable to SonoTran intervention.
3. Chemotherapy-naïve in terms of chemotherapy for metastatic CRC (patients can have received adjuvant chemotherapy as long as this has been completed at least 3 months prior to

planned intervention within the study)
4. ≥ 18 years of age.
5. Written (signed and dated) informed consent and be capable of cooperating with treatment and follow-up.
6. Haematological and biochemical indices within the ranges shown below within 14 days prior to enrolment:
6.1. Haemoglobin (Hb) ≥9.0 g/dL (can be transfused to this value)
6.2. Absolute neutrophil count ≥1.5 x 10e9/L
6.3. Platelet count ≥100 x 10e9/L
6.4. Serum bilirubin ≤1.5 x upper limit of normal (ULN)
6.5. Alanine aminotransferase (ALT) ≤5 x ULN
6.6. Aspartate aminotransferase (AST) ≤5 x ULN
6.7. Serum creatinine ≤1.5 x ULN
6.8. PT and APTT ≤1.25 x ULN
6.9. Albumin ≥28g/l
7. Confirmed RAS wild-type CRC
8. Female subjects of childbearing potential must have negative pregnancy test within 14 days prior to SonoTran intervention.
9. ECOG performance status of 0 or 1.
10. Female subjects of childbearing potential and male subjects whose sexual partners are of childbearing potential must agree to abstain from sexual intercourse or to use an effective method of contraception during the study and up to 6 months after the end of study. Examples of effective methods of contraception include oral or injected contraceptives or double barrier methods such as condom plus spermicide or condom plus diaphragm.

Previous inclusion criteria:

Cohort 1 (safety):
1. ≥18 years of age
2. Written (signed and dated) informed consent and be capable of cooperating with treatment and follow-up
3. Haematological and biochemical indices within the ranges shown below within 14 days prior to enrolment:
3.1. Haemoglobin (Hb) ≥9.0 g/dl (can be transfused to this value)
3.2. Absolute neutrophil count ≥1.5 x 10e9/l
3.3. Platelet count ≥100 x 10e9/l
3.4. Serum bilirubin ≤1.5 x upper limit of normal (ULN)
3.5. Alanine aminotransferase (ALT) ≤5 x ULN
3.6. Aspartate aminotransferase (AST) ≤5 x ULN
3.7. Serum creatinine ≤1.5 x ULN
3.8. PT and APTT ≤1.25 x ULN
3.9 Albumin ≥28 g/l
4. Female subjects of childbearing potential must have a negative pregnancy test within 14 days prior to SonoTran intervention.
5. Patients with a diagnosis of mCRC with at least 1 liver metastasis more than 1cm in size, who are not eligible to receive the standard of care chemotherapy or who have exhausted all lines of standard of care; or who are presently on a planned break from SOC chemotherapy
6. ECOG performance status of 0, 1 or 2

Cohort 2 (performance):
1. ≥18 years of age
2. Written (signed and dated) informed consent and be capable of cooperating with treatment

and follow-up
3. Haematological and biochemical indices within the ranges shown below within 14 days prior to enrolment:
3.1. Haemoglobin (Hb) ≥9.0 g/dL (can be transfused to this value)
3.2. Absolute neutrophil count ≥1.5 x 10e9/l
3.3. Platelet count ≥100 x 10e9/L
3.4. Serum bilirubin ≤1.5 x upper limit of normal (ULN)
3.5. Alanine aminotransferase (ALT) ≤5 x ULN
3.6. Aspartate aminotransferase (AST) ≤5 x ULN
3.7. Serum creatinine ≤1.5 x ULN
3.8. PT and APTT ≤1.25 x ULN
3.9. Albumin ≥28g/l
4. Female subjects of childbearing potential must have a negative pregnancy test within 14 days prior to SonoTran intervention.
5. Patients with a diagnosis of mCRC which is IMMEDIATELY amenable to resection without neoadjuvant chemotherapy, with at least one liver metastasis at least 1 cm in size, and who have NOT received any chemotherapy for at least 3 months (i.e. adjuvant chemotherapy must have been completed at least 3 months prior to recruitment). If there is disease outside of the liver, there must be a plan to eradicate this e.g. by surgery, ablation or SABR treatment as part of the curative strategy
6. ECOG performance status of 0 or 1

