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ChiLTERN
Children's Liver Tumour European Research Network

PHITT
Paediatric Hepatic International Tumour Trial

Paediatric Hepatic International Tumour Trial

PHITT

Version 3.0
17th October 2018

Coordinating Sponsor:	University of Birmingham
Sponsor protocol number:	RG_15-114
CAS code:	HE3026
EudraCT number:	2016-002828-85
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SIOPEL
Childhood Liver Tumours Strategy Group - SIOPEL

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TABLE OF CONTENTS

INDEX OF TABLES

INDEX OF FIGURES

INTRODUCTORY PAGES

Protocol title	Paediatric Hepatic International Tumour Trial
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SIGNATURE PAGE

PHITT Trial Protocol Version 3.0 version date 17-Oct-2018

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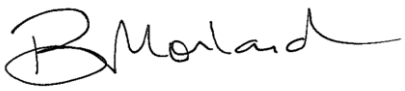
Signature:		**Date:**	22.OCT.2018

This protocol describes the PHITT trial and provides information about procedures for patients taking part in the PHITT trial. The protocol should not be used as a guide for treatment of patients not taking part in the PHITT trial.

AMENDMENTS

The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version:

Amendment number	Date of amendment	Protocol version number	Type of amendment	Summary of amendment
01	08 Dec 2016	1.0a	Non-Substantial	Changes pre- regulatory approval
02	03 Apr 2017	1.0b	Non-Substantial	Changes made following initial CTA non-acceptance and right to amend request: Additional screening requirement to address the fact that advice on conservation of sperm prior to treatment will be given (Sections 5.2 and 11.1) Clarification of true abstinence as an acceptable form of contraception. (Section 4.3)
03	24 Nov 2017	2.0	Substantial	Details of Sorafenib dosing schedule (Table 14) and administration (section 9.2.6) added following urgent safety measure
06	17 Jan 2018	2.0a	Non-Substantial	Addition of ISRCTN number, Change of contact details (Coordinating investigators, randomisation/registration number and pathologists), correcting typographical error in Eligibility (Lansky and Karnofsky performance status age ranges), guidance regarding interval between surgery and randomisation of Group B patients (section 9.2.2), clarification of timing of urine sampling (section 11.2), correction of indicated day in Table 34, correcting consistency and Typographical errors throughout
09	17 Oct 2018	3.0	Substantial	**Introductory pages** – Contacts and contact details updated as appropriate. **Trial Synopsis** – Design and objectives section clarified to better match main protocol, Sample size clarified. Group B sample size corrected to include 80 B1 patients not randomised. Treatment allocation Inclusion criteria updated to match section 4.3 **Trial Schema** changed (D1 corrected, D2 moved, D3 removed) **Background** – clarification that Group F includes patients with resected with residual disease **2.1 Primary Objectives** - Group F – clarification that Group F includes resected patients with residual disease **2.1- 2.2 Secondary Objectives/Outcome Measures** – minor rewording (“Best” removed), clarification on the definition of FFS and expected SIOPEL sample size

				clarified. **4.2 Treatment Group Specific Inclusion Criteria** –addition of INR (as equivalent to PT), addition of K, Mg, Ca to eligibility, addition of QT/QTc criteria for Group F Addition of Treatment Group Specific Exclusion criteria for Groups C, D and F **4.3 Product information** – addition of section for reference to SmPCs **5.2 Screening** – Removed sodium and blood pressure, Addition of Magnesium, PT (as equivalent to INR), other serology as per local practice. Addition of GFR and Audiology (omitted in error). See also 12.1 **6.1 Procedure for Online Trial Entry** – Clarification in text added. Website address updated **6.2 Randomisation** Clarification of text **7.0 Central Pathology Review** – Rapid reviews have been increased to include HB patients ≥8yr and/or low AFP, and all HCC patients. Also clarifications added. **8.0 Central Radiology Review** – clarification added, inclusion of surgical review section (moved from section 11.4) **9.0 Surgery Review Study** updated to be a sub-study and clarification added **10.0 Treatment Details** - Addition of flexibility in treatment and evaluation timings **10.2.2 Group B** - Criteria for randomisation clarified. Changed to specify that all patients in Group B2 will now have 6 cycles of cisplatin therapy and be recommended for transplant. **10.2.3 Group C** – "CDDP" in figure changed to "CIS" for clarity. Timings of administration of Vincristine and 5-FU in group C5VD changed to be in line with common practice **10.2.4 Group D** – Groups D2/D3 referred to as D2 throughout. Induction treatment schedule: cisplatin doses changed – 70mg on Day 1 and Dox given on days 57 & 58 in A3. Treatment figure Block A re-formatted for clarity. Criteria for randomisation clarified. Irinotecan dose amended to allow infusion 60-90min **10.2.5 Group E** Clarification of patients with no macroscopic disease **10.2.6 Group F** Clarification of patients resected with macroscopic disease. Table 14 rewording + addition of explanation for allowing suspension administration. **11. Dose Modifications** – Additional clarifications, addition of Pulmonary toxicity modifications **12.1 Screening Assessments** See 5.2 above and ECG for Group F (omitted in error) and also additional pregnancy tests added for patients in France

				12.2 Assessments All groups- addition of additional Audiograms for France patients only. Biochemical test for blood pressure, sodium and Ammonia removed as not required during treatment (at screening only). Magnesium added for toxicity study. Group B – change to table headings for clarity, clarified tumour assessments for B1 and B2. Group C SIOPEL 3HR Removal of repeat tumour assessment post op as inconsistent with figure 6 (treatment schedule). Group F – addition of additional ECGs for French patients only. **12.3 Biological and Pathological Studies.** Contact details updated, clarified samples taken, time of urgent review and sample destination **14. Supportive Treatment** –Use of Dexrazoxane comment added. Use of STS guidelines for use in Group A, B and C added. **15 Concomitant Medication** – Use of STS amended, use of live attenuated vaccines prohibited added. **18.1 AE Reporting Requirements** – An additional AE form required for Germany **18.1.2 Expected SARs** – Neutropenia removed **18.2 SAE Reporting** – optional email address added **22 Statistical Considerations** – amended by Trial Statistician **Appendix 4** – Paper is now published – referenced

TRIAL SYNOPSIS

Title

Paediatric Hepatic International Tumour Trial

Acronym

PHITT

Trial Design

An international, over-arching trial, with four randomised comparisons, for paediatric, adolescent and young adult patients with newly diagnosed hepatoblastoma (HB) and hepatocellular carcinoma (HCC). 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) and 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

The PHITT trial is an over-arching study including four randomised comparisons addressing therapeutic questions.

This trial will use a risk-adapted approach to the treatment of children diagnosed with HB. Children with HCC will also be included as a separate cohort.

Primary Objectives

- To evaluate if the treatment of Low Risk HB can be reduced (Group B1).
- To compare different treatment regimens for Intermediate Risk HB (Group C).
- To compare different post induction treatment regimens for High Risk HB (Group D2).
- To determine if the outcome is improved when interval compressed GEMOX is added to PLADO in the treatment of unresected 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 the impact of a surgical planning tool 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
- 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 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

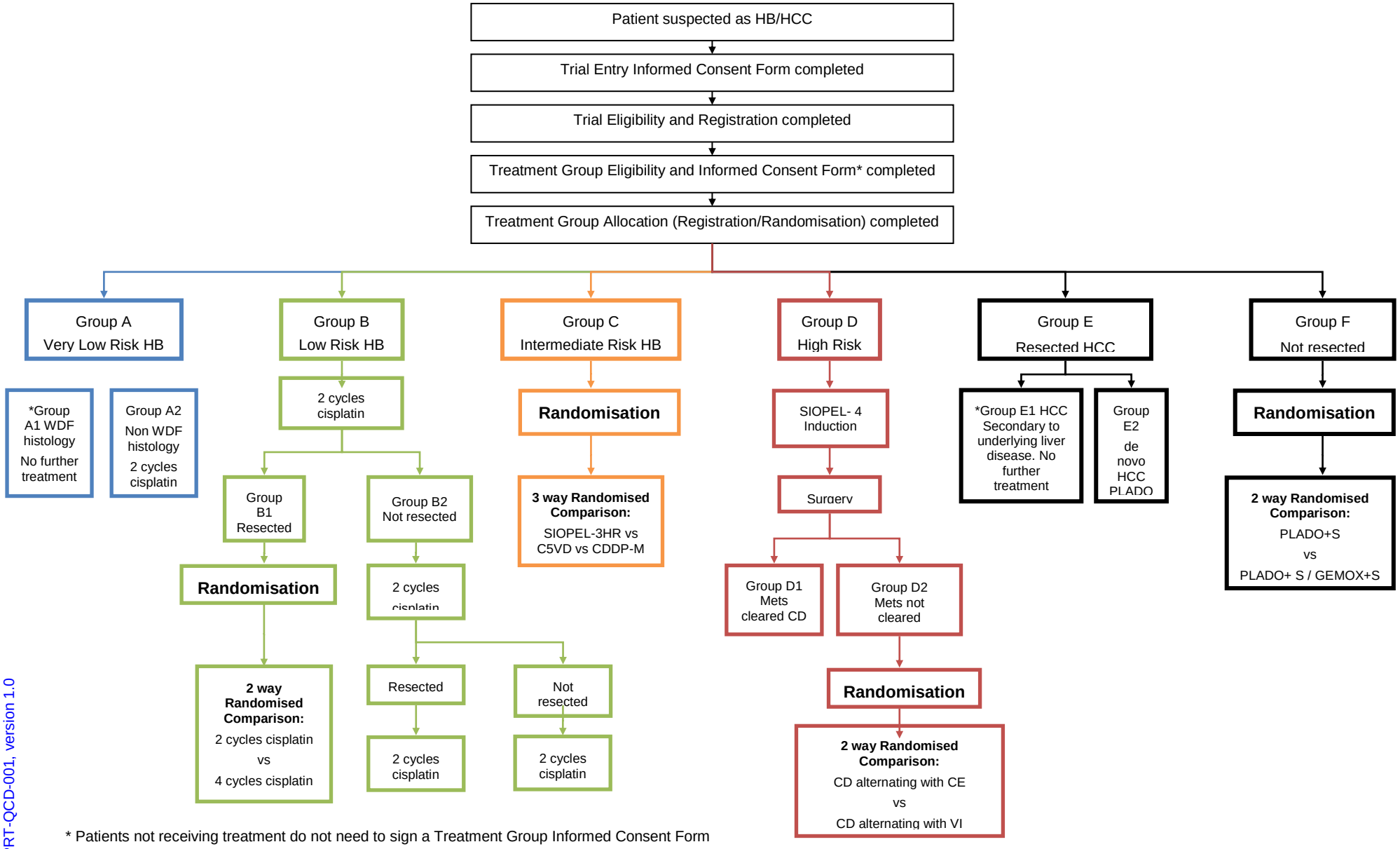
- Written informed consent for trial treatment.
- Score of ≥50% Lansky scale for patients <16 years, or Karnofsky scale for patients ≥16 years.
- For female patients of child-bearing potential, a negative pregnancy test prior to starting trial treatment is required. Any patient who is of reproductive 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.

TRIAL SCHEMA



* Patients not receiving treatment do not need to sign a Treatment Group Informed Consent Form

ABBREVIATIONS

ABPI	Association of the British Pharmaceutical Industry
AE	Adverse Event
AFP	Alpha Fetoprotein
AR	Adverse Reaction
ALP	Alkaline Phosphatase
ALT	Alanine Transferase
AST	Aspartate Aminotransferase
ANC	Absolute Neutrophil Count
AUC	Area Under Curve
CCrea	Creatinine Clearance
CDDP	cis-diamminedichloridoplatinum (II) / Cisplatin
CDDP-M	cis-diamminedichloridoplatinum (II) / Cisplatin monotherapy
CHIC	Children's Hepatic Tumours International Collaboration
CHMP	Committee for Medicinal Products for Human Use
CLCN	Childhood Liver Cancer Network
COG	Children's Oncology Group
CR	Complete Remission
CRCTU	Cancer Research UK Clinical Trials Unit
CRF	Case Report Form
CT	Computerised Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic Acid
DSUR	Development Safety Update Report
ECG	Electrocardiogram
EDTA	Ethylenediaminetetraacetic Acid
EFS	Event-Free Survival
EOT	End of Treatment
FFPE	Formalin-fixed paraffin-embedded
FFS	Failure-Free Survival
FS	Fractional Shortening
GCP	Good Clinical Practice
G-CSF	Granulocyte-Colony Stimulating Factor
GFR	Glomerular Filtration Rate
GP	General Practitioner
HB	Hepatoblastoma
HCC	Hepatocellular Carcinoma
hCG	Human Chorionic Gonadotropin
HE	Hematoxylin and Eosin
HR	Hazard Ratio
ICF	Informed Consent Form
IDMC	Independent Data Monitoring Committee

IMP	Investigational Medicinal Product
ISF	Investigator Site File
ITT	Intention-To-Treat
MDT	Multi-Disciplinary Team
MHRA	Medicines and Healthcare products Regulatory Agency
MRI	Magnetic Resonance Imaging
NCC	National Coordinating Centre
NCI	National Cancer Institute
NIMP	Non-Investigational Medicinal Product
OLT	Orthotopic liver transplantation
OS	Overall Survival
MUGA	Multi-gated Radionuclide Angiography
PBSC	Peripheral Blood Stem Cell
PET	Positron Emission Tomography
PIS	Patient Information Sheet
PT	Prothrombin Time
RDE	Remote Data Entry
REC	Research Ethics Committee
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SPC	Summary Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TSC	Trial Steering Committee
UK	United Kingdom
WDF	Well Differentiated Fetal histology
WMA	World Medical Association

1. BACKGROUND AND RATIONALE

1.1 Background

Primary liver tumours (hepatoblastoma (HB) and hepatocellular carcinoma (HCC)) in children account for 1% of paediatric tumours. The incidence, however, has been increasing with improved neonatal care for preterm infants, who have an increased risk of developing HB [1]. HB has an annual incidence of 0.8 per million children. HCC is less common with over 500,000 people affected worldwide.

Currently, the 5 year overall survival (OS) for children with HB is variable and ranges from about 50-100% depending on the disease characteristics. Among those 'cured', current treatment regimens have a risk of significant toxicities including cisplatin-induced oto-toxicity and nephrotoxicity, doxorubicin-induced cardiomyopathy and secondary leukaemia. In patients treated for HB with 600 mg/m^2 of cumulative cisplatin, hearing loss to the point of requiring augmentation devices occurs in half of all patients [2], severely impacting childhood development and quality of life. The lethal impact of anthracycline-induced cardiomyopathy and secondary leukaemia is self-evident. The Paediatric Hepatic International Tumour Trial (PHITT) will investigate whether reductions in therapy reduce the risk of both short- and long-term side effects for patients with good prognosis without compromising their good outcomes and whether intensifying treatments with the introduction of new agents improves outcomes for those with a poor prognosis.

Results of previous studies (treatment approaches) in hepatoblastoma

Studies in HB have previously been conducted by the four main paediatric oncology consortia, namely the Liver Tumour Strategy group of the International Society of Paediatric Oncology (SIOPEL) in Europe, the Children's Oncology group (COG) in North America, the Japanese Study Group for Paediatric Tumours (JPLT) and German Society for Paediatric Oncology and Haematology (GPOH). These are summarized below.

SIOPEL studies

The SIOPEL-1 (1990-1994) study established the efficacy of cisplatin / doxorubicin (PLADO) combination therapy in HB. Patients were treated with 4 pre-operative cycles of PLADO followed by resection or transplant and two further post-operative courses of PLADO. The 5-year event free survival (EFS) was 66% (95% CI 59-74%) and the overall survival (OS) was 75% (95% CI 68-82%) [3]. This trial also validated the pre-treatment extent of tumour (PRETEXT) staging system (see Appendix 4), which has since been used to stage patients with HB.

SIOPEL-2 (1994-98) was a pilot study that stratified patients into two groups - standard-risk (SR) patients with tumour confined to the liver and involving no more than three hepatic sectors, and high-risk (HR) patients with HB extending into all four sectors and/or with lung metastases or intra-abdominal extra hepatic spread. SR-HB patients were treated with four courses of cisplatin monotherapy (CDDP 80mg/m^2) every 14 days, delayed surgery and then two more CDDP courses. HR-HB patients were given CDDP alternating every 14 days with carboplatin (CARBO) 500 mg/m^2, and doxorubicin (DOXO) 60 mg/m^2. Two courses of CARBO/DOXO and one of CDDP were given postoperatively. For SR-HB patients (n=77), 3-year OS and PFS were 91% and 89% respectively, suggesting that cisplatin alone was sufficient to treat this group of patients. Despite intensification of therapy in the HR-HB group (n=58), OS was 53% and progression-free survival (PFS) was 48%, respectively [4]. Multivariate analysis of prognostic factors identified the adverse prognostic value of AFP< 100 ng/mL in HR-HB patients.

SIOPEL-3 (1998-2006) compared CDDP monotherapy and CDDP/DOXO (PLADO) in SR-HB patients in a prospective randomised trial. Three-year EFS and OS were similar in both groups: 83% (95% CI 77 to 90) and 95% (95% CI 91 to 99) in the cisplatin group, and 85% (95% CI 79 to 92) and 93% (95% CI 88 to 98) in the PLADO group. Thus cisplatin monotherapy was shown to be sufficient in the treatment of patients with SR-HB [4]. In the high-risk patients, the efficacy of the dose-intense multi-agent chemotherapy regimen piloted in SIOPEL2-HR was tested in this multicentre prospective trial. Of the 150 patients evaluable for response, 118 (79%) achieved a partial response to chemotherapy. Complete resection of the tumour could be achieved in 115 patients (76%) either by partial

hepatectomy (56%) or by liver transplantation (21%). In 106 patients (70%), complete resection of all tumour lesions (including metastases) was achieved. Among the patients with initial lung metastases, 52% achieved complete remission of the lung lesions with chemotherapy alone. EFS and OS estimates at 3 years were 65% (95% CI 57% to 73%) and 69% (95% CI 62% to 77%) for the whole group. EFS and OS for all patients with PRETEXT-IV tumours were 68% and 69%, respectively, and 56% and 62%, respectively, for patients with metastasis. This strategy significantly improved the resectability of tumours in HR-HB patients [5].

SIOPEL-4 (2005-09) was a prospective single-arm feasibility study in patients with HR-HB with further intensification of platinum chemotherapy with weekly administration in combination with doxorubicin followed by surgical removal of all remaining tumour lesions if feasible (including liver transplantation and metastasectomy). Patients whose tumour remained unresectable received additional preoperative chemotherapy with CARBO and DOXO. After surgery, postoperative chemotherapy with CARBO and DOXO was given to patients who didn't receive this regime pre-operatively. The primary endpoint was complete remission at the end of treatment. Sixty-two patients were evaluated and complete resection of all tumour lesions was achieved in 46 patients (74%). At the end of therapy, 49 of 62 patients (79%, 95% CI 67 to 88) were in complete remission. 3-year EFS was 76% (95% CI 65 to 87) and 3-year OS was 83% (73 to 93). 19 out of 20 patients with lung metastases at presentation cleared their metastases and achieved remission at the end of treatment.

COG studies

INT-0098 (1989-92) was a randomised trial comparing the two regimens known to be effective in HB: cisplatin, vincristine, and fluorouracil (C5V) and PLADO. Five-year EFS estimates were 57% (SD = 5%) and 69% (SD = 5%) for patients on C5V and PLADO, respectively (P =0.09). Toxicities were greater with PLADO with 2 toxic deaths. Therefore, C5V was adopted as the preferred regimen for treating HB [6].

