ISRCTN17869351 https://doi.org/10.1186/ISRCTN17869351

Paediatric hepatic international tumour trial

Submission date 19/04/2017	**Recruitment status** No longer recruiting	[X] Prospectively registered [_] Protocol
Registration date 24/04/2017	**Overall study status** Ongoing	[_] Statistical analysis plan [_] Results
Last Edited 26/03/2024	**Condition category** Cancer	[_] Individual participant data [_] Record updated in last year

Plain English summary of protocol
https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-looking-at-improving-treatment-and-outcome-for-children-with-liver-cancer-phitt

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Type(s)
Public

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Additional identifiers

Clinical Trials Information System (CTIS)
2016-002828-85

Integrated Research Application System (IRAS)
212527

ClinicalTrials.gov (NCT)
NCT03017326

Protocol serial number
CPMS 33836

Study information

Scientific Title
Paediatric Hepatic International Tumour Trial (PHITT)

Acronym
PHITT

Study objectives
This study aims to:
1. Reduce treatment for very low and low risk group patients, while maintaining the excellent event-free survival (EFS) in these groups to reduce side effects of treatment.
2. Intensify therapy in the high risk group to improve the surgery options available and the event free survival, while testing the use of new drugs in a clinical trial setting.
3. Compare different regimens to improve surgical options in intermediate risk HB
4. Evaluate the biology and genetics of HB and HCC to identify prognostic and toxicity biomarkers.

Ethics approval required
Old ethics approval format

Ethics approval(s)
West Midlands REC – Edgbaston, 10/04/2017, ref: 17/WM/0110

Study design
Randomised; Both; Design type: Treatment, Drug, Cross-sectional

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Hepatoblastoma or hepatocellular carcinoma

Interventions
The patient will be approached with the option of joining the trial early in the diagnosis. The patient will be asked to confirm their consent to participate in the trial and for a sample of their tumour to be sent for research purposes. An assessment will be made to categorise the level of disease (called PRETEXT staging) using the age, AFP level, presence of metastases and tumour location. The level of disease will be categorised according to analysis by Children's Hepatic tumour International Collaboration (CHIC) - Hepatoblastoma Stratification. If appropriate, the patient will be asked to consent to receive treatment.

The patient will be allocated to one of six different treatment groups, depending on their disease:

Group A: Very Low Risk Hepatoblastoma (HB)
The results from the Central Pathology review of the patient's tumour tissue will be used to determine if the patient should receive cisplatin treatment or no treatment. If the tumour shows "WDF" histology, the patient receives no treatment and is seen at routine visits for follow up assessment only. If the tumour shows "non-WDF" histology, the patient receives a dose of cisplatin on Day 1 of two 21 day cycles.

Group B: Low Risk Hepatoblastoma
These patients will receive a dose of Cisplatin on Day 1 of two 14 day cycles.
The patient is then assessed for surgery to remove the tumour by the Consultant working on the study. If surgery is carried out, the patient is randomised to one of the following two arms:
1. Patient receives cycle 3 and cycle 4 of Cisplatin treatment or
2. Patient receives cycles 4-6 of Cisplatin treatment.
If surgery is not feasible after cycle 1 and cycle 2, the patient receives cycles 3 and 4 of Cisplatin treatment and is re-assessed for surgery. If surgery is still not feasible, the patient receives cycles 5 and 6 of Cisplatin treatment.

Group C: Intermediate Risk Hepatoblastoma
These patients will be randomised to receive one of the following three treatments.
1. SIOPEL3HR: A cardiology assessment to check the patient's heart function will be done prior to receiving treatment. Patients will receive Cisplatin on Day 1, Carboplatin on Day 15 and Doxorubicin on Days 15 & 16 in five 28 day cycles.
2. C5VD: A cardiology assessment will be done prior to receiving treatment. Patients will receive Cisplatin and Doxorubicin on Days 1 & 2; Doxorubicin, 5-Fluorouracil and Vincristine on Day 2; and Vincristine on Days 9 & 16. Each cycle of treatment is repeated after 21 days, and six cycles in total are given.
3. CDDP monotherapy: Patients will receive Cisplatin on Day 1 in six 14 day cycles.
Patients will have a CT/MRI scan after the 2nd and 4th cycles of treatment to assess their disease, and have their tumour removed by surgery at an appropriate point in the treatment, depending on the scan results and the decision by their doctor. Following surgery, patients will have further cycles of treatment, until all cycles have been given.