Cohort 3 (efficacy):
1. ≥18 years of age
2. Written (signed and dated) informed consent and be capable of cooperating with treatment and follow-up
3. Haematological and biochemical indices within the ranges shown below within 14 days prior to enrolment:
3.1. Haemoglobin (Hb) ≥9.0 g/dL (can be transfused to this value)
3.2. Absolute neutrophil count ≥1.5 x 10e9/L
3.3. Platelet count ≥100 x 10e9/L
3.4. Serum bilirubin ≤1.5 x upper limit of normal (ULN)
3.5. Alanine aminotransferase (ALT) ≤5 x ULN
3.6. Aspartate aminotransferase (AST) ≤5 x ULN
3.7. Serum creatinine ≤1.5 x ULN
3.8. PT and APTT ≤1.25 x ULN
3.9. Albumin ≥28g/l
4. Confirmed RAS wild-type CRC
5. Female subjects of childbearing potential must have a negative pregnancy test within 14 days prior to SonoTran intervention.
6. Patients with a diagnosis of mCRC which is NOT IMMEDIATELY amenable to resection without neoadjuvant chemotherapy, who require 1st line metastatic chemotherapy, with at least one liver metastasis at least 1cm in size, and who have NOT received any chemotherapy for at least 3 months (i.e. adjuvant chemotherapy must have been completed at least 3 months prior to recruitment).
7. ECOG performance status of 0 or 1

Participant type(s)
Patient

Age group

Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
Planned Sample Size: 48; UK Sample Size: 48

Total final enrolment
26

Key exclusion criteria
Current participant exclusion criteria as of 12/06/2023:
Cohort 1 (safety):
1. Any active anti-cancer therapy (chemotherapy / small molecule inhibitors / immunotherapy) within 4 weeks or liver radiotherapy within 8 weeks, prior to planned intervention in the study.
2. Persistent, unresolved CTCAE v5.0 Grade 2 or higher drug-related toxicity (except alopecia, erectile dysfunction, hot flashes, decreased libido, chronic neuropathy) following previous treatment.
3. Inadequate recovery from any prior surgical procedure or major surgical procedure performed within 4 weeks prior to enrolment.
4. Any other medical or psychiatric condition that, in the opinion of the investigator, might interfere with the subject's participation in the clinical investigation or interfere with the interpretation of clinical investigation results.
5. Serious/symptomatic active infection or infection requiring antibiotics, within 7 days prior to enrolment.
6. Presence of active cholangitis.
7. Known Human Immunodeficiency Virus (HIV) infection or a known HIV-related malignancy.
8. Known bleeding diathesis.
9. Inability to comply with the protocol requirements.
10. Participation in any other clinical trials involving therapeutic agents within the last 4 weeks prior to enrolment.
11. Pregnant or lactating females.
12. Patients with liver metastases eligible for immediate surgical resection or other radical therapy such as ablation, unless these interventions are not expected to occur within the next 8 weeks, allowing participation in the study and completion of follow-up, prior to that specified intervention

Cohort 2 (performance):
1. Any active anti-cancer therapy (chemotherapy / small molecule inhibitors / immunotherapy) within 4 weeks or liver radiotherapy within 8 weeks, prior to SonoTran intervention.
2. Persistent, unresolved CTCAE v5.0 Grade 2 or higher drug-related toxicity (except alopecia, erectile dysfunction, hot flashes, decreased libido, chronic neuropathy) following previous treatment.
3. Inadequate recovery from any prior surgical procedure or major surgical procedure performed within 4 weeks prior to enrolment.
4. Any other medical or psychiatric condition that, in the opinion of the investigator, might interfere with the subject's participation in the clinical investigation or interfere with the

interpretation of clinical investigation results.
5. Serious/symptomatic active infection or infection requiring antibiotics, within 7 days prior to enrolment.
6. Presence of active cholangitis.
7. Known Human Immunodeficiency Virus (HIV) infection or a known HIV-related malignancy.
8. Known bleeding diathesis.
9. Inability to comply with the protocol requirements.
10. Participation in any other clinical trials involving therapeutic agents within the last 4 weeks prior to enrolment.
11. Pregnant or lactating females.
12. Known UGT-1A1 polymorphism.
13. Patients with liver metastases that require formal neoadjuvant chemotherapy to downstage prior to resection.
14. Patients whose main radical intervention to the liver at outset is planned to be ablation rather than surgery.