The next COG study, P9645 (1999-2002) was a randomised trial comparing a novel regimen with increased platinum dose-intensity alternating carboplatin and cisplatin (CC) every 2 weeks with C5V in patients with unresectable HB. The 1-year EFS was 37% for patients receiving CC and 57% for those receiving C5V (P = 0.017). The study concluded that alternating platinum analogues increased the risk of adverse outcome in children with unresectable or metastatic HB [7]. This study also demonstrated that surgical resection alone may be sufficient for patients with Stage I HB with pure foetal histology (PFH).

In the ongoing COG study, AHEP0731 (2009-present), patients with stage I PFH are classified as very low risk and treated with resection only. Patients with stage I non-PFH and stage I and II non-small cell undifferentiated histology (SCU) are termed as low risk and treated with resection and 2 cycles of C5V chemotherapy. Patients with stage I and II SCU histology and all stage III patients are classified as intermediate risk and receive 6 cycles of C5V plus doxorubicin (C5VD) in total with surgery after either 2 or 4 cycles of chemotherapy. Patients with stage IV disease or any stage plus an alpha-fetoprotein (AFP) level at diagnosis of <100 ng/mL are classified as high risk and receive up-front window therapy with vincristine and irinotecan followed by C5VD.

JPLT studies:

JPLT-1 (1991-99) was a non-randomised study of 154 patients with malignant liver tumour including 145 cases of HB. Patients with stage I or II HB received courses of lower dose cisplatin (CDDP), 40 mg/m^2 and tetrahydropyranyl (THP)-Adriamycin, 30 mg/m^2. Patients with stage IIIA, IIIB, or IV hepatoblastoma received CDDP, 80 mg/m^2 and THP-Adriamycin, 30 mg/m^2/day for 2 days. Courses were repeated every 4 weeks as tolerated. OS (3-year/ 6-year) was 100%/100% for stage I (n = 9), 100%/96% for stage II (n = 32), 77%/74% for stage IIIA (n = 48), 50%/50% for stage IIIB (n = 25), 65%/39% for stage IV (n = 20), and 78%/73% overall. For stage IIIA and B disease, intravenous chemotherapy was better than intra-arterial chemotherapy (66% v 38% for EFS and 69% v 57% for OS). The OS and EFS rates were comparable with the results of other multi-centre studies in Europe and the United States [8].

JPLT-2 (1999-2008) included 212 HB patients and used the PRETEXT staging system. PRETEXT I patients were treated with primary resection followed by low doses of cisplatin–pirarubicin (tetrahydropyranyl-adriamycin). Otherwise, patients received preoperative cisplatin–pirarubicin (CITA),

followed by surgery and postoperative chemotherapy. Ifosfamide, pirarubicin, etoposide, and carboplatin (ITEC) were given as a salvage treatment. High-dose chemotherapy with hematopoietic stem cell transplantation (SCT) was reserved for patients with metastatic disease. The 5-year OS in non-metastatic cases was 100% for PRETEXT I, 87.1% for PRETEXT II, 90% for PRETEXT III, and 78% for PRETEXT IV. The 5-year OS in metastatic cases was 44% [9].

GPOH Studies

HB 94 (1994-97) was a prospective, single-arm study to assess the efficacy of chemotherapy consisting of cisplatin, ifosfamide, and doxorubicin (IPA) and the addition of etoposide and carboplatin (VP16/CARBO) for recurrent or advanced Stage III or IV tumours (post-surgical staging system). 69 children were enrolled. OS was 77%. Disease free survival (DFS) and EFS were Group I DFS 89%, EFS 96%; Group II DFS and EFS 100%, Group III DFS 68% and EFS 76% and group IV DFS 21% and EFS 36%. The pre-treatment prognostic factors identified included vascular tumour invasion (p= 0.0039), occurrence of distant metastases (p< 0.0001), initial extremely high (>1,000,000ng/mL) or very low (<100ng/mL) AFP level (p= 0.0034) and extent of resection (p=0.0001) [10].

The HB-99 (1999-2008) study aimed to improve the outlook for the HR patients with HB. 142 patients were analysed, 91 had SR HB and 51 had HR disease. The SR patients were treated with two to three courses of IPA, followed by a tumour resection and a postoperative course of IPA. 21 patients with a small tumour underwent primary resection followed by two courses of IPA. The HR patients were treated with two courses of CARBO/VP16. Responders then received high dose chemotherapy with CARBO/VP16 with stem cell transplantation followed resection of the primary tumour and if necessary, resection of the metastases. Poor responders received IPA. 6 out of the 51 high risk patients had an AFP less than 100 ng/mL. All 6 patients died [11].

1.2 Trial Rationale

The aim of the PHITT trial is to build on the cooperative experience of the different consortia to undertake four randomised comparisons in groups of patients with tumours (HB and HCC).

The SIOPEL and JPLT consortia utilized the PRETEXT system while COG has used a surgical based staging system. This difference in staging systems used to stratify patients has made direct comparison of results between cooperative group specific trials difficult. To address this issue, the recently formed Childhood Hepatic tumour International Consortium (CHIC) group combined the clinical data from 8 prior multicentre trials conducted by COG, SIOPEL, GPOH, and the JPLT establishing a database consisting of 1,605 patients. Analyses of the database have been performed with the goal to create an evidence-based risk stratification that would serve as the foundation for this study. Identified risk factors, associated with varying EFS include PRETEXT group, age at diagnosis, AFP level and the presence of a PRETEXT annotation factor. In this trial, a common risk stratification schema integrating the CHIC identified risk factors will be, for the first time, used to stage patients into four risks groups: Very Low (Group A), Low (Group B), Intermediate (Group C), and High (Group D) (see Appendix 5).

This trial will evaluate whether reducing treatment for low risk patients maintains their excellent EFS and decreases acute and long-term toxicity. Intensification of therapy with the use of novel agents will be evaluated in the high risk group. The trial will also compare three different regimens in intermediate risk HB. Patients with HCC will be divided into two groups, E and F, based on whether the tumour is resectable (group E) or unresectable and/or metastatic (group F). The aim is to evaluate whether survival in patients in group E with *de-novo* HCC using PLADO chemotherapy is improved and to evaluate whether resectability and survival is improved in patients in group F using novel therapeutic agents in combination with PLADO as detailed later.

Evaluation of the biology of HB and HCC, using the identification/validation of novel and already reported prognostic biomarkers as well as toxicity biomarkers is a key strand of this trial, so patients in all risk groups can be registered. The trial is also designed to optimise the collection of clinically annotated biologic specimens and establish the world's largest repository of blood and tissue samples from paediatric patients with HB and HCC.

Justification of design, patient population and therapy in HB

Due to the rarity of HB, this trial has been designed as the first international co-operative liver tumour trial based on a consensus approach involving SIOPEL, COG and JPLT in order to recruit the number of patients required to answer the research questions. NB: JPLT was incorporated into the Japanese Children's Cancer Group (JCCG) in summer of 2016 and has been renamed as the Liver tumour committee in JCCG.

Group A (Very Low Risk) - These patients will receive standard treatment and there are no therapeutic research questions. When feasible, definitive surgical resection at presentation has been an integral part of the treatment strategy for patients treated in COG and JPLT trials resulting in excellent outcomes with >90% EFS. In contrast, patients treated in SIOPEL trials commonly receive neo-adjuvant chemotherapy. In previous COG trials, outcomes in patients with completely resected tumours with central review confirmed well-differentiated foetal (WDF) histology (previously classified as PFH with low mitotic activity) were excellent with surgery alone [12]. In PHITT patients with localized tumours with WDF histology will be treated with surgery alone.

In the P9645 study, patients who were completely resected at diagnosis but did not have WDF histology received 4 cycles of C5V (cisplatin/5-fluorouracil/vincristine) with a 5-year EFS and OS of 84% and 96%, respectively [13]. AHEP0731 built upon these results reducing therapy from 4 to 2 cycles of C5V with an EFS of >90% (personal communication, Howard Katzenstein). Data supporting the benefit of 5-FU and vincristine in the management of HB remain indirect; SIOPEL studies have demonstrated high cure rates with single agent cisplatin monotherapy alone [4] . Therefore, patients with completely resected disease at diagnosis but who do not have WDF histology will receive two cycles of adjuvant cisplatin therapy. These patients will be resected without pre-treatment chemotherapy. This cohort will contribute to the evaluation of the HB molecular profile and a substantial reduction of therapy across the consortia. The outcome following upfront surgery in this group of patients and the outcome for patients following post-operative surgery will be reported. The linking of molecular profiles to clinical features and PRETEXT is instrumental to guide therapy reduction in future trials.

Group B (Low Risk) - PHITT divides patients with localised disease (with AFP >100ng/mL and age less than 8 years old) into two groups based on results from the CHIC analysis. Group B includes patients with initially unresectable disease defined as PRETEXT I, II and III tumours with no PRETEXT annotation factors (VPEFR). In AHEP0731, these patients received 4 cycles of adjuvant chemotherapy with C5V. In SIOPEL-3, most such patients were treated effectively with 6 cycles of cisplatin monotherapy [4], with surgical resection typically after the fourth neo-adjuvant cycle and OS approaching 90%. This suggests that this group of patients may be over-treated. Cisplatin ototoxicity remains a significant long term side effect of therapy, and among other risk factors, correlates with exposure, with the highest risk for hearing impairment occurring in the dose range > 400mg/m^2 [2, 14, 15]. In this group, therapy reduction will be investigated by randomising patients who undergo early resection with a randomisation between a total of 4 versus 6 cycles of cisplatin. The study of the HB molecular profile of this group of patients could help in predicting patient response and improving current risk stratification to adapt chemotherapy regimens according to biology in future trials.

Group C (Intermediate Risk) - Group C will consist of patients with locally advanced tumours including PRETEXT I, II and III tumours with a positive annotation factor and all PRETEXT 4 tumours. In this group, a three way randomisation will compare C5VD versus SIOPEL-3HR versus dose-compressed cisplatin every 2 weeks. The rationale for this approach is based on the following considerations.

In the recent AHEP 0731 study, the intermediate risk group (which included this type of patient treated with C5VD chemotherapy) outcome at 3-years was OS of 94%, (personal communication, Howard Katzenstein). Anthracycline toxicity (cardiac, added marrow suppression) is a targetable challenge for all non-metastatic HB patients with a favourable prognosis and, given this excellent outcome, may now include Group C patients. Additionally, the role of vincristine and 5-flourouracil is unclear having never been reliably established in HB. Interestingly, vincristine was the agent dose-modified most frequently on AHEP0731 due to toxicity (3-fold compared with other agents) (personal communication, Howard Katzenstein).

In the SIOPEL-3 standard risk study where dose compressed cisplatin was compared to dose compressed cisplatin/doxorubicin in PRETEXT I-III patients without advanced positive annotation

factor components, dose compressed cisplatin alone was sufficient as both arms had similar response rates, resection rates, EFS and OS [4]. These results raise the question as to the benefit of doxorubicin used front-line for non-metastatic patients. In the SIOPEL-3HR study, advanced PRETEXT I-III tumours with positive annotation factors or PRETEXT IV tumours were treated with alternating courses of cisplatin and carboplatin with doxorubicin with an improvement in EFS (65%) and OS (69%) compared to previous studies. Based on these data, it is worth investigating whether giving an effective agent (i.e. cisplatin or doxorubicin) every 1-2 weeks is the important determinant for survival; cisplatin every 2 weeks might be equally, if not more, efficacious than q 3 weekly standard combination therapy. Evolution of surgical treatment approaches may be another important factor leading to improved survival in this cohort. The proposed randomised question is a rational progression forward based on results achieved in recent SIOPEL and COG trials.

Group D (High Risk) - Outcomes of children with metastatic HB are poor, with 5-year EFS of <30% and 5-year OS of <60%. In SIOPEL-4, a cisplatin timing intensified treatment strategy was used. The 3-year EFS for patients who cleared (n = 20; rapid complete pulmonary responders) and did not clear (n = 19; incomplete pulmonary responders) metastatic disease by the end of Induction therapy was 95% and 53%, respectively [5]. 19/20 patients who cleared metastases before surgery achieved CR at the end of treatment with few relapses past remission [16].These data suggest that a pulmonary response-based approach could optimise outcomes for patients with metastatic HB. In PHITT, patients will receive SIOPEL-4 induction therapy as standard treatment; favourable responders (those who are clear of metastatic disease at the end of induction, or those who qualified for the high risk cohort because age>8 or AFP<100 in the absence of metastatic disease) will be assigned to Group D1. Unfavourable responders (those who have residual metastatic disease at the end of induction) will be assigned to Group D2.

Group D1 - Consolidation with Carboplatin/Doxorubicin will be given as standard therapy, with no therapeutic research question in this group.

Group D2 - Randomisation between two novel consolidation regimens, with no standard treatment control arm - Carboplatin/Doxorubicin and Irinotecan/Vincristine versus Carboplatin/Doxorubicin and Carboplatin/Etoposide - In SIOPEL-4, inducing metastatic remission was the key to preventing mortality, as relapses post remission were uncommon [16]. Consequently, Group D2 will evaluate two extended consolidation regimens using additional agents with demonstrated activity in HB. The rationale for including irinotecan/vincristine in an extended consolidation is that the activity of irinotecan has been established both in SIOPEL and COG trials. In a SIOPEL Phase II trial of irinotecan in relapsed and refractory HB, twenty-four patients (11 relapses, 13 refractory diseases) were treated. Of the 23 evaluable patients, six had an overall partial response and 11 had stable disease [17]. In AHEP0731, thirty patients with metastatic disease were treated with two cycles of irinotecan and vincristine in an upfront window of which twenty-three of these patients responded to therapy (personal communication, Howard Katzenstein). The selection of carboplatin/etoposide for the other extended consolidation arm is based on the activity of this combination in GPOH trials. Although this combination adds only one “new agent” (etoposide) to the SIOPEL-4 backbone, carboplatin/etoposide is the only chemotherapy combination shown to be effective in relapsed or refractory HB [10]. Etoposide in combination with carboplatin was used in a window trial design analogous to that used in AHEP0731 in GPOH HB 94, where 18 children with advanced HB were treated with carboplatin and etoposide, with a response achieved by 12 children (67%) [10]. Additionally, the SIOPEL 1-3 studies showed that this regimen had a similarly high response rate in patients with relapsed HB (62%, 8/13 patients) [16]. A benefit of the prolongation of the consolidation course is that it provides additional time and opportunity to perform surgical interventions in the context of systemic chemotherapy to control metastatic disease based on the effectiveness of metastectomy in recurrent HB.

Rationale of HCC therapy

Background:

Patients with HCC have previously been treated on the same protocols as patients with HB. In the INT0098 study, 46 HCC patients were enrolled. After initial surgery or biopsy patients were randomised to C5VD or PLADO as described in the HB section with comparable outcomes. For the entire cohort, 5-year EFS was 19% (SD=6%). Patients with stage I (n=8), III (n=25), and IV (n=13) had 5-year EFS of 88% (SD=12%), 8% (SD=5%), and 0% respectively. Therefore, while children with resectable HCC had a good prognosis, those with advanced disease had a poor outcome [18].

Similarly, 39 children with HCC were treated on the SIOPEL-1 protocol. 37 received PLADO chemotherapy. 33% of patients had underlying cirrhosis. Partial response was observed in 18 (49%) of 37 patients; there was either no response or progression in the remainder. Complete tumour resection was achieved in 14 patients (36%). Twenty patients (51%) never became operable. OS at 5 years was 28% and EFS was 17%. Presence of metastases and pre-treatment extent of disease system grouping at diagnosis had an adverse influence on overall survival in multivariate analysis. Prognosis of patients with HCC was significantly inferior to those with HB [19].

The SIOPEL-2 and -3 studies included 85 patients with HCC. 13 underwent upfront surgery whilst 72 patients received PLADO chemotherapy [20]; 40% of patients responded to chemotherapy with an OS of 22%. These data confirm the need for novel approaches to improve survival in patients with HCC. The GPOH group has tested the role of sorafenib in combination with PLADO chemotherapy in a small series of 12 patients, 7 of whom had unresectable disease at diagnosis. Sorafenib was well tolerated and achieved CR in 50% of patient at a median follow up of 20 months [21].

HCC Risk Stratification - Outcomes for patients with HCC are critically dependent upon the ability to achieve complete resection. In PHITT, patients will be stratified into two study cohorts, those with resected disease at diagnosis and those with unresected or metastatic disease at diagnosis. The trial is designed to optimise the collection of clinically annotated biologic specimens and establish the world's largest repository of paediatric HCC specimens which can be analysed to help determine why paediatric HCC exhibits a heterogeneous spectrum of clinical behaviour [22] and determine which biologic features correlate best with treatment response and survival.

HCC Biology - Paediatric HCC is a biologically heterogeneous group of tumours. HCC may present in children with underlying liver pathology, but will also occur *de novo*. Underlying liver diseases in which paediatric HCC has been reported include familial cholestatic syndromes (Progressive familial intrahepatic cholestasis and Alagille's syndromes), extrahepatic biliary atresia, total parenteral nutrition and in association with tyrosinemia, glycogenosis, neurofibromatosis, ataxia-telangiectasia, Fanconi's anaemia and other constitutional and genetic abnormalities [23]. The fibrolamellar variant of HCC (FL_HCC) constitutes a distinctive variant of HCC that occurs almost exclusively in adolescents and young adults without underlying liver disease, accounting for almost a third of HCCs in patients under 20 years of age [24]. A unique, pathognomonic DNAJB1-PRKACA chimeric transcript has been detected in these patients, suggesting its importance in the pathogenesis this subtype [25]. Additionally, a small number of paediatric tumours demonstrate a mixture of histological patterns of both HB and HCC in the same tumour, or intermediate features, precluding their exact classification. Some of these tumours diagnosed in older children and carrying *CTNNB1* mutations, may represent HB with HCC molecular features [26], particularly those with TERT promoter mutations. The molecular genetic alterations of HCC and the abnormalities involved in hepatocarcinogenesis, have been extensively studied in adult tumours [27, 28]. Gene expression profiling studies have specifically addressed differences between clinical HCC subtypes and searched for biomarkers that could serve as prognostic predictors, or therapeutic targets [29, 30]. A number of recently published NGS (Next Generation Sequencing) studies on HCC identified additional genetic alterations including mutations in genes involved in epigenetic regulation, WNT, cell cycle and chromatin remodelling pathways [31-33]. Unfortunately, most of the studies did not include paediatric cases.

In PHITT, the characterisation of the molecular profile of all HCCs will be done using a comprehensive next-generation sequencing mutation panel (Oncomine Comprehensive Array, Thermo Fisher Scientific), and a whole-genome scanning SNP array platform to detect gains, losses, LOH, and genomic stability (Affymetric Oncoscan FFPE Assay). In addition, immunohistochemical analysis will be performed to determine the expression of prognostic hepatic progenitor markers and activation of key signalling pathways, following testing algorithms previously described for HBs. In Europe, large scale genomic, transcriptomic, and epigenetic profiling of banked, clinically annotated frozen HCC tumour specimens collected in the study, will be performed to address strictly biological aims of the study, as previously described. The HB biomarker panel studied for HB patients will also be assessed in HCC samples to evaluate its diagnostic and prognostic performance in this patient population.

