TRIAL SYNOPSIS

Title

Paediatric Hepatic International Tumour Trial

Acronym

PHİTT

Trial Design

The PHITT trial is a collaborative trial involving three major clinical groups running paediatric liver tumour trials the International Society of Paediatric Oncology Epithelial Liver Tumour Group (SIOPEL), the Liver Tumour Committee of the Children's Oncology Group, USA (COG), the Japanese Children's Cancer Group (JCCG).The Society for Paediatric Oncology and Haematology, Germany (GPOH) is closely collaborating in the European trial. The European arm of the study is led by the SIOPEL group and is sponsored by the University of Birmingham, UK and detailed in this protocol. It is anticipated that the other trial groups will use a similar protocol, with an overall analysis of all patients taking place.

Objectives

Primary Objectives

- To evaluate if the treatment of Low Risk hepatoblastoma (HB) can be reduced (Group B1)
- To compare different treatment regimes for Intermediate risk HB (Group C)
- To compare different post induction treatment regimes for High Risk HB (Group D2)
- To determine the outcome is improved when GEMOX is added to PLADO in the treatment of unresected hepatocellular carcinoma HCC (Group F)
- To collect samples for biological and toxicity studies. (All groups)

Secondary Objectives

- To report outcome (including event-free survival (EFS), failure-free survival (FFS), overall survival (OS), toxicity and surgical outcome) in all patient groups.
- To validate a new global risk stratification, defined by Children's Hepatic Tumours International Collaboration (CHIC)
- To evaluate clinically relevant factors, including the following:
    - Provide a comprehensive and highly-validated panel of diagnostic and prognostic biomarkers
    - Determine if paediatric HCC is a biologically different entity to adult HCC
    - Develop genomic and/or biomarker analysis to predict children who may have an increased risk of developing toxicity with chemotherapy.
- To establish a collection of clinically and pathologically-annotated biological samples.
- Evaluate a surgical planning tool for an impact on decision making processes in POST-TEXT III and IV HB

Outcome Measures

- EFS
- FFS
- OS
- Toxicity
- Chemotherapy-related cardiac, nephro- and oto-toxicity
- Response in HCC
- Best Response
- Surgical resectability
- Adherence to surgical guidelines
- Hearing loss

Patient Population

Patients ≤30 years of age with newly diagnosed hepatic cancers: primary paediatric hepatic malignancies HB and hepatocellular carcinoma HCC

Sample Size

	Expected Sample Size SIOPEL (Europe)	Expected Sample Size across 3 collaborative groups
Group A – Very Low Risk HB	80	200
Group B – Low Risk HB	130	400
Group C – Intermediate Risk HB	80	210
Group D – High Risk HB	80	210
Group E – Resected HCC	20	50
Group F – Unresected/metastatic HCC	60	150

Key Eligibility Criteria

Trial Entry Inclusion Criteria

- Clinical diagnosis of HB* and histologically defined diagnosis of HB or HCC.
  *Histological confirmation of HB is required except in emergency situations where:
  a) the patient meets all other eligibility criteria, but is too ill to undergo a biopsy safely, the patient may be enrolled without a biopsy;
  b) there is anatomic or mechanical compromise of critical organ function by tumour (e.g., respiratory distress/failure, abdominal compartment syndrome, urinary obstruction, etc.);
  c) uncorrectable coagulopathy.
- Age ≤30 years.
- Written informed consent for trial entry.

Trial Entry Exclusion Criteria

- Any previous chemotherapy or currently receiving anti-cancer agents;
- Recurrent disease;
- Previously received a solid organ transplant; other than orthotopic liver transplantation (OLT);
- Uncontrolled infection;
- Unable to follow or comply with the protocol for any reason;
- Second malignancy;
- Pregnant or breastfeeding women.

Treatment Allocation Inclusion Criteria

- Written informed consent for trial treatment.
- Score of ≥50% Lansky scale for patients <16 years, or Karnofsky scale for patients ≥16 years.
- For female patients of child-bearing potential, a negative pregnancy test prior to starting trial treatment is required. Any patient who is of reproductive age must agree to use adequate contraception for the duration of the trial. For further details see Section 4.2.3.
- Patient meets specific eligibility criteria for their allocated treatment group, for example:
  - tumour pathology type;
  - risk definition according to CHIC;
  - adequate renal function: serum creatinine in the normal range or ≥60mL/min/1.73m^2 by formal creatinine clearance method;
  - haematology: absolute neutrophil count (ANC) >0.75 x 10^9/L, platelet count >75 x 10^9/L, potassium (K), magnesium (Mg) and calcium (Ca) within normal range for age;
  - coagulation: International normalised ratio (INR) or prothrombin time (PT) <1.2x upper limit of normal (ULN);
  - adequate cardiac function: shortening fraction ≥28% or ejection fraction ≥47%, no prolonged QT/QTc interval.

Trial Duration

Anticipated 4 years of recruitment.

Patients must have follow-up assessments for a minimum of 2 years, following trial entry. Patients will be followed up for progression and death until all trial objectives have been met.