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CRUK HUNTER Accelerator – delivering immunotherapy for liver cancer

Submission date 07/10/2019	**Recruitment status** Suspended	☐ Prospectively registered ☐ Protocol
Registration date 10/12/2019	**Overall study status** Ongoing	☐ Statistical analysis plan ☐ Results
Last Edited 18/12/2023	**Condition category** Cancer	☐ Individual participant data ☐ Record updated in last year

Plain English summary of protocol

Background and study aims

Primary liver cancer, predominantly hepatocellular carcinoma (HCC), is the second commonest cause of cancer death in the world. Deaths continue to rise, as most HCCs present at advanced stages when surgical cure is not possible and the only available medical treatment extends life by just a few weeks. There is therefore an urgent need to develop new treatments for HCC. There is excitement around a new class of immune system-based therapies that work by stimulating aspects of the immune system surrounding the tumour to promote anti-cancer immune responses. Preliminary clinical studies with one type of immune therapy suggest that 15- 20% of HCC patients benefit by gaining months or even years of life. CRUK has funded the creation of HUNTER: the Hepatocellular Carcinoma Expediter Network, to support an in-depth study of the immune components of the tissue microenvironment in which HCC develops, so that novel immune approaches for HCC can be developed. The HUNTER team has the combined expertise to recruit the patients, collect their tissues and data, study the immune cells around the cancers and how they talk to each other, while identifying the blood-based biomarkers that reflect what is happening in the tumour – to find out which new treatment to use for individual patients and how to monitor them. The team will also use the same tissues to create models that enable the development and testing of new biomarker-guided treatment approaches. The goal is to study the cancers and their immune surroundings in order to:

1. Identify biomarkers that predict patient survival and outcome with current therapies
2. Develop novel immune-based treatment approaches, possibly in combination with current therapies
3. Identify biomarkers to guide immune-based treatments or combination treatments
4. Develop models to test immune-based therapies or combinations

Who can participate?

Patients aged over 18 with primary liver cancer, secondary liver cancer or chronic liver disease, attending the Newcastle upon Tyne NHS Foundation Trust, or one of the collaborating centres, for consideration of liver-related treatment

What does the study involve?

The study involves participants giving consent for some extra blood (about two to three tablespoons) to be taken at the same time as routine blood samples which are taken during outpatient clinic visits as well as before and after investigations or treatments on the liver, surgical or oncology wards. Participants could also be asked for extra samples (at the same time as routine samples) at follow up appointments. In addition, leftover tissue may be collected from the liver after a liver biopsy or a liver operation (this would not involve any extra procedure). After the study is finished the researchers would like to keep the samples for use in future studies.

What are the possible benefits and risks of participating?
There will be no direct clinical benefit to participants. However, the outcome of the research could influence the care of other patients in the future. Participating in the study is expected to have no implications for participants or their treatment. All data will be stored securely. The researchers do not anticipate any disadvantages of taking part.

Where is the study run from?
University Of Newcastle Medical School

When is the study starting and how long is it expected to run for?
December 2018 to November 2025

Who is funding the study?
Cancer Research UK

Who is the main contact?
Tom Ewen
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Contact information

Type(s)
Scientific

Contact name
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Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)

Nil known

ClinicalTrials.gov (NCT)

Nil known

Protocol serial number

CPMS: 42961

Study information

Scientific Title

HUNTER: Hepatocellular Carcinoma Expediter Network - created to define the hepatocellular carcinoma immune environment, the key mechanisms and biomarkers, and to develop the pre-clinical models needed, to deliver immunotherapy to patients with liver cancer