Group D: High Risk Hepatoblastoma
These patients will first undergo induction therapy before undergoing surgery and further treatment.
During induction treatment, patients will receive Cisplatin on Day 1, Cisplatin and Doxorubicin on Day 8, Doxorubicin on Day 9 and Cisplatin again on Day 15 in three 15 day cycles.
If disease metastases are present after receiving the induction treatment, the patient will be randomised to receive one of the two following treatments:
1. CD/CE: Patients will receive Carboplatin and Doxorubicin (CD) on Day 1, followed by another dose of Doxorubicin on Day 2. Each cycle is 21 days. The patient will receive Carboplatin and Etoposide (CE) on Days 1-4 of Cycle 2. Cycle 1 (CD) and Cycle 2 (CE) will alternate until a total of 6 cycles are given.
2. CD/VI: Patients will receive Carboplatin and Doxorubicin (CD) on Day 1, followed by another dose of Doxorubicin on Day 2. Each cycle is 21 days. The patient will receive Vincristine and Irinotecan (VI) on Day 1 of Cycle 2, followed by more doses of Irinotecan on Days 2-5 of Cycle 2. Cycle 1 (CD) and Cycle 2 (VI) will alternate until a total of 6 cycles are given.
If disease metastases are not present following the induction treatment and surgery, the patient receives Carboplatin and Doxorubicin (CD) as described above.

Group E: Resectable Hepatocellular Carcinoma (HCC)
The type of HCC tumour removed during surgery will determine if the patient should receive PLADO (Cisplatin & Doxorubicin) treatment or no treatment. If the tumour is deemed Fibrolamellar, the patient receives no treatment and is seen at routine visits for follow up assessment only. If the tumour is deemed de novo HCC, the patient should receive a dose of Cisplatin and Doxorubicin on Day 1, and Doxorubicin on Day 2 of four 21 day cycles.

Group F: Unresectable/metastatic Hepatocellular Carcinoma
These patients will be randomised to receive one of the following two treatments:
1. PLADO + Sorafenib: Patients will receive Cisplatin and Doxorubicin on Day 1, Doxorubicin on Day 2 (PLADO) and Sorafenib on Days 3-21 of three 21 day cycles.
2. PLADO + Sorafenib/GEMOX + Sorafenib: Patients will receive Cisplatin and Doxorubicin on Day 1, Doxorubicin on Day 2 (PLADO) and Sorafenib on Days 3-14. Each cycle is 14 days. The patient will receive Gemcitabine, Oxaliplatin and Sorafenib on Day 1, and Sorafenib on Days 2-14 of Cycle 2. Cycle 1 (PLADO+Sorafenib) and Cycle 2 (PLADO+Sorafenib/GEMOX) will alternate until a total of 4 cycles are given.

At the end of the treatment patients will be seen at routine visits once every 3 months for the next 2 years for follow up assessment, including a physical examination, a CT/MRI scan and a blood test for disease indicator Alphafetoprotein levels.

Intervention Type
Other

Phase
Phase III

Primary outcome(s)
1. Event-free survival (EFS) is measured as the time from randomisation (or registration into the trial for non-randomised patients) to first failure event or last follow-up date
2. Response in HCC is measured using RECIST version 1.1 criteria, after 3 cycles of PLADO, or 4 cycles of PLADO+S/GEMOX+S in Group F
3. Best Response is measured using RECIST version 1.1 criteria and AFP decline at end of treatment for Groups A, B, C, D and E

Key secondary outcome(s))
1. Overall survival (OS) is measured as the time from randomisation (or registration for non-randomised patients) to death from any cause
2. Toxicity is measured using Common Terminology Criteria for Adverse Events (CTCAE), at the end of each cycle of treatment
3. Hearing loss is measured using SIOP Boston Scale for oto-toxicity at end of treatment and follow up
4. Surgical resectability is measured using surgical outcome during treatment after surgery
5. Adherence to surgical guidelines is measured using the current SIOPEL surgical guidelines and the local clinician’s surgical decision to resect after surgical assessment

Completion date
30/06/2026

Eligibility

Key inclusion criteria
1. Clinical diagnosis of HB and histologically defined diagnosis of HB or HCC
2. Aged 0-30 years
3. Written informed consent for trial entry

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
0 years

Upper age limit
30 years

Sex
All

Key exclusion criteria
1. Any previous chemotherapy or currently receiving anti-cancer agents
2. Recurrent disease
3. Previously received a solid organ transplant
4. Uncontrolled infection
5. Unable to follow the protocol for any reason
6. Second malignancy
7. Pregnant or breastfeeding women

Date of first enrolment
25/08/2017

Date of final enrolment
31/12/2023

Locations

Countries of recruitment
United Kingdom

England

Northern Ireland

Scotland

Wales

Austria

Belgium

Czech Republic

Finland

France

Germany

Ireland

Israel

Netherlands

Norway

Spain

Switzerland

Study participating centre
Aberdeen Royal Infirmary
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Study participating centre
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Study participating centre
Birmingham Children's Hospital
Steelhouse Lane
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Study participating centre
Bristol Royal Hospital for Children
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Study participating centre
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Study participating centre
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Study participating centre
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Sponsor information

Organisation
University of Birmingham

ROR
https://ror.org/03angcq70

Funder(s)

Funder type
Government

Funder Name
European Commission

Results and Publications

Individual participant data (IPD) sharing plan
The current 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			26/07/2023	No	No
Study website	Study website	11/11/2025	11/11/2025	No	Yes