Determination of effective chemotherapeutic regimens in HCC

Group E - HCC completely resected at diagnosis (no residual disease). Studies in adult HCC do not support a role for post resection chemotherapy; however, all three paediatric consortia have reported good survival rates using cisplatin and doxorubicin [18, 19, 21]. The group of HCC patients undergoing resection at diagnosis, either by means of a subtotal or complete hepatectomy during liver transplantation, are a heterogeneous cohort consisting of: 1) HCC arising in the context of underlying metabolic, genetic or viral infection-mediated predisposition for liver dysfunction/cirrhosis, 2) HCC arising de novo. The de novo group is comprised of patients with one of two histopathologic diagnoses: FL or non-FL-HCC. While there is substantial variation in the chemotherapeutic approach used to treat this group of patients, there is growing expert consensus regarding the post-resection observation of patients diagnosed with HCC arising in the context of genetic predisposition (as the patient's tolerance for chemotherapy in the context of cirrhosis or in the post-transplant period is not ideal). The remaining patients, those with de novo, non-FL HCC are typically felt to warrant therapy. The only existing data supporting treatment in these patients come from INT-0098 [18] which demonstrated an 88% 5-yr EFS for stage I patients treated either with C5V or cisplatin and continuous infusion of doxorubicin (n=8) and from the SIOPEL-1 trial [19] which described a PR rate of 49% in patients treated with PLADO and a resectability rate of 36% in these patients.

Patients with HCC arising in the context of predisposition to underlying liver dysfunction due to infection, metabolic, genetic, or anatomic considerations (Group E1) will be observed and patients with de novo HCC (both FL-HCC and non-FL-HCC - Group E2) will receive standard treatment with 4 cycles of PLADO. There are no therapeutic research questions in this group. As described above, we also propose a uniform approach towards exploratory genomic transcriptomic and proteomic analysis of the tumours to correlate biologic heterogeneity with treatment approach and patient outcome.

Group F - HCC unresected, resected with residual disease and/or metastatic at diagnosis - The outcome of patients who present with unresected or metastatic disease is poor. However, while adult studies show less than 20% response to chemotherapy, paediatric studies have demonstrated a nearly 50% response. While no standard of therapy has been established for paediatric patients with advanced HCC, data so far supports the use of PLADO and sorafenib [21]. Adult studies have demonstrated the therapeutic efficacy and feasibility of gemcitabine/oxaliplatin (GEMOX) [34-36]. A recent paediatric-focused abstract compiling retrospective data has demonstrated a nearly 30% response rate with these agents [37]. Given the dismal outcomes of paediatric patients with advanced HCC and the crucial importance of achieving complete resection, PHITT will study chemotherapeutic efficacy in this patient cohort. Patients will be randomised to receive either PLADO plus sorafenib given every 21 days versus interval-compressed PLADO plus sorafenib alternating with GEMOX plus sorafenib every 14 days with assessment for safety, response and surgical resection rates. Previously published data has demonstrated the tolerability of sorafenib in combination with PLADO as well as GEMOX [21, 38]. The selected sorafenib dose for this trial is below that recommended for paediatric monotherapy (200 mg/m^2 q12hrs [39]) and the median of that reported for use in PLADO/sorafenib combination therapy [21].

Role of molecular stratification in HB

Current patient stratification and treatment rely only on clinical and pathological criteria. Nowadays, there is an urgent need to incorporate biological data into clinical practice, which has been successful in other cancers (e.g. lung, breast cancer). To date, few biomarkers of liver cancer have been identified, the majority of them in limited series of patients and their incorporation into the clinical practice have been impeded by the lack of validation studies in large series of cases. This trial offers a unique opportunity to discover and validate diagnostic and prognostic biomarkers in an extensive prospective cohort of patients. The next step will be to apply the highly-validated panel of biomarkers discovered during this trial to the current and future therapies and stratification systems.

In Europe, a tri-national validation study of liver cancer prognostic biomarkers in a retrospective cohort of 161 cases from Spain, France and Germany demonstrated the improvement of current clinical classification by incorporating the 16-gene signature and NQO1 gene expression as well as NFE2L2 and TERT promoter mutations [26, 40]. Moreover, a recent proteomic study identified a 3-protein signature which is able to classify patients into three different prognostic groups and complements clinical stratification [41].

In the US, the largest and most recent HB genomic profiling study [42], identified three distinct risk-stratifying molecular HB subtypes: low, intermediate and high risk tumours. High-risk tumours are characterized by a combination of high NFE2L2 activity, high levels of LIN28B, HMGA2, SALL4 and AFP expression, along with low let-7 expression and HNF1A activity. High-risk tumours are also characterized by high coordinated expression of onco-fetal proteins and stem cell markers. Genomic instability was primarily found in the high and intermediate risk groups, while low risk groups were genetically stable. Parallel testing of a 35 sample HB validation set suggested that immunohistochemical analysis using a panel of antibodies targeting NFE2L2, LIN28B, HNF1A, HMGA2, SALL4 and AFP, particularly when used in combination with targeted mutation testing and cytogenomic analysis, may serve to identify molecular profiles predictive of response to therapy.

This trial will collect and molecularly characterise the tumour specimens with the aim to identify and validate diagnostic and prognostic biomarkers for improving current patient stratification by incorporating biological data. Accordingly, all HCC tumours including key gene mutations and hypermethylations, copy number changes as well as gene and protein expression signatures will be molecularly profiled, to determine the clinical value and role in future treatment algorithms. Specifically, diagnostic and resection formalin-fixed, paraffin embedded as well as frozen tissue specimens from every patient will be tested using targeted sequencing (CTNNB1, NFE2L2, TERT promoter), a comprehensive next-generation sequencing mutation panel (Oncomine Comprehensive Array, Thermo Fisher Scientific), and a whole-genome scanning SNP array platform to detect gains, losses and LOH, (Affymetric Oncocan FFPE Assay) and to assess genomic stability. Secreted biomarkers will be also assessed in blood (e.g. DKK1). In Europe, it is also planned to perform large scale genomic, transcriptomic, proteomic and epigenetic profiling of banked, clinically annotated frozen tumour specimens collected in the study in order to identify new biomarkers of aggressive HBs (see chapter 12.3 for details). In addition, immunohistochemical analysis will be performed to determine the expression of prognostic hepatic progenitor markers and activation of signalling pathways as well as the 3-protein signature among other markers, using diagnostic and resection specimens, and to determine its utility to predict response to therapy. It is expected that integration of biomarkers associated with response to therapy and prognosis into clinical stratification algorithms will provide therapeutic guidance and help to better prognostically classify HB patients in the future. Finally, patient-derived xenografts and primary cell cultures will be established from fresh tumour specimens for future pre-clinical studies.

2. OBJECTIVES AND OUTCOME MEASURES

2.1 Objectives

The PHITT trial is an over-arching study including 4 randomised comparisons addressing therapeutic questions.

This trial will use a risk-adapted approach to the treatment of children diagnosed with HB. Children with HCC will also be included as a separate cohort.

Primary Objectives

Group A - Very Low Risk HB

Patients depending on their tumour histology will be treated with standard treatment as defined by the protocol. The primary aim for this group is to collect samples for biological and toxicity studies.

Group B - Low Risk HB

In patients who are resected after 2 courses (Group B1), the aim is to evaluate whether the outcome with a total of 4 cycles of treatment is not inferior to those receiving a total of 6 cycles of treatment.

Patients who are not resected after 2 courses (Group B2) will be treated with standard treatment as defined by the protocol. The primary aim for this group is to collect samples for biological and toxicity studies.

Group C - Intermediate Risk HB

To compare outcome and toxicity in patients treated with:

- cisplatin/5-fluorouracil/vincristine/doxorubicin (C5VD);
- SIOPEL-3 high risk chemotherapy with cisplatin, carboplatin and doxorubicin (SIOPEL-3HR);
- dose compressed cisplatin monotherapy (CDDP-M).

Group D - High Risk HB

In patients who have cleared metastatic disease with induction chemotherapy, treatment is standard as defined by the protocol. The primary aim for this group is to collect samples for biological and toxicity studies.

In patients who have not cleared metastatic disease with induction chemotherapy +/- surgery, the aim is to compare the outcomes of the following post induction treatments:

(i) carboplatin and doxorubicin (CD) alternating with carboplatin and etoposide (CE);
(ii) carboplatin and doxorubicin (CD) alternating with vincristine and irinotecan (VI).

Group E - Resected HCC

Patients will be treated with standard treatment as defined by the protocol. The primary aim for this group is to collect samples for biological and toxicity studies.

Group F - Unresected HCC: Patients with microscopic residual disease after resection will be included in this group.

The aim is to determine whether the addition of gemcitabine, oxaliplatin and sorafenib (GEMOX + sorafenib) to cisplatin, doxorubicin and sorafenib (PLADO+Sorafenib), in a dose compressed fashion improves outcome.

Secondary Objectives

- To report outcome (including EFS, OS, toxicity following treatment 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:
    - To provide a comprehensive and highly-validated panel of diagnostic and prognostic biomarkers;
    - To determine if paediatric HCC is a biologically different entity to adult HCC;
    - To 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.

2.2 Outcome Measures

2.2.1 Definition of Outcome Measures

The trial includes a common set of outcomes that will be measured in randomised groups with group specific measures selected from the common set. Table 1 below specifies the outcome measures for each group.

Event-free survival (EFS) is defined as the time from randomisation (or registration into the trial for non-randomised patients) to first failure event. Patients who have not had an event will be censored at their last follow-up date.

Failure events are:

- progression of existing disease or occurrence of disease at new sites,
- death from any cause prior to disease progression,
- diagnosis of a second malignant neoplasm.

Failure-free survival (FFS) is defined as per EFS (above) with the addition of failure to go to resection as a failure event.

Overall survival (OS) is defined as the time from randomisation (or registration for non-randomised patients) to death from any cause. Patients who have not died will be censored at their last follow-up date.

Toxicity will be recorded in relation to each cycle of *randomised treatment* and will be categorised and graded using Common Terminology Criteria for Adverse Events (CTCAE) (see Appendix 3).

Chemotherapy-related cardiac, nephro- and oto-toxicity will be recorded in relation to each cycle of treatment and will be categorised and graded using Common Terminology Criteria for Adverse Events (CTCAE) (see Appendix 3).

Hearing loss will be measured according to the SIOP Boston Scale for oto-toxicity (see Appendix 6). The assessment will be performed at end of treatment (EOT) and follow up.

Response in HCC is defined as complete (CR) or partial (PR) response according to RECIST version 1.1 criteria, see Appendix 7. The assessment will be performed after 3 cycles of PLADO, or 4 cycles of PLADO+S/GEMOX+S in Group F. Patients who are not assessable for response – e.g. because of early stopping of treatment or death – will be assumed to be non-responders.

Response is defined as CR or PR and is defined in Appendix 8 based on radiological response (RECIST v1.1) and AFP decline. Response will be measured throughout treatment period. Patients who are not assessable for response – e.g. because of early stopping of treatment or death – will be assumed to be non-responders.

Surgical resectability is defined as complete resection, partial resection or transplant following randomisation (or enrolment for non-randomised patients).

Adherence to surgical guidelines is defined as the local clinician's surgical decision to resect or not compared to the current SIOPEL surgical guidelines.

Table 1 Outcome Measures

Group		Randomisation	Outcome measures *Primary outcomes	Expected Total N** (SIOPEL)	Total N** (All collaborators)
A - Very Low Risk HB Patients	Group A1- WDF histology	No	• EFS • OS • Adherence to surgical guidelines	10	30
	Group A2- Non WDF histology	No	• EFS • OS • Chemotherapy-related toxicity • Hearing loss • Adherence to surgical guidelines	70	170
B - Low Risk HB Patients	Group B1- Resected after 2 cycles	Yes	• **EFS*** • OS • Toxicity • Chemotherapy-related toxicity • Response • Hearing loss • Adherence to surgical guidelines	50	150
	Group B2-Not resected after 2 cycles***	No	• EFS • FFS • OS • Chemotherapy-related toxicity • Response • Surgical resectability • Hearing loss • Adherence to surgical guidelines	80	250

Group		Randomisation	Outcome measures	Expected Total N** (SIOPEL)	Total N** (All collaborators)
C - Intermediate Risk HB Patients	N/A	Yes	• **EFS*** • FFS • OS • Toxicity • Chemotherapy-related toxicity • Response • Hearing loss • Adherence to surgical guidelines	80	210
D - High Risk HB Patients	Group D1 - Good responders	No	• EFS • FFS • OS • Chemotherapy-related toxicity • Response • Hearing loss • Adherence to surgical guidelines	40	100
	Group D2 - Poor responders	Yes	• **EFS*** • FFS • OS • Toxicity • Chemotherapy-related toxicity • Response • Surgical resectability • Hearing loss • Adherence to surgical guidelines	40	110
E - Resected HCC Patients	Group E1 - HCC secondary to underlying disease	No	• EFS • OS • Surgical resectability	5	15
	Group E2 - *de novo* HCC	No	• EFS • OS • Chemotherapy-related toxicity • Toxicity • Hearing loss	15	35

F – Un resected /metastatic HCC Patients	Not resected	Yes	• **Response*** • FFS • OS • Toxicity • Chemotherapy -related toxicity • Surgical resectability • Hearing loss	60	150

* Primary outcomes

** Over 4 years

***Group B excludes 80 patients who are unresected at any stage

Recruitment period and follow up:

Patients will be enrolled for 4 years with a minimum of 2 years of follow-up from trial entry. The design considerations are different for the four randomised groups. The projected annual enrolment for each of the categories across all three collaborative groups of patients is shown above in Table 1.

3. TRIAL DESIGN

An international, over-arching phase III trial, with four randomised comparisons, for paediatric, adolescent and young adult patients with newly diagnosed HB and HCC. This trial includes a registration phase (trial entry) where patients will give consent for the analysis of their biological samples, tumour pathology and imaging reports to determine the grading and status of the disease, before being allocated to a Treatment Group

Patients with HB are classed into four risk-stratified groups and treated using different regimens. HCC patients are treated in two risk-stratified groups.

PHITT is the clinical trial within the Children's Liver Tumour European Research Network (ChiLTERN) Programme. The ChiLTERN Programme will address the following key issues facing children with liver cancer recruited in the PHITT trial:

- Provide a comprehensive and highly validated panel of diagnostic and prognostic biomarkers in both HB and HCC;
- Determine if paediatric HCC is a biologically different entity to adult HCC;
- Validate prospectively a clinical risk stratification;
- Establish a robust repository of clinical and pathological-annotated biological samples from paediatric patients with HB or HCC, including a collection of patient-derived xenografts and primary cell cultures;
- Develop genomic and biomarker analysis to predict children who may have an increased risk of developing toxicity with chemotherapy;
- Evaluate a surgical planning tool for an impact on decision making processes in POST-TEXT III and IV HB.

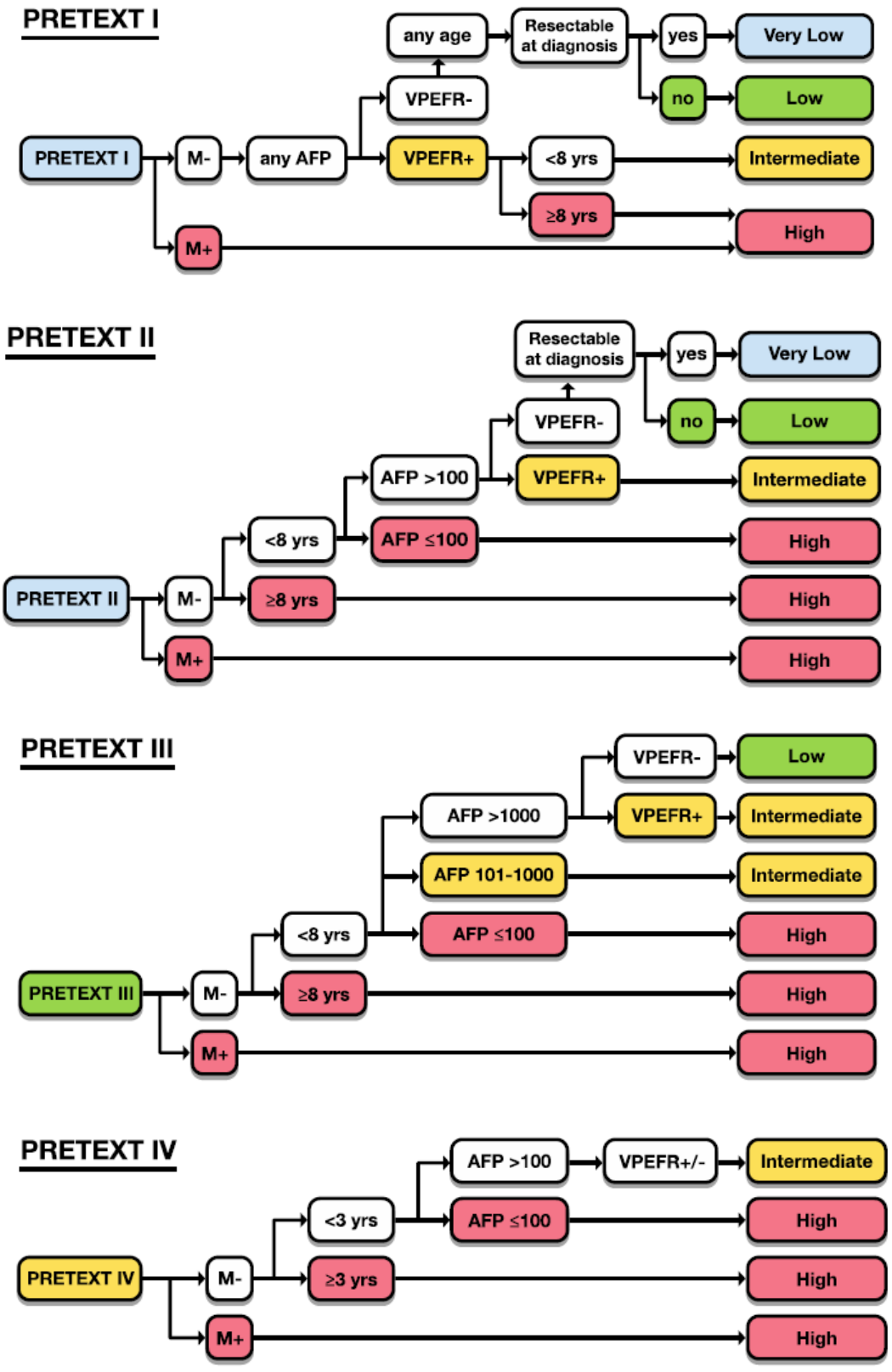
3.1 Risk Group Assignment

Patients with HB will be assigned to one of four risk cohorts according to a new staging system developed by CHIC.

Surgery outcome, PRETEXT grouping, age and AFP level are used to stratify patients into Very Low, Low, Intermediate and High Risk Groups as shown in Figure 1 CHIC Risk Group below.

Current available SIOPEL surgical guidelines and details on PRETEXT grouping (Appendix 4) should be referred to.

Figure 1 CHIC Risk Group



M: Metastases

VPEFR: PRETEXT Annotation Factors (V, ingrowth vena cava all hepatic veins; P, ingrowth both R & L portal veins or bifurcation; E, contiguous extrahepatic tumor; F, multifocal tumor; R, tumor rupture prior to diagnosis)

4. ELIGIBILITY

4.1 Trial Entry

Patients must meet the following criteria to be eligible for registration into the trial.

4.1.1 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.

4.1.2 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

4.2 Allocation to Treatment Group

Patients must meet the specific eligibility criteria for their allocated treatment group, as listed in the table below before entry into a treatment group. Patients who will not receive treatment are not required to sign an additional Treatment Group consent.