Acronym

HUNTER

Study objectives

Primary liver cancer, predominantly hepatocellular carcinoma (HCC), is the second commonest cause of cancer death in the world. Deaths continue to rise, as most HCCs present at advanced stages when surgical cure is not possible and the only available medical treatment extends life by just a few weeks. There is therefore an urgent need to develop new treatments for HCC. There is excitement around a new class of immune system-based therapies that work by stimulating aspects of the immune system surrounding the tumour to promote anti-cancer immune responses. Preliminary clinical studies with one type of immune therapy suggest that 15- 20% of HCC patients benefit by gaining months or even years of life. CRUK has funded the creation of HUNTER: the Hepatocellular Carcinoma Expediter Network, to support an in-depth study of the immune components of the tissue microenvironment in which HCC develops, so that novel immune approaches for HCC can be developed. The HUNTER team has the combined expertise to recruit the patients, collect their tissues and data, study the immune cells around the cancers and how they talk to each other, while identifying the blood-based biomarkers that reflect what is happening in the tumour – so that we will know which new treatment to use for individual patients and how to monitor them. The team will also use the same tissues to create models that enable the development and testing of new biomarker-guided treatment approaches.

The goal is to study the cancers and their immune surroundings, so that we can:
1. Identify biomarkers that predict patient survival and outcome with current therapies

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4. Develop models to test immune-based therapies or combinations

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 13/09/2019, North East - Newcastle & North Tyneside 2 Research Ethics Committee (NHS BT Blood Donor Centre, Holland Drive, Newcastle upon Tyne, Tyne and Wear, NE2 4NQ, United Kingdom; +44 (0)207 1048091; nrescommittee.northeast-newcastleandnorthtyneside2@nhs.net), ref: 19/NE/0251

Study design
Observational; Design type: Cohort study

Primary study design
Observational

Study type(s)
Diagnostic

Health condition(s) or problem(s) studied
Liver cancer

Interventions
The study aims are to understand the immune changes that occur in patients with liver disease that promote the development of liver cancer. With this information, the researchers aim to identify novel strategies that are urgently needed to treat patients with Liver cancer. Alongside this, they need to identify the biomarkers that will help us choose the best treatment, or combination of treatments. To explore how interventions or treatments manipulating the immune system will work, the researchers need to develop modelling systems that recreate the diseased environment and immune system and cancer, in which to test them.

To deliver this, the researchers need patients (with cancer and without) and their tissues, teams of people who can recruit patients and collect tissues and data, expert scientists and immunologists who know how to interrogate the cancers and the immune cells, translational scientists who can develop the models, and people who can analyse the data and translate it back to patient care. The researchers also need to communicate well, sharing and integrating all the data from the patients and their tissues effectively. To support this key project, CRUK have funded the creation of the HUNTER network.

Hypothesis: Defining the HCC immune environment will accelerate the delivery of effective immunotherapies for our patients.

KEY ASPECTS OF THE STUDY DESIGN & METHODOLOGY
1. STORED HISTORICAL SAMPLES. Shared tissues and data from patients who have previously consented to research studies. Within the HUNTER network of co-investigators, the researchers have a number of stored tissues resources available, which will be shared.
2. NATIONWIDE PATIENT RECRUITMENT. To study these inter-related aspects of the tumour

immune response, the researchers need to recruit patients undergoing treatments as part of their usual care and collect their data, but also their tissues (liver and blood). Despite liver cancer being common, suitable patients undergoing treatments are not common, in part because so many patients are too unwell to be treated. The researchers need to study liver tissues, but surgery is offered to few, either because their cancer is too advanced to cure by surgery, or their liver function is not good enough for an operation. We do get biopsy tissues to confirm the diagnosis in some patients, but this is also relatively rare as in most patients, you can make the diagnosis on a scan, and biopsy is avoided because it is risky. So to recruit enough patients and their tissues, it is essential to work together to recruit patients and share their precious tissues for this comprehensive immune characterisation. Support from the Clinical Research Network (CRN) will enable us to recruit suitable patients from as many centres as possible.