Cohort 3 (efficacy):
1. Metastatic disease outside of the liver that is reasonably expected to cause acute deterioration or death within 14 weeks of entry into the study i.e. the patient's life expectancy should be at least 14 weeks in order to allow completion of protocolled intervention and primary endpoint read-out.
2. Any active anti-cancer therapy (chemotherapy / small molecule inhibitors / immunotherapy) within 4 weeks or liver radiotherapy within 8 weeks, prior to SonoTran intervention.
3. Persistent, unresolved CTCAE v5.0 Grade 2 or higher drug-related toxicity (except alopecia, erectile dysfunction, hot flashes, decreased libido, chronic neuropathy) following previous treatment.
4. Inadequate recovery from any prior surgical procedure or major surgical procedure performed within 4 weeks prior to enrolment.
5. Any other medical or psychiatric condition that, in the opinion of the investigator, might interfere with the subject's participation in the clinical investigation or interfere with the interpretation of clinical investigation results.
6. Serious/symptomatic active infection or infection requiring antibiotics, within 7 days prior to enrolment.
7. Presence of active cholangitis.
8. Known Human Immunodeficiency Virus (HIV) infection or a known HIV-related malignancy.
9. Known bleeding diathesis.
10. Inability to comply with the protocol requirements.
11. Participation in any other clinical trials involving therapeutic agents within the last 4 weeks prior to enrolment.
12. Patients with history of QT prolongation, clinically significant VT, VF, heart block, myocardial infarction within 6 months, CHF NYHA Class III or IV, unstable angina.
13. Pregnant or lactating females.
14. Known DPD deficiency or UGT-1A1 polymorphism.
15. Patients with liver metastases that are IMMEDIATELY amenable to surgical resection without neoadjuvant treatment.
16. Patients for whom IMMEDIATE ablation is felt to be appropriate.

Previous participant exclusion criteria from 26/04/2023 to 12/06/2023:
Cohort 1 (safety):
1. Any active anti-cancer therapy (chemotherapy/small molecule inhibitors/immunotherapy) within 4 weeks or liver radiotherapy within 8 weeks, prior to SonoTran intervention
2. Persistent, unresolved CTCAE v5.0 Grade 2 or higher drug-related toxicity (except alopecia,

erectile dysfunction, hot flashes, decreased libido, chronic neuropathy) following previous treatment
3. Inadequate recovery from any prior surgical procedure or major surgical procedure performed within 4 weeks prior to enrolment
4. Any other medical or psychiatric condition that, in the opinion of the investigator, might interfere with the subject's participation in the clinical investigation or interfere with the interpretation of clinical investigation results
5. Serious/symptomatic active infection or infection requiring antibiotics, within 7 days prior to enrolment
6. Disease requiring metal biliary stent(s) (plastic stents allowed)
7. Presence of active cholangitis
8. Known Human Immunodeficiency Virus (HIV) infection or a known HIV-related malignancy
9. Known bleeding diathesis
10. Inability to comply with the protocol requirements
11. Participation in any other clinical trials involving therapeutic agents within the last 4 weeks prior to enrolment
12. Patients with history of QT prolongation, clinically significant VT, VF, heart block, myocardial infarction within 6 months, CHF NYHA Class III or IV, unstable angina
13. Pregnant or lactating females
14. Patients with liver metastases eligible for immediate surgical resection or other radical therapy such as ablation

Cohort 2 (performance):
1. Any active anti-cancer therapy (chemotherapy/small molecule inhibitors/immunotherapy) within 4 weeks or liver radiotherapy within 8 weeks, prior to SonoTran intervention
2. Persistent, unresolved CTCAE v5.0 Grade 2 or higher drug-related toxicity (except alopecia, erectile dysfunction, hot flashes, decreased libido, chronic neuropathy) following previous treatment
3. Inadequate recovery from any prior surgical procedure or major surgical procedure performed within 4 weeks prior to enrolment
4. Any other medical or psychiatric condition that, in the opinion of the investigator, might interfere with the subject's participation in the clinical investigation or interfere with the interpretation of clinical investigation results
5. Serious/symptomatic active infection or infection requiring antibiotics, within 7 days prior to enrolment
6. Presence of active cholangitis
7. Known Human Immunodeficiency Virus (HIV) infection or a known HIV-related malignancy
8. Known bleeding diathesis
9. Inability to comply with the protocol requirements
10. Participation in any other clinical trials involving therapeutic agents within the last 4 weeks prior to enrolment
11. Pregnant or lactating females
12. Known UGT-1A1 polymorphism
13. Patients with liver metastases that require neoadjuvant chemotherapy to downstage prior to resection
14. Patients whose main radical intervention to the liver at outset is planned to be ablation rather than surgery

Cohort 3 (efficacy):
See Cohort 2 exclusion criteria with the excluding of criteria 3, and the additional criteria below:
1. Known DPD deficiency or UGT-1A1 polymorphism
2. Patients with liver metastases that are IMMEDIATELY amenable to surgical resection without

neoadjuvant treatment
3. Patients for whom IMMEDIATE ablation is felt to be appropriate
4. Patients who have metastatic disease outside of the liver that is likely to progress significantly over the next 3 months and limit life expectancy and prevent measurement of the required endpoints of the study in terms of response within the liver