Note: patients with a diagnosis of hepatic neoplasm NOS should be treated according to HB arms.

4.2.1 Treatment Group Specific Inclusion Criteria

- Written Informed Consent for trial treatment
- Patient assessed as fit to receive group specific treatment as defined below
- 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 4.4.

4.2.2 Inclusion Criteria Specific to Each Group

GROUP	TUMOUR	RISK DEFINITION	PATHOLOGY	RENAL FUNCTION[1]	HAEMATOLOGY/ BIOCHEMISTRY[2]	CARDIOLOGY[3]
A1	Resected	Very Low Risk HB	Real time review required– WDF histological result	N/A	N/A	N/A
A2	Resected	Very Low Risk HB	Real time review required– Non-WDF histological result	Serum creatinine in the normal range OR GFR ≥60mL/min/1.73m^2	ANC >0.75x10^9/L Platelet count >75x10^9/L INR/PT <1.2x ULN;	N/A
B1 B2	N/A	Low Risk HB	Real time review required if age>8 and/or AFP<100 – confirm HB diagnosis	Serum creatinine in the normal range OR GFR ≥60mL/min/1.73m^2	ANC >0.75x10^9/L Platelet count >75x10^9/L INR/PT <1.2x ULN;	N/A
C (all treatments)	N/A	Intermediate Risk HB	Real time review required if age>8 and/or AFP<100 – confirm HB diagnosis	Serum creatinine in the normal range OR GFR ≥60mL/min/1.73m^2	ANC >0.75x10^9/L Platelet count >75x10^9/L INR/PT <1.2x ULN;	Shortening fraction ≥28% OR Ejection fraction ≥47%
D (all treatments)	N/A	High Risk HB	Real time review required if age>8 and/or AFP<100 – confirm HB diagnosis	Serum creatinine in the normal range OR GFR ≥60mL/min/1.73m^2	ANC >0.75x10^9/L Platelet count >75x10^9/L INR/PT <1.2x ULN;	Shortening fraction ≥28% OR Ejection fraction ≥47%
E1	Resected with negative margins HCC secondary to underlying liver disease	N/A	Real time review required – HCC histological result	N/A	N/A	N/A
E2	Resected with negative margins HCC *de novo*, including fibrolamellar	N/A	Real time review required – HCC histological result	Serum creatinine in the normal range OR GFR ≥60mL/min/1.73m^2	ANC >0.75x10^9/L Platelet count >75x10^9/L INR/PT <1.2x ULN;	Shortening fraction ≥28% OR Ejection fraction ≥47%
F	Not resected or metastatic HCC or resected with residual margin	N/A	Real time review required – HCC histological result	Serum creatinine in the normal range OR GFR ≥60mL/min/1.73m^2	ANC >0.75x10^9/L Platelet count >75x10^9/L INR/PT <1.2x ULN;	Shortening fraction ≥28% OR Ejection fraction ≥47% QT/QTc interval ≤450msec for males and ≤470msec for females

[1] Normal range based on age-based local reference values. If Creatinine is outside normal range for age, formal GFR should be estimated according to local practice.

[2] ANC – Absolute neutrophil count, INR – International normalised ratio, PT – Prothrombin Time, ULN – Upper limit of normal for age-based local reference values.

[3] Shortening fraction or Ejection fraction by local institution assessment method

4.2.3 Treatment Group Specific Exclusion Criteria

All Groups:

- Hypersensitivity to any medicines used in allocated group.

Group C:

- Patients who have known deficiency of dihydropyrimidine dehydrogenase (DPD)

Group D:

- Chronic inflammatory bowel disease and/or bowel obstruction
- Concomitant use with St John's Wort which cannot be stopped prior to start of trial treatment

Group F:

- Low K, Mg or Ca which remains uncorrected by electrolyte supplementation
- Peripheral Sensory Neuropathy with functional impairment
- Personal or family history of congenital long QT syndrome
- QT/QTc interval >450msec for males and >470msec for females
- Patients who are unable to swallow tablets where an oral suspension is not available or not approved (See Section 10.2.6)

4.3 Product Information

Investigators should refer to the current and relevant Summary Product Characteristics for patient care, especially special warnings and precautions for use, criteria for stopping treatment in case of toxicity, patient monitoring and interaction with other medicinal products and other forms of interaction.

4.4 Lifestyle Guidelines

Patients with reproductive potential must agree to use an adequate (i.e. with a failure rate of less than 1% per year) method of birth control during the period of therapy. Men should be advised not to father a child up to 6 months after receiving the last dose. Women of childbearing potential should be advised to use effective contraception to avoid pregnancy up to 6 months after the last dose of study treatment. Effective contraceptive methods include implants, injectables, combined oral contraceptives, intrauterine device (IUD or coil) and true sexual abstinence* or vasectomised partner.

*Sexual abstinence must be in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of the trial, and withdrawal are not acceptable methods of contraception.

5. SCREENING AND CONSENT

5.1 Informed Consent

It is the responsibility of the Investigator or person to whom the Investigator delegates the responsibility, to obtain written informed consent for each patient prior to performing any trial related procedure in compliance with national regulations. Where this responsibility has been delegated, this must be explicitly stated on a Site Signature and Delegation Log (or country specific equivalent).

There will be two steps of informed consent: at Trial Entry and then at allocation to the Treatment Group. Consent must be obtained separately. Country specific Patient/Parent Information Sheets (PIS) are provided to facilitate this process.

Investigators must ensure that they adequately explain the aim, trial treatment, anticipated benefits and potential hazards of taking part in the trial to the patient and/or parent/legal guardian as appropriate. The Investigator should also stress that the patient and/or parent/legal guardian is completely free to refuse to take part or withdraw from the trial at any time. The patient and/or parent/legal guardian should be given sufficient time (e.g. 24 hours) to read the PIS and to discuss the patient's participation with others outside of the site research team if they wish to. The patient and/or

parent/legal guardian must be given an opportunity to ask questions which should be answered to their satisfaction. The right of the patient and/or parent/legal guardian to refuse to participate in the trial without giving a reason must be respected.

As the trial includes both child and adult patients, written consent/assent will be obtained from the patient wherever it is possible to do so (as appropriate according to age and national legislation). There is a section on the parent consent form where assent can be obtained from the patient. For those children who are not able to read, write or understand regarding assent, the clinician will explain the study and obtain verbal assent which will be documented in the patient's medical records. Patients should be re-consented at the age of majority in accordance with national guidance/legislation.

If the patient and/or parent/legal guardian agrees to participate in the trial, they should be asked to sign and date the latest version of the Informed Consent Form (ICF). The Investigator must then sign and date the form on the same day. A copy of the ICF should be given to the patient and/or parent/legal guardian, a copy should be filed in the patient's medical records, and the original placed in the Investigator Site File (ISF) or country specific equivalent. Once the patient is entered into the trial, the patient's trial number should be entered on the ICF filed in the ISF. If allowed by country specific legislation/guidance and if the patient and/or parent/legal guardian has given explicit consent, a copy of the signed ICF must be sent in the post to the applicable National Coordinating Centre (NCC) for review.

Details of the informed consent discussions should be recorded in the patient's medical records; this should include date of, and information regarding, the initial discussion, the date consent was given, with the name of the trial and the version number of the PIS and ICF. Throughout the trial, the patient and/or parent/legal guardian should have the opportunity to ask questions about the trial and any new information that may be relevant to the patient's continued participation should be shared with them in a timely manner. On occasion it may be necessary to re-consent the patient, in which case the process above should be followed and the patient's right to withdraw from the trial respected.

Electronic copies of the PIS and ICF are available from the applicable NCC and should be printed or photocopied onto the headed paper of the local institution where required by country specific legislation/guidance.

Investigators will be expected to maintain a screening log of all potential study participants. This log will contain limited information about the potential participant and will include the date and outcome of the screening process.

With the patient's or patient's parent/guardian's prior consent, their medical practitioner (General Practitioner (GP) in the UK) should also be informed that they are taking part in the trial. A GP Letter is provided electronically for this purpose but it is anticipated that both this letter and the PIS will be translated and adapted in accordance with national practices.

5.2 Screening

Note that assessments conducted as standard of care do not require informed consent and may be provided as screening data. The date protocol therapy is projected to start should be no later than 15 days from trial entry. Investigators are encouraged to enrol patients immediately following histological diagnosis and begin protocol therapy within 28 days of the initial surgical procedure.

5.2.1 Screening prior to Trial Entry

Trial specific investigations must not be undertaken without prior written informed consent.
To determine eligibility for Trial Entry, a histologically confirmed diagnosis of HB* or HCC is required.
*Histological confirmation of HB is required except in emergency situations where:

a) The patient is too ill to undergo a biopsy safely
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

5.2.2 Screening prior to Treatment Group Allocation

All clinical and laboratory studies to determine eligibility for treatment must be performed within 28 days prior to treatment group allocation.

- Medical history
- PRETEXT staging assessment completed. Refer to Risk Group Assignment (Section 3.1) and Appendix 4 (PRETEXT) for further details.
- Full physical examination (including weight, height and surface area)
- Performance status using Lansky or Karnofsky grading systems
- Laboratory tests
    - Haematology (includes Haemoglobin (Hb), white blood cells (WBC), differential cell count, neutrophil count, lymphocytes and platelets)
    - Biochemistry (includes magnesium, potassium, calcium, urea, creatinine, total protein, albumin, bilirubin, alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGT), lactate dehydrogenase (LDH), alanine transaminase (ALT) or aspartate transaminase (AST), ammonia)
    - Coagulation (including International normalised ratio (INR) or Prothrombin time (PT), and activated partial thromboplastin time (APTT))
    - AFP
    - Hepatitis B and C serology (other serology to be conducted as per local practice)
    - GFR when serum creatinine is above normal limit for age
    - A pregnancy test (serum or urine) will be done on female patients who are of child bearing potential
- Audiology assessment (according to Boston scale)
- Radiological assessments:
    - Tumour evaluation of primary tumour disease (MRI or CT)
    - Tumour evaluation of metastases (Chest CT)
- Cardiology assessment by local institution assessment method is required for Intermediate (Group C) and High (Group D) Risk HB, and HCC (Groups E and F) patients
- ECG assessment is required for unresected/metastatic HCC patients (Group F)
- Tissue samples for Pathology/Biology studies (refer to section 12.3)
- Blood samples for Pathology/Biology and Toxicity studies (refer to section 12.3)

In addition, male patients should be counselled on the conservation of sperm prior to treatment because of the possibility of irreversible infertility.

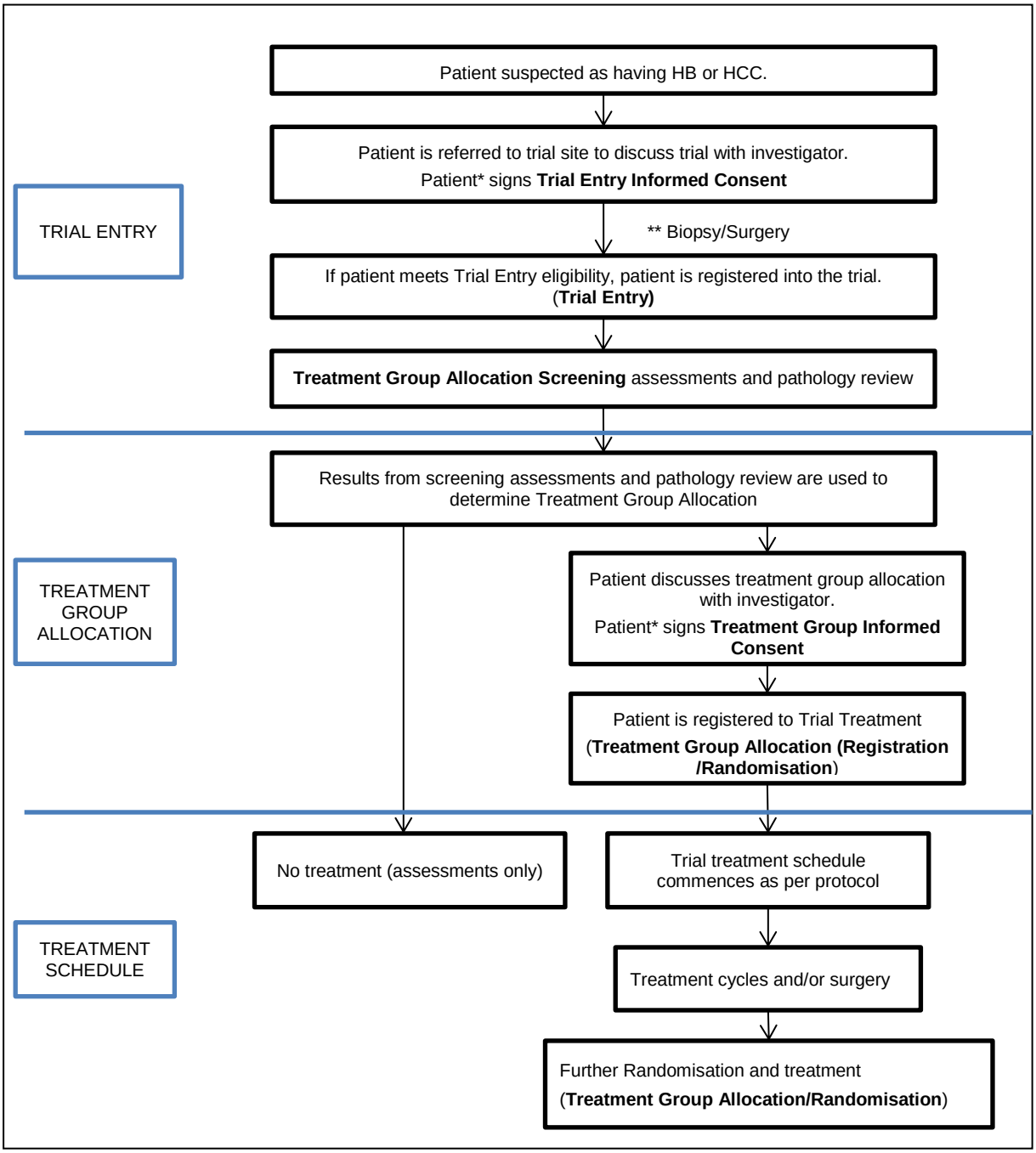
6. TRIAL ENTRY

Patients can be entered into the trial once the applicable NCC has confirmed that all regulatory requirements have been met by the trial site and the site has been activated by the UK Coordinating Centre.

It will be proposed to the patient and/or patient's parent/guardian to participate in the PHITT trial by signing the Trial Entry ICF. Investigators are encouraged to approach patients and obtain written informed consent ahead of any planned biopsy/surgery, to allow the required tissue samples to be taken and used for the purposes of the PHITT Trial. Once informed consent has been obtained, patients are assessed for eligibility and disease staging using screening assessments and pathology review (if required). See Screening (Section 5.2) for further details. Importantly, samples taken at diagnosis represent the most important biological material of this trial and should be reserved for biology. Subsequent samples during and after the treatment of enrolled patients should also be taken for biology (please refer to most recent version of PHITT Laboratory Manual before taking samples).

The treatment group allocation and treatment details are then discussed with the patient, and the patient and/or patient's parent/guardian signs a Treatment Group ICF to confirm the patient's participation in the trial treatment. Allocation into a Treatment Group must be performed prior to the commencement of any trial treatment. This procedure is outlined in the diagram (Figure 2) below.

Figure 2 Trial Entry Process



*Patient and/or patient's parent/guardian

** Investigators are encouraged to arrange biopsy/surgery to confirm diagnosis following obtaining informed consent, to enable pathology sample collection (refer to section 12.3).

6.1 Procedure for Online Trial Entry

Informed consent must be obtained prior to performing Trial Entry. Trial Entry, Treatment Group allocation and randomisation, where appropriate, should be performed by sites using the online remote data entry (eRDE) system provided by CINECA at the protocol specified time point/s. In order to register a patient into the trial, allocate a patient to a treatment group or randomise a patient, an appropriate eligibility checklist must be completed. See Eligibility (Section 4) for details. All of the required information, including stratification factors, must be available at the time of trial entry, treatment group allocation or randomisation.

The date protocol therapy is projected to start should be no later than 15 days from trial entry. Investigators are encouraged to enrol patients immediately following histological diagnosis and begin protocol therapy within 28 days of the initial surgical procedure.

Registration, Treatment Group allocation and randomisation of patients can be achieved by logging on to the PHITT eRDE system.

Go to www.chilternproject.eu

Refer to PHITT eRDE User Manual for more details.

A confirmation of the trial entry, treatment group allocation and randomisation result, as appropriate, should be printed and retained in the ISF and the patient's hospital records.

If allowed by country specific legislation/guidance, a copy of the patient's ICF must be sent to the applicable NCC, if explicit consent has been given for this.

6.2 Randomisation

This section covers the specifications for all collaborative groups. The randomisation programs will allocate treatment via a computerised algorithm, developed by CINECA for the SIOPEL and JCCG groups. COG will develop a separate randomisation algorithm with the specifications below. Permuted block randomisation (block size of 4) will be used to ensure balance of the stratification factor for each randomisation. For randomisation in Groups B, C, D and F patients will be stratified by collaborative group (SIOPEL/COG/JCCG). In addition to the collaborative group, Group F will be stratified by presence/absence of residual/microscopic margins after resection and presence/absence of metastases at diagnosis. Patients will be allocated in a 1:1 ratio for each randomised comparison in groups B, C (treatments C5VD and CDDP-M in COG and JCCG), D and F. Group C will be randomised in a 1:1:1 ratio in SIOPEL to SIOPEL-3HR, C5VD and CDDP-M treatments.

6.3 Emergency Trial Entry

In case of any problems with online registration/randomisation, the appropriate eligibility checklist and registration/randomisation forms should be completed. These details can be phoned through to the UK Coordinating Centre at the CRCTU using the numbers below:

RANDOMISATION

(09:00 to 17:00 GMT / BST, Monday to Friday)

☎ +44 (0)121 415 1061

General enquiries:

☎ +44 (0)121 414 8040

7. CENTRAL PATHOLOGY REVIEW

Rapid Central Pathology Review

Representative HE stained slides of a completely embedded slice of the tumour should be submitted for rapid central review to the International reference pathologists for the groups listed below as soon as possible after surgery; ideally within 3-5 days. The pathology review has to be completed within 14 days after resection to plan the subsequent postoperative treatment.

Group A patients:
Patients with resected very low risk HB (Group A) require rapid review by the International reference pathologists within 14 days of resection.

Other HB Patients:
Rapid review of HB must be carried out by the International reference pathologists in cases of HB ≥8y of age and/or AFP≤100 within 14 days of resection.

HCC Patients:
Rapid review of all suspected cases of HCC must be carried out by the international pathologists within 14 days of resection.

Retrospective Central Pathology Review

In all cases: a retrospective central pathology review will be performed for all patients entering the study where a sample is obtained (please see section 12.3 for details). HE stained slides of the biopsy or HE stained slides of a completely embedded slice of the resected tumour and a representative FFPE block should be sent for central review to the national reference pathologist as soon as possible.

Additional tumour specimens (snap-frozen, FFPE, fresh tumour and non-tumour tissue samples) should be taken at diagnosis and surgery for biological studies and sent to the biorepository as indicated in the laboratory manual. These samples will be included in the Childhood Liver Cancer Network (CLCN) collection. These samples will be used to address biological secondary objectives of the trial and for future investigations. Please refer to Biological and Pathological Studies (Section 12.3) and the current PHITT Laboratory Manual for more details about Pathology and Biology sampling and for contact details of the national reference pathologist.