3. SAMPLES SHARING. The centres using fresh tissues to isolate cells will do this immediately on site. Where possible, samples may be shared directly between units on the same day (e.g. London centres). Organoids (see RESEARCH DESIGN below) will be cultured where possible from all cases with tissue available – either on a site with the expertise (training is part of the award), or by funded technical staff in Newcastle – with samples shipped immediately in culture media to Newcastle. For the all the samples not used immediately in the recruiting centre, Newcastle will act as the storage and redistribution hub. In particular, this will be for the circulating biomarker identification, validation and quantification studies. Organoids made and stored in Newcastle will be distributed to the participating centres for modelling projects.

4. WHAT WILL HAPPEN TO THE PATIENTS - The project will start as soon as all regulatory approvals at the participating institutions are in place. The researchers will purposefully recruit patients with a range of stages of liver cancer, treated in different ways. The patients with cancers will be approached soon after their first presentation, at the specialist centre to which they are referred. The research study will be explained after their consultation, and the patient information and consent sheet given to them then – either by their doctor or one of the research nurses. Samples and data will be subsequently be collected from consenting patients. This would only be at planned visits – either to outpatients, day units or wards - for their planned treatment and follow up. There would be no additional visits. When patients attend follow up after their treatment, they may be asked to give more blood samples to look for changes in the candidate biomarkers in patients who do and don't respond. If patients receive treatment, they will be monitored with CT or MRI as per their local management guidelines. The details of which samples will be taken and when, is provided in the study protocol. While patients remain under follow-up, the researchers will continue to monitor their progress and record this. If patients become too unwell to attend, they will not be approached directly for research purposes. Their date of death would subsequently be recorded by their clinical care team.

5. THE NUMBERS OF PATIENTS - The researchers would like to recruit 1500 patients nationwide, including ~1000 with HCC and ~500 controls. They need tissues to study and the numbers of patients is partly based on practical issues, in terms of how many will likely be seen nationwide that are fit for treatment. Much of the tissues and living cells studies and models development will be performed on site at the centre recruiting the patient. Blood samples taken at the same time will be used to explore the changes in the blood that reflect changes in the tissues. Regardless of the centre, however, whether patients have resection or biopsy liver tissues available or not - the researchers want their blood for research. They need the blood to identify and validate prognostic blood test based biomarkers that will help predict prognosis, as well as potentially responses to treatments. They have planned to try to recruit roughly equal numbers at each stage (between 300 and 400) and Professor James Wason (Statistician) has advised on the numbers within each stage that would be needed to report a range of hazards ratios with 90% power.

The control patients will include patients with liver disease but no cancer, who are attending our hospitals for management of their underlying liver disease. These patients at risk of developing liver cancer and the research is therefore relevant to them personally. They will have samples

collected after consent, in a similar fashion to patients with cancer. The nature of their liver disease and their liver function will be recorded as data. When candidate biomarkers are identified, it is important to be sure that these are cancer-specific changes, rather than relating to other variables that patients with HCC may also have (eg. viral hepatitis B or C, alcohol excess, obesity, type 2 diabetes, medications, presence of cirrhosis, liver function tests). Controls will also include patients having a biopsy or a liver resection of a different kind of liver tumour (eg. benign, cholangiocarcinoma, or secondary liver cancer). It is important to compare candidate biomarkers to see if they are specific for HCC tumours.
6. DATA & REPORTING - All clinical datasets will be collected by clinical research staff using a case record form. Clinical staff will not be aware of the research data, avoiding any researcher bias in clinical datasets. The data will be entered – in a coded fashion without identifying personal information – into a centralised data registry managed by Newcastle University Learning Department. Correlations between clinical datasets and research findings will be analysed periodically, most often before annual investigator meetings and for the generation of interim reports for CRUK, as well as at the time of abstract submission to scientific meetings. Reports, outputs and strategic future strategic direction will be monitored by the HUNTER advisory board, made up of representatives from each coinvestigator centre, as well as representatives from CRUK.
7. PPI - Prior to submitting the HUNTER application, the researchers sought advice and input from the LiverNorth patient support group. The patient information and consent forms have been reviewed and modified by LiverNorth members. At least one LiverNorth representative will be a part of the HUNTER advisory board. Part of their contribution will be to advise and help to develop the patient public interaction aspects for HUNTER, with the funding provided by CRUK for that purpose, within the award.