Previous participant exclusion criteria:
Cohort 1 (safety):
1. Any active anti-cancer therapy (chemotherapy/small molecule inhibitors/immunotherapy) within 4 weeks or liver radiotherapy within 8 weeks, prior to SonoTran intervention
2. Persistent, unresolved CTCAE v5.0 Grade 2 or higher drug-related toxicity (except alopecia, erectile dysfunction, hot flashes, decreased libido, chronic neuropathy) following previous treatment
3. Inadequate recovery from any prior surgical procedure or major surgical procedure performed within 4 weeks prior to enrolment
4. Any other medical or psychiatric condition that, in the opinion of the investigator, might interfere with the subject's participation in the clinical investigation or interfere with the interpretation of clinical investigation results
5. Serious/symptomatic active infection or infection requiring antibiotics, within 7 days prior to enrolment
6. Disease requiring metal biliary stent(s) (plastic stents allowed)
7. Presence of active cholangitis
8. Known Human Immunodeficiency Virus (HIV) infection or a known HIV-related malignancy
9. Known bleeding diathesis
10. Inability to comply with the protocol requirements
11. Participation in any other clinical trials involving therapeutic agents within the last 4 weeks prior to enrolment
12. Patients with history of QT prolongation, clinically significant VT, VF, heart block, myocardial infarction within 6 months, CHF NYHA Class III or IV, unstable angina
13. Pregnant or lactating females
14. Patients with liver metastases eligible for immediate surgical resection or other radical therapy such as ablation

Cohort 2 (performance):
1. Any active anti-cancer therapy (chemotherapy/small molecule inhibitors/immunotherapy) within 4 weeks or liver radiotherapy within 8 weeks, prior to SonoTran intervention
2. Persistent, unresolved CTCAE v5.0 Grade 2 or higher drug-related toxicity (except alopecia, erectile dysfunction, hot flashes, decreased libido, chronic neuropathy) following previous treatment
3. Inadequate recovery from any prior surgical procedure or major surgical procedure performed within 4 weeks prior to enrolment
4. Any other medical or psychiatric condition that, in the opinion of the investigator, might interfere with the subject's participation in the clinical investigation or interfere with the interpretation of clinical investigation results
5. Serious/symptomatic active infection or infection requiring antibiotics, within 7 days prior to enrolment
6. Disease requiring metal biliary stent(s) (plastic stents allowed)
7. Presence of active cholangitis
8. Known Human Immunodeficiency Virus (HIV) infection or a known HIV-related malignancy
9. Known bleeding diathesis
10. Inability to comply with the protocol requirements
11. Participation in any other clinical trials involving therapeutic agents within the last 4 weeks

prior to enrolment
12. Patients with a history of QT prolongation, clinically significant VT, VF, heart block, myocardial infarction within 6 months, CHF NYHA Class III or IV, unstable angina
13. Pregnant or lactating females
14. Known UGT-1A1 polymorphism
15. Patients with liver metastases that require neoadjuvant chemotherapy to downstage prior to resection
16. Patients whose main radical intervention to the liver at outset is planned to be ablation rather than surgery
17. Female subjects of childbearing potential and male subjects whose sexual partners are of childbearing potential must agree to abstain from sexual intercourse or to use an effective method of contraception during the study and up to 6 months after the end of study. Examples of effective methods of contraception include oral or injected contraceptives or double barrier methods such as condom plus spermicide or condom plus diaphragm.

Cohort 3 (efficacy):
See Cohort 2 exclusion criteria with the excluding of criteria 3, and the additional criteria below:
1. Known DPD deficiency or UGT-1A1 polymorphism
2. Patients with liver metastases that are IMMEDIATELY amenable to surgical resection without neoadjuvant treatment
3. Patients for whom IMMEDIATE ablation is felt to be appropriate
4. Patients who have metastatic disease outside of the liver that is likely to progress significantly over the next 3 months and limit life expectancy and prevent measurement of the required endpoints of the study in terms of response within the liver

Date of first enrolment
31/10/2021

Date of final enrolment
30/08/2024

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Churchill Hospital
Department of Oncology
Headington
Oxford
United Kingdom
OX3 7LE

Study participating centre

Queen Elizabeth Hospital
Mindelsohn Way
Edgbaston
Birmingham
United Kingdom
B15 2GW

Sponsor information

Organisation
University of Oxford

Sponsor details
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OX3 7GB
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Sponsor type
University/education

Website
http://www.ox.ac.uk/

ROR
https://ror.org/052gg0110

Funder(s)

Funder type
Government

Funder Name
NIHR Central Commissioning Facility (CCF); Grant Codes: NIHR201655

Funder Name

Results and Publications

Publication and dissemination plan
Planned publication in a high-impact peer-reviewed journal.

Intention to publish date
01/03/2025

Individual participant data (IPD) sharing plan
The data-sharing plans for the current study are unknown and will be made available at a later date.

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No