8. CENTRAL RADIOLOGICAL REVIEW

A retrospective central radiology review will be performed for all patients entering the study by a panel of international radiologists.

Please refer to PHITT Surgery and Radiology Review Guidelines for further information.

9. SURGICAL REVIEW STUDY

For patients with POST-TEXT III and IV HB (See Appendix 4)

POST-TEXT III/IV patients may be entered into an optional surgical review study. A real-time surgical review will be provided following the submission of pre-operative images.

The surgical review study will evaluate surgical treatment of POST-TEXT III and IV HB. Data obtained from this study will be the basis for assessing the optimal surgical approach for these complex

tumours. The aim of this investigation is an evidence-based contribution to the formulation of surgical recommendations concerning extended liver resection or liver transplantation.

The surgical review investigation within the PHITT trial will be coordinated by the Department of Paediatric Surgery and Paediatric Urology at the University Hospital Tuebingen (Germany). This study is sponsored by the ChiLTERN project within the Horizon 2020 grant from the European Commission.

The main objectives of the study are

- to evaluate a surgical planning tool for an impact on decision making processes in POST-TEXT III and IV HB;

- to offer imaging results from this tool to treating centres and operating physicians;

- to assess data from local surgical reviews alongside surgical and oncological outcomes of patients in order to produce guidelines for extended hepatic resection or liver transplantation.

To reach the formulated aims it is necessary to centrally collect cross section imaging data from PRETEXT III and IV HB patients at diagnosis as well as before surgery. The preoperative imaging data will be processed for 3-dimensional reconstruction and virtual simulation for resection. Resulting interactive imaging data will also be supplied to the treating centre and operating physicians to be included in the patient surgical planning process.

Please refer to PHITT Surgery and Radiology Review Guidelines for further information.

The Radiological and Surgical review studies investigators (listed in the Introductory pages) may be contacted to discuss individual cases.

10. TREATMENT DETAILS

10.1 Trial Treatment

The following drugs are regarded as Investigational Medicinal Products (IMPs) for the purposes of this trial:

- Cisplatin
- Carboplatin
- Doxorubicin
- Fluorouracil (5-FU)
- Vincristine
- Irinotecan
- Etoposide
- Sorafenib
- Gemcitabine
- Oxaliplatin

All IMPs are expected to be held as routine hospital stock and should therefore be stored and handled according to local institutional policy. Labels will be produced by each NCC in accordance with Annex 13 guidelines and national legislation.

Treatment should be prepared and administered according to the relevant Summary of Product Characteristics (SmPC) and local practice unless the trial protocol requires otherwise.

In the event of scheduling conflicts due to administrative reasons, dosing and study evaluations may take place on the designated day +/- 3 days.

Please also see the country specific Pharmacy Manual for further details.

Current guidelines for the surgical management of liver tumours should be referred to.

Large scale genomic, transcriptomic, and epigenetic profiling of banked, clinically annotated primary and recurrent tumour specimens obtained from these patients will be performed with the aim of understanding the biology and identifying molecular risk factors linked to chemo-responsiveness. Investigators should comply with the biological sample requirements detailed in section 12.3.

10.2 Treatment Schedule

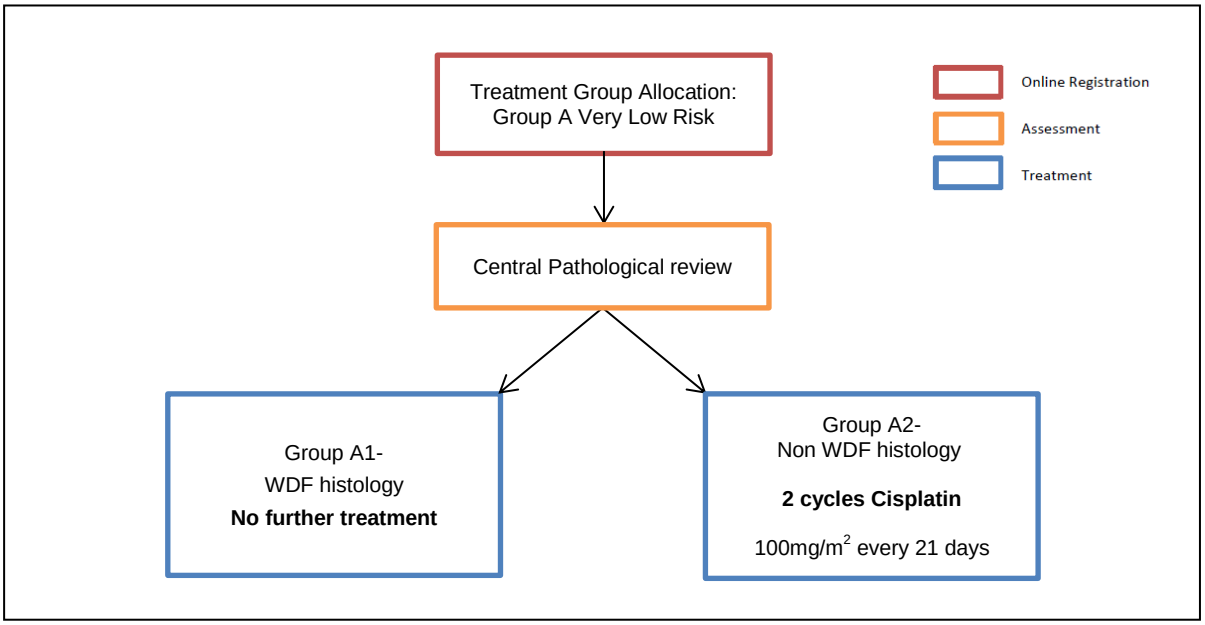
10.2.1 Group A - Very Low Risk HB Patients

Overview

These patients will have a primary resection of their tumour. Selection of the appropriate patients for consideration for up-front surgery requires good quality imaging at diagnosis and careful radiological review anticipating clear resection margins, especially adjacent to vascular structures. In borderline cases we would recommend patients enter Arm B of the protocol and receive preoperative chemotherapy.

Following surgical resection, all patients MUST have rapid central review of their pathology with an expected central review response within 14 days (refer to Section 7) to confirm eligibility for this treatment group. Centrally confirmed WDF patients will receive no adjuvant chemotherapy. All non-WDF patients will receive 2 cycles of cisplatin chemotherapy.

Figure 3 Group A Very Low Risk: Overview



Group A Very Low Risk HB Patients: Agents and Dosing

Patients in this group will be divided into two cohorts depending on the result of the histology subtype:

- Group A1: Patients with WDF histology will receive no further adjuvant chemotherapy (follow up for disease progression and death only)
- Group A2: Patients with Non-WDF histology will receive 2 cycles of standard dose cisplatin

Haematological recovery to ANC >0.75x10^9/L and platelets >75x10^9/L should be ensured prior to Day 1 of each 21 day cycle.

Hydration fluids should be given according to local guidelines.

Table 2 Group A2 Treatment Cycle Schedule

Group A	Day 1	Day 22
Non WDF Histology	Cisplatin 100mg/m^2 as an IV infusion over 6 hours	Day 1 of next cycle

For patients with body weight <10kg, the following doses should be used instead of those quoted above:

- Cisplatin 3.3mg/kg

10.2.2 Group B – Low Risk HB Patients

Overview

These patients will have a tumours deemed unresectable at diagnosis but no other adverse features. The main aim of this group is to compare treatment with 2 or 4 cycles of post-operative chemotherapy. Selection of patients for consideration for early resection requires good quality imaging at diagnosis and careful radiological review anticipating clear resection margins especially adjacent to vascular structures.

PLEASE NOTE THAT RESECTION OF THE PRIMARY TUMOUR MAY OCCUR EARLY (WITHIN 2 CYCLES / 4 WEEKS FROM START OF CHEMOTHERAPY) IN THE PATIENT PATHWAY. SURGICAL PLANNING FOR A POTENTIAL RESECTION SHOULD THEREFORE COMMENCE AT THE TIME OF INITIAL DIAGNOSIS

Patients resected after 2 cycles of chemotherapy will be eligible for a randomisation comparing 2 vs. 4 cycles of post-operative chemotherapy. Patients should normally be randomised within 14 days of surgery.

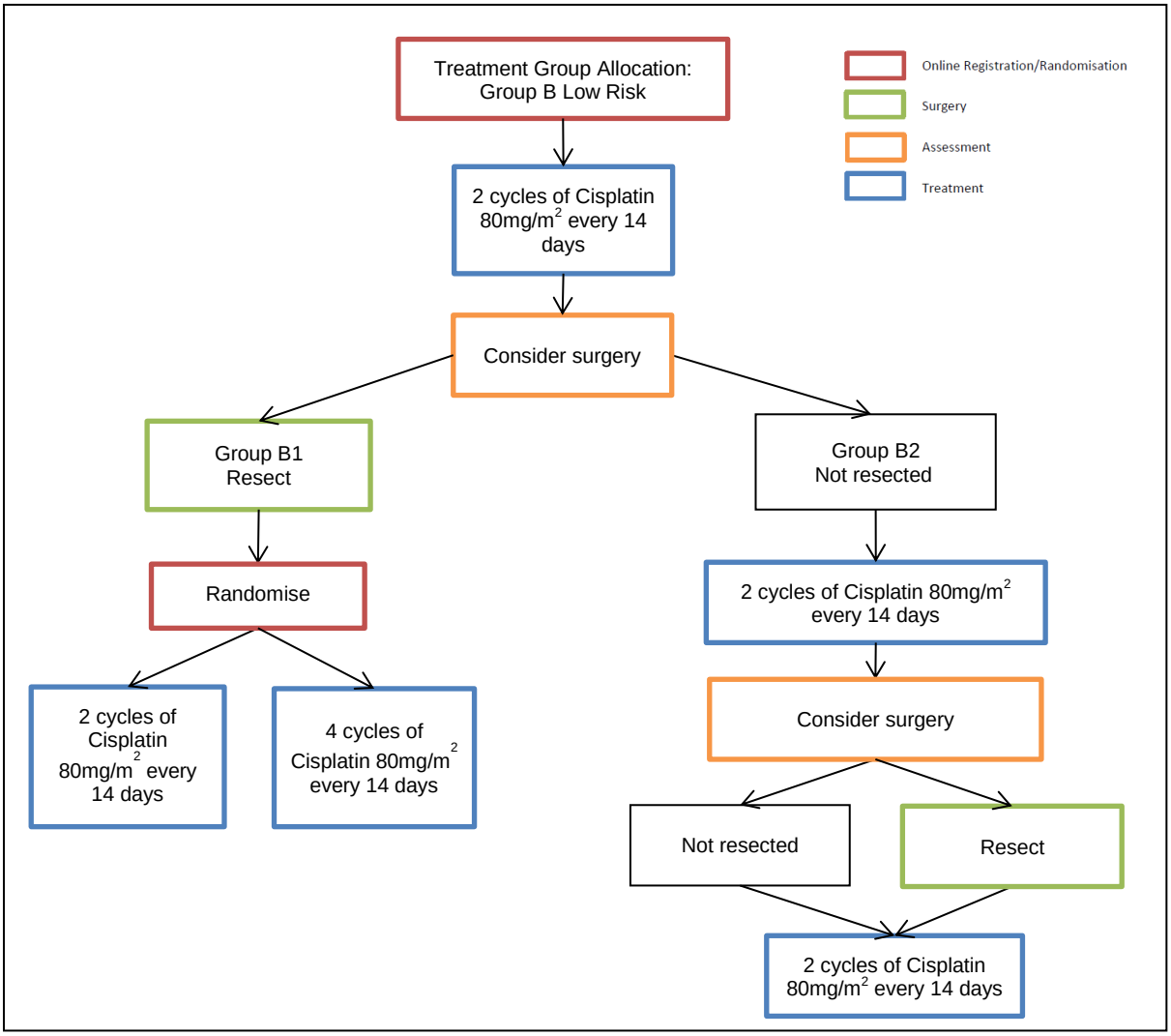
Eligibility Criteria for Group B1 randomisation:

- Completed two cycles of cisplatin
- Primary tumour resected following 2 cycles of cisplatin

Patients not resected after 2 cycles of chemotherapy should continue to receive cisplatin in the absence of disease progression and follow the standard approach of resection after 4 cycles of chemotherapy followed by 2 post-operative cycles.

Patients who are not resected after receiving 4 cycles of cisplatin treatment should continue to cycles 5&6 of cisplatin and should be considered for transplantation and, if not already considered, referred to a transplant centre. Patients deemed unresectable after 6 cycles of cisplatin should be considered for further salvage strategies at the discretion of the treating centre and should be referred for consideration of transplantation. If in doubt please contact one of the chemotherapy subcommittee members.

Figure 4 Group B Low Risk HB Patients: Overview



Group B Low Risk HB Patients: Agents and Dosage

Patients in this group will receive:

- Two cycles of cisplatin.
  Patients will then be assessed for resection:
  - If resection is performed, patients may then be randomised to receive an additional 2 or 4 cycles of cisplatin (4 cycles vs 6 cycles in total).
    OR
  - If resection is not possible, patients will receive a further 2 cycles of cisplatin and ability to perform surgery will be re-assessed. A further 2 cycles of cisplatin should be given unless the patient has discontinued trial treatment and this should be reported on the appropriate Case Report Forms (CRFs).

Haematological recovery to ANC >0.75x10^9/L and platelets >75x10^9/L should be ensured prior to each Day 1 of each 14 day cycle.

Hydration fluids should be given according to local guidelines.

Table 3 Group B1 & B2 Treatment Cycle Schedule

Group B	Day 1	Day 15
Low Risk	Cisplatin 80mg/m^2 as an IV infusion over 6 hours	Day 1 of next cycle

For patients with body weight <10kg, the following doses should be used instead of those quoted above:

- Cisplatin 2.7mg/kg

10.2.3 Group C – Intermediate Risk HB Patients

Overview

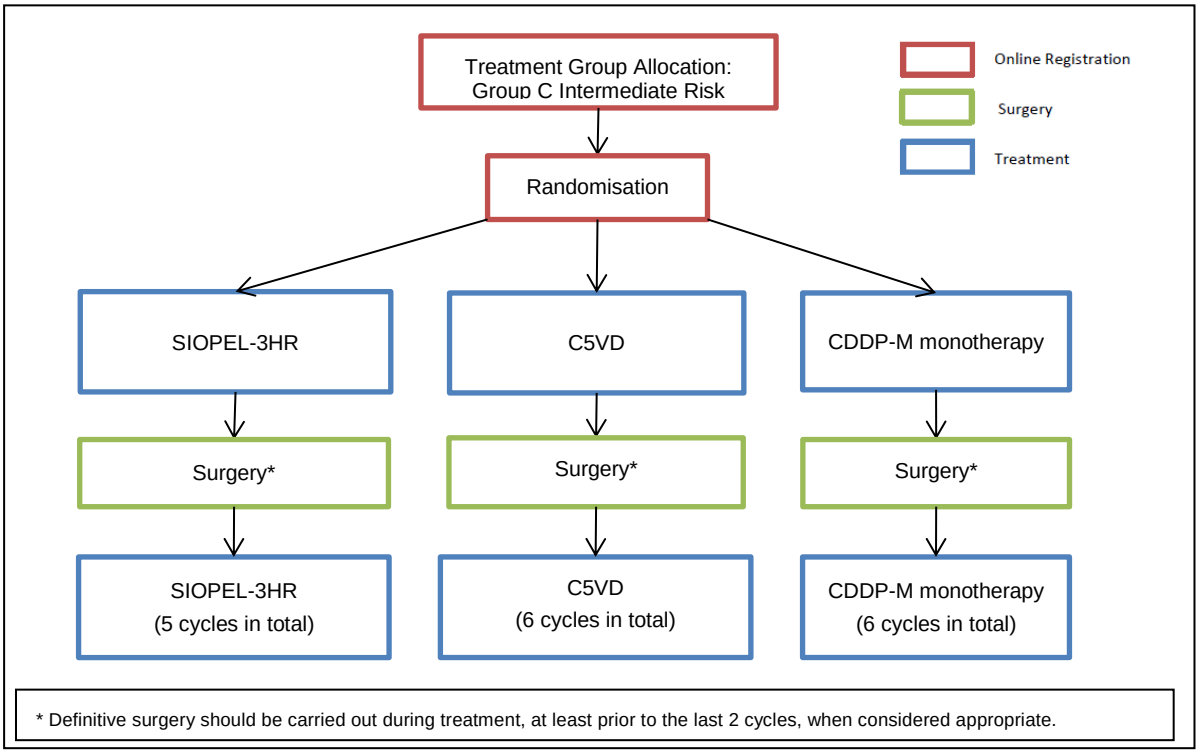
Patients in Group C will have locally advanced tumours including PRETEXT I-III tumours with a positive annotation factor and all PRETEXT IV tumours. Early referral (at the time of diagnosis) to a transplant centre is encouraged so that sufficient time can be allowed for the surgical planning and/or transplant workup to take place. For the purposes of this study, consultation will be defined and may be accomplished in one of two ways:

1) The FIRST TIME the patient is seen face to face by the transplant physician/team in the same institution or another institution.

2) The FIRST TIME radiographic films and referral material are sent to the transplant physician/team at the same or another institution and are formally reviewed by the transplant physician/team. The transplant physician/team will communicate the result of this consultation back to the referring physician.

Patients will be randomised to one of 3 chemotherapy arms SIOPEL-3HR, C5VD or higher dose CDDP-M. The resection of the primary tumour can be considered at ANY point during therapy. The protocol gives an outline of the timing of response evaluations and possible surgical intervention but this is not mandated. However, irrespective of the timing of surgery, patients should complete all planned protocol cycles of chemotherapy (including post transplantation) and definitive surgery should occur at least prior to the last 2 cycles of chemotherapy whenever possible.

Figure 5 Group C Intermediate Risk HB Patients: Overview



Group C Intermediate Risk HB Patients: Agents and Dosage

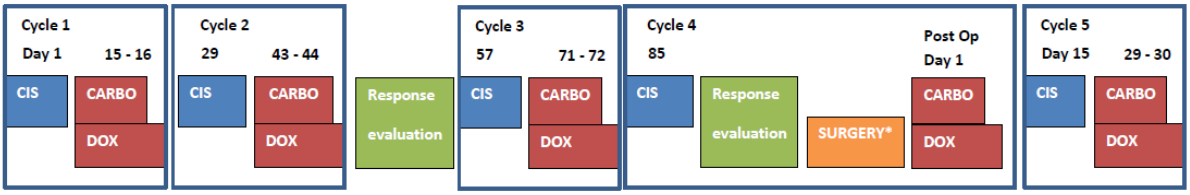
Patients in this group will be randomised to receive one of the following regimens:

- **SIOPEL-3HR**
- **C5VD**
- **CDDP-M**

Definitive surgery should be carried out during treatment, at least prior to the last 2 cycles, when possible.

SIOPEL-3HR

Figure 6 Group C SIOPEL-3HR Treatment Schedule



*Surgery can be considered at ANY time during protocol therapy. Irrespective of the timing patients should receive all protocol courses of chemotherapy.

Blocks of cisplatin chemotherapy are not dependent on haematological recovery.

Haematological recovery to ANC >0.75x10^9/L and platelets >75x10^9/L should be ensured prior to each Carboplatin/Doxorubicin block. Hydration fluids should be given according to local guidelines. Dexrazoxane can be used alongside Doxorubicin as per local guidelines.