Intervention Type
Other

Primary outcome(s)
Patient survival measured in months after diagnosis of HCC

Key secondary outcome(s))
1. Radiological response to treatment measured using CT scans 1 month after treatment, and 3-monthly thereafter
2. Clinical response to treatment measured using clinical assessment and blood tests 1 month after treatment, and 3-monthly thereafter
3. Time to radiological progression measured using CT scans at 1-3 monthly intervals
4. Time to clinical progression measured using outpatient visits at 1-3 monthly intervals
5. Time to recurrence measured using CT scans at 1-3 monthly intervals

Completion date
30/11/2025

Eligibility

Key inclusion criteria
1. Patients will be over 18 years of age
2. The recruited patients will have primary liver cancer, secondary liver cancer or chronic liver disease
3. Patients will be attending the Newcastle upon Tyne NHS Foundation Trust, or one of the collaborating centres, for consideration of liver related treatment

4. The patient will be willing and able to provide written informed consent to take part in the study

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Key exclusion criteria
1. Patients who have received previous treatment for HCC, unless recruited just prior to starting 2nd line treatment
2. Patients deemed too distressed or unwell to approach about taking part in the research project
3. Patients who lack capacity to give informed consent
4. Patients who are not able to undertake study procedures

Date of first enrolment
01/11/2019

Date of final enrolment
01/11/2025

Locations

Countries of recruitment
United Kingdom

England

Scotland

Study participating centre
The Newcastle Upon Tyne Hospitals NHS Foundation Trust
Freeman Hospital
Freeman Road
High Heaton
Newcastle Upon Tyne
United Kingdom
NE7 7DN

Study participating centre
University Hospitals Birmingham NHS Foundation Trust
Trust HQ, PO Box 9551
Queen Elizabeth Medical Centre
Edgbaston
Birmingham
United Kingdom
B15 2TH

Study participating centre
Royal Free London NHS Foundation Trust
Royal Free Hospital
Pond Street
London
United Kingdom
NW3 2QG

Study participating centre
University Hospital Southampton NHS Foundation Trust
Mailpoint 18
Southampton General Hospital
Tremona Road
Southampton
United Kingdom
SO16 6YD

Study participating centre
King's College Hospital NHS Foundation Trust
Denmark Hill
London
United Kingdom
SE5 9RS

Study participating centre
Imperial College Healthcare NHS Trust
St. Marys Hospital
Praed Street
London
United Kingdom
W2 1NY

Study participating centre
The Christie NHS Foundation Trust
550 Wilmslow Road
Withington
Manchester
United Kingdom
M20 4BX

Study participating centre
NHS Greater Glasgow and Clyde
J B Russell House
Gartnavel Royal Hospital
1055 Great Western Road
Glasgow
United Kingdom
G12 0XH

Study participating centre
The Clatterbridge Cancer Centre NHS Foundation Trust
Clatterbridge Hospital
Clatterbridge Road
Bebington
Wirral
United Kingdom
CH63 4JY

Sponsor information

Organisation
The Newcastle Upon Tyne Hospitals NHS Foundation Trust

ROR
https://ror.org/05p40t847

Funder(s)

Funder type
Charity

Funder Name
Cancer Research UK; Grant Codes: C9380/A26813

Alternative Name(s)
CR_UK, Cancer Research UK - London, Cancer Research UK (CRUK), CRUK

Funding Body Type
Private sector organisation

Funding Body Subtype
Other non-profit organizations

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan

The datasets generated during and/or analysed during the current study will be stored in a non-publically available repository. The HUNTER registry is an online resource, https://hunter-registry.ncl.ac.uk/. Access to the data will be available to those within the consortium. Requests from outside of the HUNTER consortium will be considered by the HUNTER Steering Group and may be subject to a charge.

IPD sharing plan summary

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Study website	Study website	11/11/2025	11/11/2025	No	Yes