Table 4 Group C SIOPEL-3HR Treatment Cycle Schedule

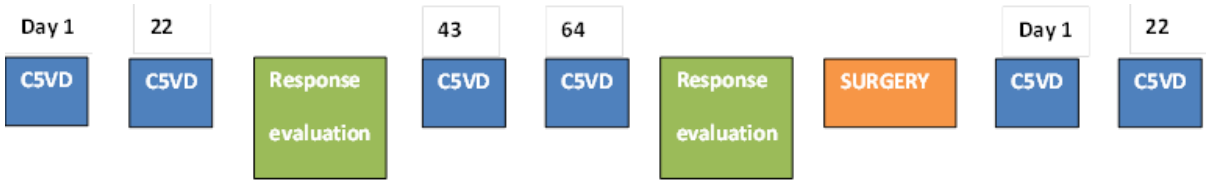
Group C	Day 1	Day 15	Day 16	Day 29
SIOPEL-3HR	Cisplatin 80mg/m^2 as an IV infusion over 6 hours	Carboplatin 500mg/m^2 as an IV infusion over 1 hour		Day 1 of next cycle
		Doxorubicin 30mg/m^2 as an IV infusion over 15 minutes – 6 hours	Doxorubicin 30mg/m^2 as an IV infusion over 15 minutes – 6 hours	

For patients with body weight <10kg, the following doses should be used instead of those quoted above:

- Cisplatin 2.7mg/kg
- Carboplatin 16.7mg/kg
- Doxorubicin 1mg/kg

C5VD

Figure 7 Group C C5VD Treatment Schedule



*Surgery can be considered at ANY time during protocol therapy beyond cycle 2 (Day 22) but should occur at least prior to the last 2 cycles of chemotherapy when possible. Irrespective of the timing of surgery patients should receive all protocol courses of chemotherapy.

Cycles of C5VD should be given at 21 day intervals with haematological recovery to ANC >0.75x10^9/L and platelets >75x10^9/L.

Hydration fluids should be given according to local guidelines. Dexrazoxane can be used alongside Doxorubicin as per local guidelines.

Table 5 Group C C5VD Treatment Schedule

Group C	Day 1	Day 2	Day 8	Day 15	Day 22
C5VD	Cisplatin 100mg/m^2 as an IV infusion over 6 hours				Day 1 of next cycle
	Doxorubicin 30mg/m^2 as an IV infusion over 15 minutes – 6 hours	Doxorubicin 30mg/m^2 as an IV infusion over 15 minutes – 6 hours			
	Vincristine 1.5mg/m^2 as an IV bolus Max dose 2mg		Vincristine 1.5mg/m^2 as an IV bolus Max dose 2mg	Vincristine 1.5mg/m^2 as an IV bolus Max dose 2mg	
	5-FU 600mg/m^2 as an IV bolus				

For patients with body weight <10kg, the following doses should be used instead of those quoted above:

- Cisplatin 3.3mg/kg
- Doxorubicin 1mg/kg
- 5-Fluorouracil (5-FU) 20mg/kg
- Vincristine 0.05mg/kg

CDDP-M Monotherapy

Figure 8 Group C CDDP-M Treatment Schedule

*Surgery can be considered at ANY time during protocol therapy beyond cycle 2 (Day 15), but should occur at least prior to the last 2 cycles of chemotherapy when possible. Irrespective of the timing of surgery patients should receive all protocol courses of chemotherapy

Cycles of CDDP-M should be given at 14 day intervals with ANC >0.5x10^9/L and platelets >50x10^9/L.

Hydration fluids should be given according to local guidelines.

Table 6 Group C CDDP-M Treatment Cycle Schedule

Group C	Day 1	Day 15
CDDP-M monotherapy	Cisplatin 100mg/m^2 as an IV infusion over 6 hours	Day 1 of next cycle

For patients with body weight <10kg, the following doses should be used instead of those quoted above:

- Cisplatin 3.3mg/kg

10.2.4 Group D – High Risk HB Patients

Overview

These patients may have pulmonary metastatic disease. Often patients will also have challenging primary tumours and a significant number may be considered suitable for transplantation (assuming a lung CR can be achieved). We would encourage early referral (at the time of diagnosis) to a transplant centre so that sufficient time can be allowed for the surgical planning and/or transplant workup to take place as well as to avoid extra cycles of chemotherapy that may accompany delayed transplant consultation.

Patients will receive initial chemotherapy according to the cisplatin-intensive SIOPEL-4 regimen. Following 3 blocks of chemotherapy patients will be stratified into 2 risk groups. In Group D1, patients will either have had a chemotherapy-induced lung CR, or will be rendered a lung CR by surgical metastectomy (recommended before resection of the primary tumour). These patients will have chemotherapy consolidation with carboplatin/doxorubicin. The timing of the resection of the primary tumour (including transplant) can be planned at any time after completion of the A blocks of induction therapy. Patients should receive all planned protocol doses of therapy. If surgical resection of the primary tumour is delayed until the end of therapy, no further post-operative chemotherapy should be given.

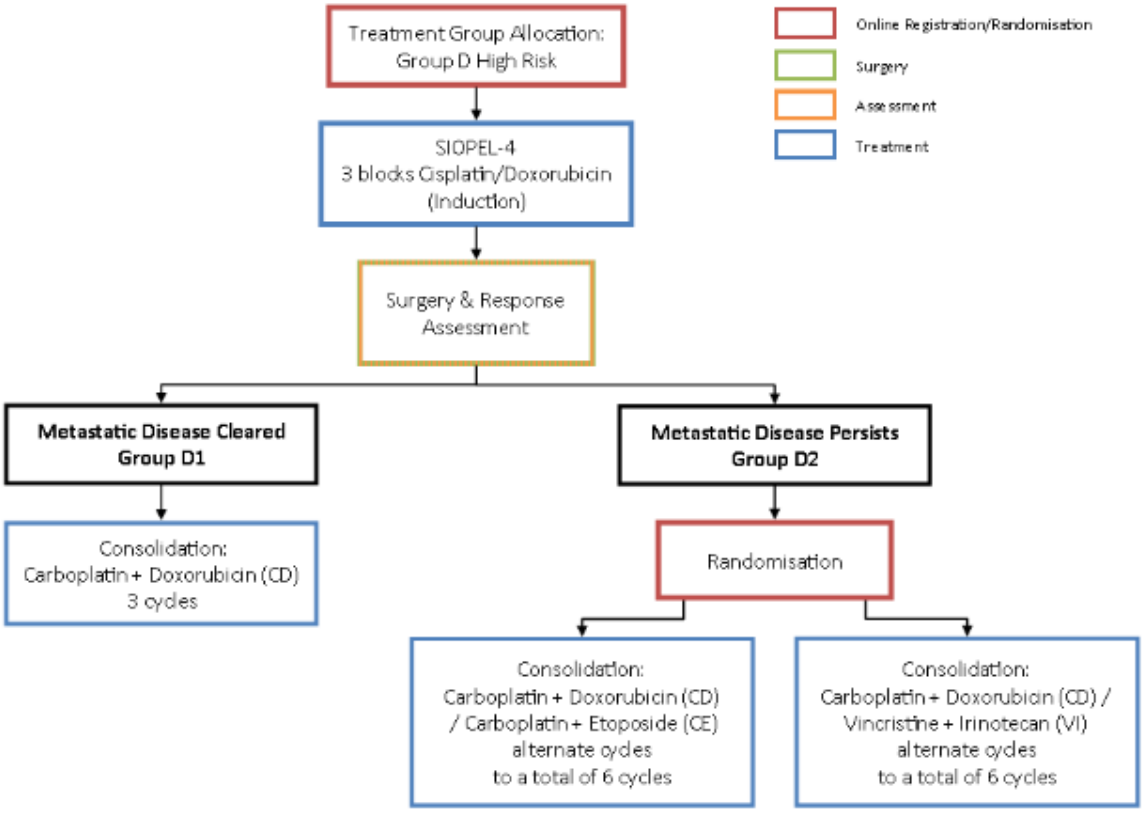
Patients who have not achieved a lung CR (either with chemotherapy and/or surgery) at the end of block A3 will be randomised (Group D2) to intensified consolidation therapy of carboplatin/doxorubicin with either carboplatin/etoposide or vincristine/irinotecan.

Eligibility Criteria for Group D2 randomisation:

- Completed three blocks of induction treatment;
- Metastases not cleared at the end of induction.

Surgical resection of the primary tumour can be considered at any time after the initial A blocks of induction therapy. Lung metastectomy should be considered in all patients if continuing to respond to consolidation therapy. Patients with delayed lung CR should still be considered for transplant, if applicable. Patients with residual disease (primary and/or metastatic) at the end of planned therapy should be discussed with one of the study co-ordinators.

Figure 9 Group D High Risk Overview

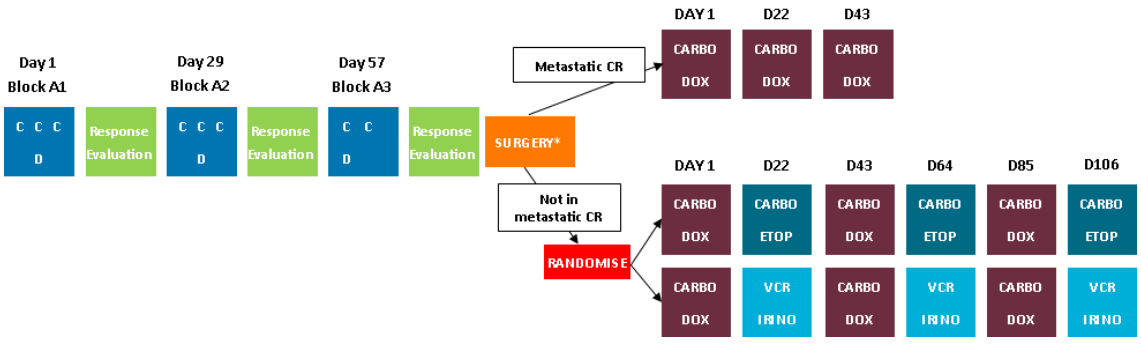


Group D High Risk Patients: Agents and Dosage

All patients in this group will receive 3 blocks of SIOPEL-4 Induction, followed by consolidation therapy, determined by their response assessment.

In SIOPEL-4 Induction, cisplatin is administered 3x in each block. Doxorubicin is administered over 2 days in each block.

Figure 10 Group D Treatment Schedule



*Surgery can include liver transplantation and lung metastectomy where applicable to achieve CR.

In the absence of life-threatening or grade 4 toxicities treatment in blocks A1, A2 and A3 should remain on schedule irrespective of blood counts.

Induction therapy blocks A2 and A3 should commence only with haematological recovery to ANC of >1.0x10^9/L and platelets >100x10^9/L. Postponing up to 2 weeks to allow count recovery is permissible. G-CSF should not be given initially and should only be administered prophylactically if there is a 1 week delay in administration of chemotherapy or if the patient requires hospitalisation for fever and neutropenia or for sepsis. Refer to Dose Modification Section 11.3.

Table 7 Group D SIOPEL-4 Induction Treatment Schedule

Group D SIOPEL-4 Induction Block A1	Day 1	Day 8	Day 9	Day 15
	Cisplatin 70mg/m^2 as an IV infusion over 6 hours	Cisplatin 70mg/m^2 as an IV infusion over 6 hours		Cisplatin 70mg/m^2 as an IV infusion over 6 hours
		Doxorubicin 30mg/m^2 as an IV infusion over 15 minutes – 6 hours	Doxorubicin 30mg/m^2 as an IV infusion over 15 minutes – 6 hours	

Group D SIOPEL-4 Induction Block A2	Day 29	Day 36	Day 37	Day 43
	Cisplatin 70mg/m^2 as an IV infusion over 6 hours	Cisplatin 70mg/m^2 as an IV infusion over 6 hours		Cisplatin 70mg/m^2 as an IV infusion over 6 hours
		Doxorubicin 30mg/m^2 as an IV infusion over 15 minutes – 6 hours	Doxorubicin 30mg/m^2 as an IV infusion over 15 minutes – 6 hours	

Group D SIOPEL-4 Induction Block A3	Day 57	Day 58	Day 64	Day 65
	Cisplatin 70mg/m^2 as an IV infusion over 6 hours		Cisplatin 70mg/m^2 as an IV infusion over 6 hours	
	Doxorubicin 30mg/m^2 as an IV infusion over 15 minutes – 6 hours	Doxorubicin 30mg/m^2 as an IV infusion over 15 minutes – 6 hours		

For patients with body weight <10kg, the following doses should be used instead of those quoted above:

- Cisplatin 70mg/m^2: 2.3mg/kg
- Doxorubicin 1mg/kg.

Following SIOPEL-4 Induction, patients will be assessed for response (metastatic clearance by chemotherapy and/or surgery).

- If metastases are cleared by chemotherapy, patients will receive Group D1 consolidation therapy.
- If metastases are *not* cleared by chemotherapy (Group D2), patients may be randomised to receive either:

  Carboplatin + Doxorubicin alternating with Carboplatin + Etoposide (CD/CE)

  OR

  Carboplatin + Doxorubicin alternating with Vincristine + Irinotecan (CD/VI)

Group D1 Carboplatin + Doxorubicin (CD)

Haematological recovery to ANC >0.75x10^9/L and platelets >75x10^9/L should be ensured prior to each Day 1 of each 21 day cycle.

Table 8 Group D1 (CD) Treatment Schedule

Group D1 Mets cleared (CD)	Day 1	Day 2	Day 22
	Carboplatin 500mg/m^2 as an IV infusion over 1 hour		Day 1 of next cycle
	Doxorubicin 20mg/m^2 as an IV infusion over 15 minutes – 6 hours	Doxorubicin 20mg/m^2 as an IV infusion over 15 minutes – 6 hours	

For patients with body weight <10kg the following doses should be used instead of those quoted above:

- Carboplatin 16.7mg/kg
- Doxorubicin 0.67mg/kg

Group D2:

Carboplatin + Doxorubicin / Carboplatin + Etoposide

Haematological recovery to ANC >0.75x10^9/L and platelets >75x10^9/L should be ensured prior to each Day 1 of each 21 day cycle.

Table 9 Group D2 (CD/CE) Treatment Schedule

Group D2 CD / CE	Cycles 1, 3 & 5		
	Day 1	Day 2	Day 22
	Carboplatin 500mg/m^2 as an IV infusion over 1 hour		Day 1 of next cycle
	Doxorubicin 20mg/m^{2}as an IV infusion over 15 minutes – 6 hours	Doxorubicin 20mg/m^{2}as an IV infusion over 15 minutes – 6 hours	
	Cycles 2, 4 & 6		
	Day 1	Day 2	Day 22
	Carboplatin 400mg/m^2 as an IV infusion over 1 hour Etoposide 200mg/m^2 as an IV infusion over 4 hours	Carboplatin 400mg/m^2 as an IV infusion over 1 hour Etoposide 200mg/m^2 as an IV infusion over 4 hours	Day 1 of next cycle

For patients with body weight <10kg the following doses should be used instead of those quoted above:

- Carboplatin 16.7mg/kg in cycles 1, 3 and 5
- Carboplatin 13.3mg/kg in cycles 2, 4 and 6
- Doxorubicin 0.67mg/kg
- Etoposide 6.7mg/kg

Carboplatin + Doxorubicin / Vincristine + Irinotecan

Cycles of CD and VI should be given at 21 day intervals with haematological recovery to ANC >0.75x10^9/L and platelets >75x10^9/L.

Table 10 Group D2 (CD/VI) Treatment Schedule

<table>
<tr><td rowspan="9">Group D2
CD / VI</td><td colspan="4">Cycles 1, 3 & 5</td></tr>
<tr><td>Day 1</td><td colspan="2">Day 2</td><td>Day 22</td></tr>
<tr><td>Carboplatin 500mg/m^2 as an IV infusion over 1 hour</td><td colspan="2"></td><td rowspan="2">Day 1 of next Cycle</td></tr>
<tr><td>Doxorubicin 20mg/m^2 as an IV infusion over 15 minutes – 6 hours</td><td colspan="2">Doxorubicin 20mg/m^2 as an IV infusion over 15 minutes – 6 hours</td></tr>
<tr><td colspan="4">Cycles 2, 4 & 6</td></tr>
<tr><td>Day 1</td><td>Days 2-5</td><td>Day 8</td><td>Day 22</td></tr>
<tr><td>Vincristine 1.5mg/m^2 as an IV bolus Max dose 2mg</td><td></td><td>Vincristine 1.5mg/m^2 as an IV bolus Max dose 2mg</td><td rowspan="2">Day 1 of next Cycle</td></tr>
<tr><td>Irinotecan 50mg/m^2 as an IV infusion over 60-90 minutes</td><td>Irinotecan 50mg/m^2 as an IV infusion over 60-90 minutes</td><td></td></tr>
</table>

For patients with body weight <10kg the following doses should be used instead of those quoted above:

- Carboplatin 16.7mg/kg
- Doxorubicin 0.67mg/kg
- Vincristine 0.05mg/kg
- Irinotecan 1.67mg/kg.

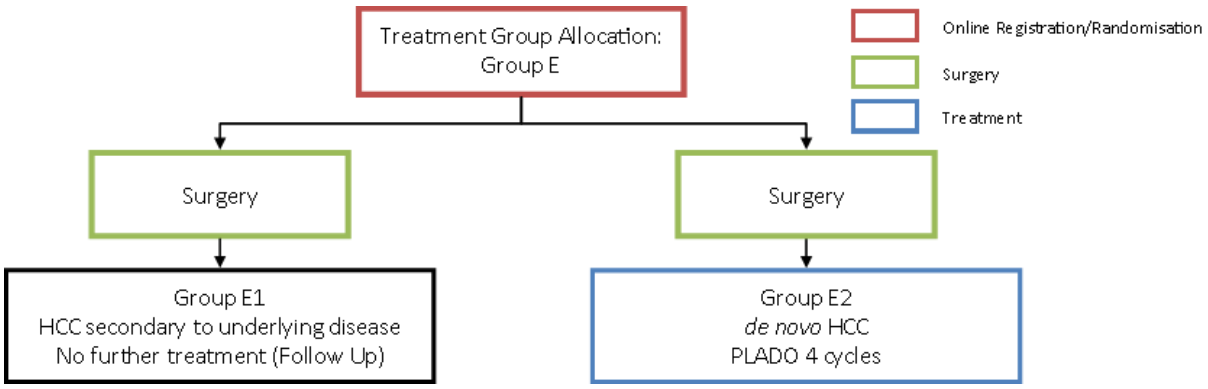
10.2.5 Group E – Resected HCC Patients

Overview

These patients have primary completely resected HCC with microscopically uninvolved surgical margins. Patients fall into two groups:

- Group E1: Patients who have an underlying predisposition to HCC through genetic, viral or metabolic conditions which often result in underlying cirrhosis. Tumours may be picked up on routine screening or as a coincidental finding in the explanted liver following transplantation. Tumours are often small and localized. Given the poor tolerability of chemotherapy either due to underlying liver disease or transplantation, the recommendation is for these patients to receive no adjuvant chemotherapy.
- Group E2: Patients with *de novo* HCC, which includes fibrolamellar. Patients will receive 4 cycles of PLADO chemotherapy.

Figure 11 Group E Resected HCC Patients: Overview



Group E – Resected HCC Patients: Agents and Dosage

Patients in this group will be divided into two groups depending on the tumour type defined following resection:

- Group E1: Patients with HCC secondary to underlying liver disease will receive no further treatment (Follow up for disease progression and death only);
- Group E2: Patients with *de novo*, including fibrolamellar, HCC will receive PLADO – 4 Cycles.

Haematological recovery to ANC >0.75x10^9/L and platelets >75x10^9/L should be ensured prior to each Day 1 of each 21 day cycle.

Table 11 Group E2 HCC Treatment Cycle Schedule

Group E2	Day 1	Day 2	Day 22
PLADO	Cisplatin 80mg/m^2 as an IV infusion over 6 hours		Day 1 of next cycle
	Doxorubicin 30mg/m^2 as an IV infusion over 15 minutes – 6 hours	Doxorubicin 30mg/m^2 as an IV infusion over 15 minutes – 6 hours	

For patients with body weight <10kg, the following doses should be used instead of those quoted above:

- Cisplatin 2.7mg/kg
- Doxorubicin 1mg/kg

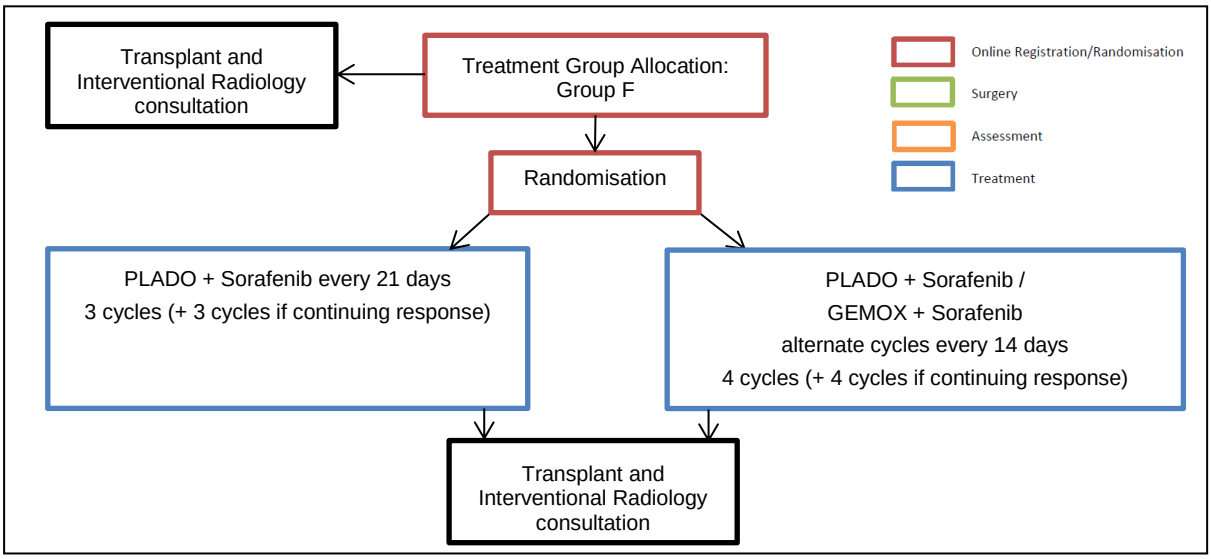
10.2.6 Group F – Unresected/metastatic HCC Patients

Overview

These patients have unresected and/or metastatic HCC. Patients with microscopic/residual disease after resection will be included in this group. Tumours in this population of patients are often large and remain a surgical challenge even following a response to chemotherapy. Since complete surgical resection is a prerequisite for cure, the outlook for these patients has historically been poor. The strategy in this arm of the study is to evaluate chemotherapy response in order to drive more tumours into being resected either through partial hepatectomy or transplantation. Patients will be randomised to preoperative chemotherapy consisting of either PLADO+sorafenib or PLADO/GEMOX+sorafenib.

Given the surgical challenges posed by these tumours and the need to consider transplantation as an option, early referral (at the time of diagnosis) to a transplant centre is encouraged so that sufficient time can be allowed for the surgical planning and/or transplant workup to take place.

Figure 12 Group F Unresected/metastatic HCC Patients: Overview



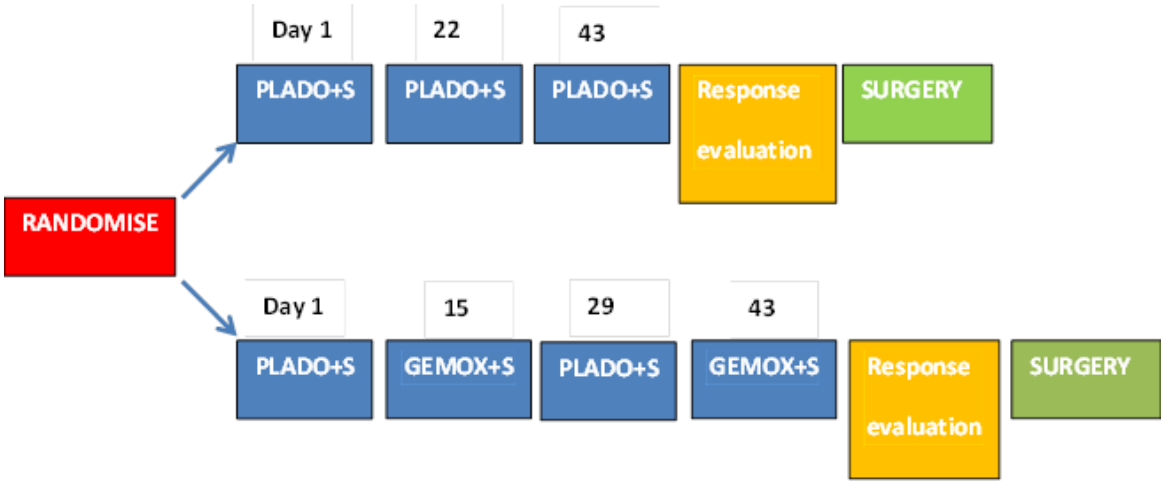
Group F – Unresected/metastatic HCC Patients: Agents and Dosage

Patients in this group will be randomised to receive one of the following regimens:

- PLADO + Sorafenib
- PLADO + Sorafenib / GEMOX + Sorafenib

PLADO + Sorafenib

Figure 13 Group F PLADO+S Treatment Schedule



*Surgical resection may include transplantation and/or referral for local therapy e.g. TACE. Patients achieving a good response to chemotherapy may continue to receive further cycles per the schematic above.

Patients achieving a continuing response after Day 43 chemotherapy may continue to receive further cycles according to their randomised allocation up to a further 3 cycles of PLADO+S and 4 cycles of PLADO/GEMOX+S.

Haematological recovery to ANC >0.75x10^9/L and platelets >75x10^9/L should be ensured prior to each Day 1 of each 21 day cycle.

Table 12 Group F PLADO+S Treatment Cycle Schedule

Group F	Day 1	Day 2	Days 3-21	Day 22
PLADO + Sorafenib	Cisplatin 80mg/m^2 as an IV infusion over 6 hours			Day 1 of next cycle
	Doxorubicin 30mg/m^2 as an IV infusion over 15 minutes – 6 hours	Doxorubicin 30mg/m^2 as an IV infusion IV over 15 minutes – 6 hours		
			Sorafenib 150mg/m^2 twice daily orally*	

For patients with body weight <10kg the following doses should be used instead of those quoted above:

- Cisplatin 2.7mg/kg
- Doxorubicin 1mg/kg

*Refer to Table 14 for details of Sorafenib dosing

PLADO + Sorafenib / GEMOX + Sorafenib

Growth factors (e.g. G-CSF) may be given following Gemcitabine, according to local guidelines.

Cycles of PLADO/GEMOX+ Sorafenib should be administered every 14 days with haematological recovery to ANC >0.5x10^9/L and platelets >50x10^9/L

Table 13 Group F PLADO+S/GEMOX Treatment Schedule

<table>
<tr><td rowspan="8">Group F

PLADO + Sorafenib / GEMOX + Sorafenib</td><td colspan="4">Cycles 1 & 3 (PLADO + Sorafenib)</td></tr>
<tr><td>Day 1</td><td>Day 2</td><td>Days 3-14</td><td>Day 15</td></tr>
<tr><td>Cisplatin 80mg/m^2 as an IV infusion for 6 hours</td><td></td><td></td><td rowspan="3">Day 1 of next cycle</td></tr>
<tr><td>Doxorubicin 30mg/m^2 as an IV infusion over 15 minutes – 6 hours</td><td>Doxorubicin 30mg/m^2 as an IV infusion IV over 15 minutes – 6 hours</td><td></td></tr>
<tr><td></td><td></td><td>Sorafenib 150mg/m^2 twice daily*</td></tr>
<tr><td colspan="4">Cycles 2 & 4 (GEMOX + Sorafenib)</td></tr>
<tr><td>Day 1</td><td colspan="2">Day 2-14</td><td>Day 15</td></tr>
<tr><td>Gemcitabine 1000mg/m^2 as an IV infusion over 90 minutes</td><td colspan="2"></td><td rowspan="3">Day 1 of next cycle</td></tr>
<tr><td>Oxaliplatin 100mg/m^2 as an IV infusion over 2 hours</td><td colspan="2"></td></tr>
<tr><td></td><td colspan="2">Sorafenib 150mg/m^2 twice daily*</td></tr>
</table>

For patients with body weight <10kg, the following doses should be used instead of those quoted above:

- Cisplatin 2.7mg/kg
- Doxorubicin 1mg/kg
- Gemcitabine 33.3mg/kg
- Oxaliplatin 3.3mg/kg

*Refer to Table 14 for details of Sorafenib dosing.

Table 14 Dosing Table for Sorafenib

Sorafenib dosing.

Since sorafenib is only available as a 200mg tablet accurate dosing on a daily basis is not possible. The table below takes a total weekly dose for patients, in bands according to their body surface area (BSA), and distribute this as evenly as possible throughout a 7 day period.

Patients who are unable to take tablets.

Whilst it is anticipated that most patients recruited to Group F will be teenagers who will be able to swallow the tablets, it is possible that younger patients will be recruited, and also those patients who, for whatever reason, may have difficulty in swallowing tablets.

Whenever possible, sorafenib tablets should be swallowed whole with a glass of water. It is suggested that patients <12 years old should take the tablets with 60 - 120mL of water and older patients with 120 - 240mL.

If this is not possible the required number of tablets for a dose should be placed in a glass with approximately 60mL of water. Allow to stand for 5 minutes, and then stir until the tablets have completely disintegrated and have formed an uniform suspension. The patient should take the prepared suspension within one hour of preparation and stir again immediately before administration. The glass should be rinsed several times with water to ensure that all of the dose is administered. Any remaining brown film coating from the tablet will not affect the dose of sorafenib administered.

If the patient has a naso-gastric tube the method above may be used provided that every precaution is taken to ensure that the suspension does not block the tube and that the tube is flushed well to ensure that the whole dose is administered.

Administration with food.

Whenever possible sorafenib should be administered on an empty stomach, at least one hour before, or two hours, after food. If this is not possible the tablets, or a prepared suspension as above, should be taken with a meal containing a low or moderate amount of fat. If the patient has had a high-fat meal, the sorafenib should be taken at least one hour before or two hours after the meal, as above.

Grapefruit or its juice should not be eaten whilst on treatment with sorafenib.

Vomited doses.

If tablets are taken: If the tablet(s) are visible in the vomit, or vomiting occurs within one hour of dosing, the dose may be repeated.

If a suspension is taken: A dose should only be repeated if vomiting occurs within one hour of dosing.

For information only: peak plasma levels occur 3 hours after oral administration. Sorafenib is virtually insoluble in water and forms a suspension in water (https://pubchem.ncbi.nlm.nih.gov/compound/Sorafenib#section=Color). Because sorafenib is a very lipophilic compound, a suspension prepared immediately prior to administration would be expected to have similar pharmacokinetic properties compared to a tablet swallowed whole.
Given the wide inter-patient variability in drug exposure seen in patients treated with sorafenib, the rounding/banding is expected to result in similar drug exposure compared to what would be seen if it were possible to accurately administer the calculated dose.

Sorafenib Dosing Table

BSA (m^2)	Daily dose (PO)	Weekly dose	**Difference from calculated (range)**	**Difference from calculated (mean)**
0.6-0.78	200 mg once daily	1,400 mg	-15% - +11%	-2.8%
0.79 – 1	200 mg BID Mon/Thur and 200 mg once daily Tues/Wed/Fri/Sat/Sun	1,800 mg	-14% - +8%	-3.7%
1.01-1.34	200 mg once daily Mon/Thur and 200 mg BID Tues/Wed/Fri/Sat/Sun	2,400 mg	-15% - +13%	-2.0%
1.35-1.79	200 mg AM & 400 mg PM on Mon/Thur and 200 mg BID Tues/Wed/Fri/Sat/Sun	3,200 mg	-15% - +13%	-2.3%
1.8-2.34	200 mg AM and 400 mg PM	4,200 mg	-15% - +11%	-2.8%
>2.35	400 mg BID	5,600 mg	+13%	+13%

11. DOSE MODIFICATIONS

11.1 Audiological Toxicity

Cisplatin

Cisplatin should not be dose modified based on audiologic reports or loss of hearing. Cisplatin is considered an essential element of successful hepatoblastoma therapy. In France, in case of audiological toxicity of grade 2 or higher or repeated doses of cisplatin higher than 400mg/m^2, the decision to continue cisplatin must be discussed with the family and must be reassessed by the investigational team.

11.2 Cardiac Toxicity

Sorafenib

Sorafenib associated hypertension is usually mild to moderate, and amenable to management with standard antihypertensive therapy. Blood pressure should be monitored regularly and clinicians should have a low-threshold for initiating therapy. In cases of severe or persistent hypertension, or hypertensive crisis despite institution of antihypertensive therapy, permanent discontinuation of sorafenib should be considered.

In case of QT/QTc interval prolongation (> 500ms), sorafenib therapy must be discontinued. Patients should undergo close and continuous ECG monitoring.

Doxorubicin

If left ventricular ejection fraction is <47% and/or the fractional shortening is <27% and the patient is asymptomatic, repeat the test in 7 days. If the ejection fraction or fractional shortening remains abnormal, omit further therapy with doxorubicin. If at any time the patient develops Grade 3 congestive heart failure or any Grade 4 cardiac toxicity not related to underlying infection or metabolic abnormality, omit further therapy with doxorubicin. The use of cardioprotectant drugs such as dexrazoxane is allowed at the discretion of the investigator and should be administered in line with their institutional guidelines. Note, dexrazoxane is contraindicated in children aged between 0 and 18 years old that must receive an anthracycline-based chemotherapy with scheduled cumulative doses of doxorubicin < 300mg/m^2 or with equivalent cumulative doses of other anthracyclines.

11.3 Haematological Toxicity

All patients will be transfused as needed at the Investigator's discretion to maintain an adequate haemoglobin level and platelet count. There are no restrictions on the use myeloid growth factors. When used, growth factors should be initiated at least 24 hours post chemotherapy. G-CSF is permitted according to institutional guidelines.

If the patient is due to begin a cycle of chemotherapy and the ANC and platelet count (at least 48 hours post transfusion) do not meet the criteria for beginning the next treatment cycle, delay chemotherapy until recovery occurs. If the ANC and platelet count recover within 7 days, proceed to the next cycle. If the delay is greater than 7 days, myeloid growth factors should be considered and are recommended for the subsequent cycle. If myelosuppression leads to a delay of greater than 14 days, despite the use of myeloid growth factors, chemotherapy should be dose reduced by 25%.

11.4 Gastrointestinal Toxicity

Irinotecan

If Grade 3 or 4 irinotecan-associated diarrhoea is experienced by a patient despite prophylaxis and maximal use of anti-diarrhoeal medications (e.g. loperamide) and cefixime/cefpodoxime, the dose of irinotecan should be reduced by 25% to 40mg/m^2 for subsequent cycles. If Grade 3 or 4 diarrhoea occurs following a 25% dose reduction in irinotecan as described above, no further irinotecan should be administered.

11.5 Nephrotoxicity / Renal Function Monitoring

Tubular toxicity

Renal loss of magnesium and consequent hypomagnesemia is expected on this trial. Dose modification is not required in the event of tubular toxicity and hypomagnesaemia is not a reason to dose modify or discontinue treatment. Oral magnesium supplementation may be prescribed as per local guidelines (see Supportive Treatment Section 14).

Glomerular Filtration Rate (GFR)

Measurement of GFR should be undertaken at the recommended time-points as indicated in the assessment tables (Section 12). In addition to affecting tubular function, cisplatin and carboplatin can affect renal glomerular filtration. If the serum creatinine increases to greater than the maximum serum creatinine for age (see table below), check a GFR or creatinine clearance. No dose reductions will be made for a decrease in the baseline GFR or creatinine clearance as long as the value remains >60mL/min/1.73m². Omit cisplatin and carboplatin therapy from a cycle of therapy if GFR or creatinine clearance is <60mL/min/1.73m². If cisplatin or carboplatin is held for a cycle of therapy, repeat the GFR or creatinine clearance prior to next cycle. Resume therapy at full dose if GFR or creatinine clearance >60mL/min/1.73m². If GFR or creatinine clearance do not recover, discontinue treatment.

GFR tests should not be done when a child is receiving IV hydration as the result will not be reliable. Repeat assessments should use the same technique, as per local practices.

Schwartz's Formula (1-18 years) (Schwartz, 1987)

According to Schwartz's formula, creatinine clearance (Ccrea) can be calculated from single serum samples:

$$C_{crea} = \frac{F \times Height\ [cm]}{Crea_{\ serum}[mg/dl]}\ [ml/min/1.73m^2]$$

where **F** is proportional to body muscle mass, hence depending on age and gender:

Infants (<1 year of age)	**F** = 0.45
Males, 1-16 years	**F** = 0.55
Females, 1-21 years	**F** = 0.55
Males, 16-21 years	**F** = 0.70

Normal values [ml/min/1.73m²]:

- Normal 120
- Normal range 90-120

Cockcroft- Gault Formula (>18 years) [43]

Females

$$\frac{1.05\,(140 - age\ (yrs))\,wt(kg)}{Crea_{\ serum}[\ \mu mol/L]}$$

Or

$$\frac{0.85\ \ (140 - age\ (yrs))\,wt(kg)}{72 \times Crea_{\ serum}[mg/dl]}$$

Males

$$\frac{1.25\,(140 - age\ (yrs))\,wt(kg)}{Crea_{\ serum}[\mu mol/L]}$$

Or

$$\frac{(140 - age\ (yrs))\,wt(kg)}{72 \times Crea_{\ serum}[mg/dl]}$$

PLEASE NOTE: These formulas have not been confirmed in patients receiving repeated cycles of

intensive chemotherapy OR in adolescents. Renal function may be overestimated by these methods.

11.6 Neurotoxicity

Vincristine

If severe peripheral neuropathy (vocal cord paralysis, inability to walk or perform usual motor functions) or ileus develops from vincristine, vincristine therapy should be stopped or withheld until the ileus resolves or the peripheral neuropathy improves. Restart vincristine at 50% dose [0.75 mg/m^2 (0.025 mg/kg)) and escalate to 75% of full dose (1.125 mg/m^2 (0.0375 mg/kg), if tolerated, with the next cycle. If tolerated then resume full dose with the next cycle. If neuropathy recurs on escalating dose, return to previously tolerated dose once neuropathy has improved.

Oxaliplatin

If Posterior Reversible Encephalopathy Syndrome (PRES) is suspected, discontinue oxaliplatin treatment.

11.7 Hepatotoxicity

In the setting of liver dysfunction and hyperbilirubinemia, dosing of all medications (study drugs and supportive care agents) should be carefully reviewed and institutional guidelines followed. The following recommendations should be considered:

Vincristine

If direct bilirubin is Grade 3 or 4 toxicity according to CTCAE prior to a cycle of chemotherapy, omit vincristine. If direct bilirubin is Grade 2 prior to chemotherapy, reduce vincristine dose by 50%. If vincristine is dose reduced because of direct hyperbilirubinemia, subsequent doses should be based on above criteria, i.e. if direct bilirubin returns to <Grade 2 toxicity, the full dose of vincristine is to be given.

Doxorubicin

If direct bilirubin is Grade 3 or 4 toxicity according to CTCAE prior to chemotherapy, omit doxorubicin. If direct bilirubin is Grade 2 prior to chemotherapy, reduce doxorubicin dose by 50%. If doxorubicin is dose reduced because of direct hyperbilirubinemia, subsequent doses should be based on above criteria, i.e. if direct bilirubin returns to <Grade 2 toxicity, the full dose of doxorubicin is to be given.

Irinotecan

In patients with hyperbilirubinemia and prothrombin time greater than 50%, the clearance of irinotecan is decreased and therefore the risk of haematotoxicity is increased. Patients with bilirubin beyond to 3 times the ULN should not be treated with irinotecan.

11.8 Mucositis

The dose of doxorubicin should be modified based on the following considerations:

- If the patient develops Grade 3 or 4 mucositis that resolves to <Grade 2 by Day 1 of the next cycle, no dose adjustments will be made in chemotherapy.
- If the patient develops Grade 3 or 4 mucositis that is NOT attributable to infectious etiology AND recovery to < Grade 2 does not occur by Day 1 of any cycle, reduce the dose of doxorubicin in the next cycle to 75% (22.5mg/m^2 (0.75 mg/kg)). If subsequent chemotherapy is tolerated without the recurrence of Grade 3 or 4 toxicity, then resume full dose in the next cycle.
- If the patient has previously received the 75% dose and again has Grade 3 or 4 mucositis that is NOT attributable to infectious aetiology AND recovery to < Grade 2 does not occur by Day 1 of the next cycle, further reduce the dose of doxorubicin in the next cycle to 50% original dose (15mg/m^2 (0.5 mg/kg)). If chemotherapy at 50% original dose is then tolerated without the recurrence of Grade 3 or 4 toxicity, then escalate back to 75% (22.5mg/m^2 (0.75 mg/kg)). If chemotherapy at 75% is then tolerated without the recurrence of Grade 3 or 4 toxicity, then resume full dose in the next cycle.
- If the patient experiences Grade 3 or 4 toxicity with the 50% dose reduction, the doxorubicin should be omitted from subsequent cycles.

11.9 Pulmonary Toxicity

Gemcitabine

Patients who develop pulmonary toxicity secondary to gemcitabine may benefit from treatment with corticosteroids; however, there are no published guidelines to suggest the most appropriate dosing or duration of treatment. A suggested dose is methylprednisolone 1 mg/kg IV every 12 hours for a minimum of seven days. Gemcitabine should be held during this treatment course. Patients who develop Grade 2 pneumonitis that resolves to Grade ≤ 1 may restart drug.

12. ASSESSMENTS

The following are the recommended assessments and monitoring before and during treatment. Further monitoring can be performed according to institutional guidance.

All study related procedures must be carried out at the trial site. The results must be recorded on the CRF as required, and the reports from the other hospitals must be available for source data verification.

Time points for the biology and toxicity sampling have been aligned in order to minimise invasiveness and reduce the volume of dead space blood that is removed from the patient. Investigators must seek advice from the Coordinating Sponsor if there is a concern regarding the volume of study related blood loss for a particular patient.

12.1 Patient Assessments at Screening

Table 15 Screening Assessments

PROTOCOL ACTIVITY	PRIOR TO TRIAL ENTRY	PRIOR TO TREATMENT ALLOCATION
Informed consent	X	X
Histological confirmation of diagnosis	X	
Medical History		X
Physical exam, including weight, height and surface area		X
Performance status		X
Cardiology assessment[1] (including ECG for Group F patients)		X
Audiogram		X
GFR assessment (if serum creatinine is above upper limit for age)		X
LABORATORY TESTS		
Haematology, including Hb, WBC, differential cell count, neutrophils, lymphocytes, platelets		X
Biochemistry, including magnesium, potassium, calcium, urea, creatinine, total protein, albumin, bilirubin, ALP, GGT, LDH, ALT/AST, ammonia		X
Coagulation (INR/PT and APTT)		X
Hepatitis B and C serology[2]		X
AFP		X
Pregnancy test (if applicable)		X[3]

Counselling about conservation of sperm (male patients)		X
RADIOLOGICAL ASSESSMENTS		
Tumour evaluation CT/MRI		X
Metastatic evaluation: CT		X
PRETEXT staging		X
SAMPLING[4]		
Tumour tissue sample for Biology		X
Non-tumour tissue sample for Biology		X
Blood sample for Biology		X

[1] A cardiology assessment by local institutional method is required for Intermediate (Group C) and High (Group D) Risk HB, and HCC (Group E and F) patients.

[2] Other serology to be conducted as per local institutional practice.

[3] Mandatory in France and Czech Republic for patients of childbearing potential who are sexually active, to undergo repeated pregnancy tests every month.

[4] See Section 11.3 and Lab Manual for details. Tumour and non-tumour samples (representative HE slides; FFPE, fresh and snap-frozen cores) are taken at diagnosis. For Very Low Risk (Group A) patients after surgery, a representative HE stained slide from each tumour block should be sent within 14days for real-time central pathology assessment of WDF histology.

12.2 Patient Assessments During Treatment

Table 16 Group A2 Assessments

PROTOCOL ACTIVITY	Prior to Cycle 1	Prior to Cycle 2	EOT
Physical exam, including weight, height and surface area	X	X	X
LABORATORY TESTS[1]			
Haematology, including Hb, WBC, differential cell count, neutrophils, lymphocytes, platelets	X	X	X
Biochemistry, including magnesium, , potassium, calcium, urea, creatinine, total protein, albumin, bilirubin, ALP, GGT, LDH, ALT/AST,	X	X	X
AFP	X	X	X
GFR	X		X
RADIOLOGICAL ASSESSMENTS			
Tumour evaluation CT/MRI			X
OTHER ASSESSMENTS			
Audiogram	X		X
SAMPLING[2]			
Tumour tissue sample for Biology	X		
Non-tumour tissue sample for Biology	X		
Blood sample for Biology			X
Blood sample for Toxicity	X	X	
Urine sample for Toxicity	X	X	

[1]Haematology should be performed weekly during trial treatment. Creatinine must be monitored carefully prior to each dose of cisplatin to monitor nephrotoxicity. If Creatinine is higher than normal range for age, formal GFR should be estimated according to local practice.

[2] See Section 11.3 and Lab Manual for details. Tumour and non-tumour samples (representative HE slides; FFPE, fresh and snap-frozen specimens) are taken at surgery and at tumour recurrence (if appropriate). After surgery, a representative HE stained slide from each tumor block should be sent within 14days for real-time central pathology assessment of WDF histology. Blood samples for Biology are taken at EOT and at tumour recurrence (if appropriate). Blood samples for toxicity analysis are taken pre-infusion, mid-infusion, end-infusion and 2hr, 6hr, 24hr and 48hr post infusion of cisplatin. Urine samples for toxicity analysis are taken pre-infusion, 24hr and 48hr post infusion of cisplatin.

Table 17 Group B Assessments

PROTOCOL ACTIVITY	Prior to Cycle 1	Prior to each cycle	Post Cycle 2	Post Cycle 3	Post cycle 4	Post Cycle 5	EOT
Physical exam, including weight, height and surface area	X	X					X
LABORATORY TESTS[1]							
Haematology, including Hb, WBC, differential cell count, neutrophils, lymphocytes, platelets	X	X					X
Biochemistry, including magnesium potassium, calcium, urea, creatinine, total protein, albumin, bilirubin, ALP, GGT, LDH, ALT/AST,	X	X					X
AFP	X	X					X
GFR	X						X
RADIOLOGICAL ASSESSMENTS							
GROUP B1 (rand)Tumour evaluation CT/MRI			X				X
GROUP B2 Tumour evaluation CT/MRI			X		X		X
OTHER ASSESSMENTS							
Audiogram	X					X[2]	X
SAMPLING[3]							
Tumour tissue sample for Biology				X			
Non-tumour tissue sample for Biology				X			
Blood sample for Biology				X			X
Blood sample for Toxicity	X			X			
Urine sample for Toxicity	X			X		X	

[1]Haematology should be performed weekly during trial treatment. Creatinine must be monitored carefully prior to each dose of cisplatin to monitor nephrotoxicity. If Creatinine is higher than normal range for age, formal GFR should be estimated according to local practice

[2] Mandatory for patients in France only

[3] See Section 11.3 and Lab Manual for details. Tumour and non-tumour samples (representative HE slides; FFPE, fresh and snap-frozen specimens) are taken at surgery and at tumour recurrence (if appropriate). Blood samples for Biology are taken just before surgery, at EOT and at tumour recurrence (if appropriate). Blood samples for Toxicity are taken pre-infusion, mid-infusion, end-infusion and 2hr, 6hr, 24hr and 48hr post infusion of cisplatin, in two cycles of treatment. Urine samples for Toxicity are taken pre-infusion, 24hr and 48hr post infusion of cisplatin, in up to 3 cycles of treatment (including Cycle 1 and cycle immediately prior to surgery)

Table 18 Group C – SIOPEL-3HR Assessments

PROTOCOL ACTIVITY	Prior to Cycle 1 (CDDP)	Prior to Carbo/ Dox (D15)	Prior to Cycle 2 (CDDP)	Prior to Carbo/ Dox (D43)	Prior to Cycle 3 (CDDP)	Prior to Carbo/ Dox (D71)	Prior to Cycle 4 (CDDP)	Prior to Carbo/ Dox (Post Op)	Prior to Cycle 5 (CDDP)	Prior to Carbo/ Dox (D29 Post-Op)	EOT
Physical exam, including weight, height and surface area	X	X	X	X	X	X	X	X	X	X	X
LABORATORY TESTS[1]											
Haematology, including Hb, WBC, differential cell count, neutrophils, lymphocytes, platelets	X	X	X	X	X	X	X	X	X	X	X
Biochemistry, including magnesium, potassium, calcium, urea, creatinine, total protein, albumin, bilirubin, ALP, GGT, LDH, ALT/AST,	X	X	X	X	X	X	X	X	X	X	X
AFP	X		X		X		X		X		X
GFR	X										X
RADIOLOGICAL ASSESSMENTS[2]											
Tumour evaluation CT/MRI					X		X				X
OTHER ASSESSMENTS											
Audiogram	X										X
Cardiac assessment	X						X		X		X
SAMPLING[3]											
Tumour tissue sample for Biology					X						
Non tumour tissue sample for Biology					X						
Blood sample for Biology					X						X
Blood sample for Toxicity	X				X						
Urine sample for Toxicity	X			X			X				

[1]Haematology should be performed weekly during trial treatment. Creatinine must be monitored carefully prior to each dose of cisplatin to monitor nephrotoxicity. If Creatinine is higher than normal range for age, formal GFR should be estimated according to local practice

[2]Tumour evaluations prior to D57 and pre surgery at D85

[3] See Section 11.3 and Lab Manual for details. Tumour and non-tumour samples (representative HE slides; FFPE, fresh and snap-frozen specimens) are taken at surgery and at tumour recurrence (if appropriate). Blood samples for Biology are taken just before surgery, at EOT and at tumour recurrence (if appropriate). Blood samples for Toxicity are taken pre-infusion, mid-infusion, end-infusion and 2hr, 6hr, 24hr and 48hr post infusion of cisplatin, in two cycles of treatment. Urine samples for Toxicity are taken pre-infusion, 24hr and 48hr post infusion of cisplatin, in up to 3 cycles of treatment (including Cycle 1 and cycle immediately prior to surgery)

Table 19 Group C C5VD Assessments

PROTOCOL ACTIVITY	Prior to Cycle 1 (D1)	Prior to Cycle 2 (D22)	Prior to Cycle 3 (D43)	Prior to Cycle 4 (D64)	Prior to Cycle 5 (D1 Post Op)	Prior to Cycle 6 (D22 Post Op)	EOT
Physical exam, including weight, height and surface area	X	X	X	X	X	X	X
LABORATORY TESTS[1]							
Haematology, including Hb, WBC, differential cell count, neutrophils, lymphocytes, platelets	X	X	X	X	X	X	X
Biochemistry, including magnesium, potassium, calcium, urea, creatinine, total protein, albumin, bilirubin, ALP, GGT, LDH, ALT/AST,	X	X	X	X	X	X	X
AFP	X	X	X	X	X	X	X
GFR	X						X
RADIOLOGICAL ASSESSMENTS							
Tumour evaluation CT/MRI			X		X		X
OTHER ASSESSMENTS							
Audiogram	X				X[3]	X[3]	X
Cardiology assessment	X				X		X
SAMPLING[2]							
Tumour tissue sample for Biology	X						
Non tumour tissue sample for Biology	X						
Blood sample for Biology	X						X
Blood sample for Toxicity	X	X					
Urine sample for Toxicity	X	X		X			

[1]Haematology should be performed weekly during trial treatment. Creatinine must be monitored carefully prior to each dose of cisplatin to monitor nephrotoxicity. If Creatinine is higher than normal range for age, formal GFR should be estimated according to local practice

[2] See Section 11.3 and Lab Manual for details. Tumour and non-tumour samples (representative HE slides; FFPE, fresh and snap-frozen specimens) are taken at surgery and at tumour recurrence (if appropriate). Blood samples for Biology are taken just before surgery, at EOT and at tumour recurrence (if appropriate). Blood samples for Toxicity are taken pre-infusion, mid-infusion, end-infusion and 2hr, 6hr, 24hr and 48hr post infusion of cisplatin, in two cycles of treatment. Urine samples for Toxicity are taken pre-infusion, 24hr and 48hr post infusion of cisplatin, in up to 3 cycles of treatment (including Cycle 1 and cycle immediately prior to surgery)

[3] Mandatory for patients in France only

Table 20 Group C CDDP-M Assessments

PROTOCOL ACTIVITY	Prior to Cycle 1	Prior to Cycle 2	Prior to Cycle 3	Prior to Cycle 4	Prior to Cycle 5	Prior to Cycle 6	EOT
Physical exam, including weight, height and surface area	X	X	X	X	X	X	X
LABORATORY TESTS[1]							
Haematology, including Hb, WBC, differential cell count, neutrophils, lymphocytes, platelets	X	X	X	X	X	X	X
Biochemistry, including magnesium, potassium, calcium, urea, creatinine, total protein, albumin, bilirubin, ALP, GGT, LDH, ALT/AST,	X	X	X	X	X	X	X
AFP	X	X	X	X	X	X	X
GFR	X						X
RADIOLOGICAL ASSESSMENTS							
Tumour evaluation CT/MRI			X		X		X
OTHER ASSESSMENTS							
Audiogram	X				X[3]	X[3]	X
SAMPLING[2]							
Tumour tissue sample for Biology	X						
Non tumour tissue sample for Biology	X						
Blood sample for Biology	X						X
Blood sample for Toxicity	X	X					
Urine sample for Toxicity	X	X				X	

[1]Haematology should be performed weekly during trial treatment. Creatinine must be monitored carefully prior to each dose of cisplatin to monitor nephrotoxicity. If Creatinine is higher than normal range for age, formal GFR should be estimated according to local practice.

[2] See Section 11.3 and Lab Manual for details. Tumour and non-tumour samples (representative HE slides; FFPE, fresh and snap-frozen specimens) are taken at surgery and at tumour recurrence (if appropriate). Blood samples for Biology are taken just before surgery, at EOT and at tumour recurrence (if appropriate). Blood samples for Toxicity are taken pre-infusion, mid-infusion, end-infusion and 2hr, 6hr, 24hr and 48hr post infusion of cisplatin, in two cycles of treatment. Urine samples for Toxicity are taken pre-infusion, 24hr and 48hr post infusion of cisplatin, in up to 3 cycles of treatment (including Cycle 1 and cycle immediately prior to surgery)

[3] Mandatory for patients in France only

Table 21 Group D Assessments

PROTOCOL ACTIVITY	Prior to Block A1	Prior to Block A2	Prior to Block A3	Prior to Surgery	Prior to each Cycle	EOT
Physical exam, including weight, height and surface area	X	X	X	X	X	X
LABORATORY TESTS[1]						
Haematology, including Hb, WBC, differential cell count, neutrophils, lymphocytes, platelets	X	X	X		X	X
Biochemistry, including magnesium, potassium, calcium, urea, creatinine, total protein, albumin, bilirubin, ALP, GGT, LDH, ALT/AST,	X	X	X		X	X
AFP	X	X	X		X	X
GFR	X					X
RADIOLOGICAL ASSESSMENTS[2]						
Tumour evaluation CT/MRI		X	X	X		X
Metastatic evaluation CT chest		X	X	X		X
OTHER ASSESSMENTS						
Audiogram	X		X[4]			X
Cardiology assessment	X			X		X
SAMPLING[3]						
Tumour tissue sample for Biology			X			
Non tumour tissue sample for Biology			X			
Blood sample for Biology			X			X
Blood sample for Toxicity	X		X			
Urine sample for Toxicity	X	X	X			

[1]Biochemistry must be performed weekly during induction blocks. Haematology should be performed weekly during trial treatment. Creatinine must be monitored carefully prior to each dose of cisplatin to monitor nephrotoxicity. If Creatinine is higher than normal range for age, formal GFR should be estimated according to local practice.

[2] Tumour/metastatic evaluations after each induction block

[3] See Section 11.3 and Lab Manual for details. Tumour and non-tumour samples (representative HE slides; FFPE, fresh and snap-frozen specimens) are taken at surgery and at tumour recurrence (if appropriate). Blood samples for Biology are taken just before surgery, at EOT and at tumour recurrence (if appropriate). Blood samples for Toxicity are taken pre-infusion, mid-infusion, end-infusion and 2hr, 6hr, 24hr and 48hr post infusion of cisplatin, in two cycles of treatment. Urine samples for Toxicity are taken pre-infusion, 24hr and 48hr post infusion of cisplatin, in up to 3 cycles of treatment (including Cycle 1 and cycle immediately prior to surgery)

[4] Mandatory for patients in France only

Table 22 Group E2 Assessments

PROTOCOL ACTIVITY	Prior to Cycle 1	Prior to Cycle 2	Prior to Cycle 3	Prior to Cycle 4	EOT
Physical exam, including weight, height and surface area	X	X	X	X	X
LABORATORY TESTS[1]					
Haematology, including Hb, WBC, differential cell count, neutrophils, lymphocytes, platelets	X	X	X	X	X
Biochemistry, including magnesium, potassium, calcium, urea, creatinine, total protein, albumin, bilirubin, ALP, GGT, LDH, ALT/AST,	X	X	X	X	X
AFP	X	X	X	X	X
GFR	X				X
RADIOLOGICAL ASSESSMENTS					
Tumour evaluation CT/MRI			X		X
OTHER ASSESSMENTS					
Audiogram	X				X
Cardiology assessment	X				X
SAMPLING[2]					
Tumour tissue sample for Biology	X				
Non tumour tissue sample for Biology	X				
Blood sample for Biology	X				X
Blood sample for Toxicity	X	X			
Urine sample for Toxicity	X	X	X		

[1]Haematology should be performed weekly during trial treatment. Creatinine must be monitored carefully prior to each dose of cisplatin to monitor nephrotoxicity. If Creatinine is higher than normal range for age, formal GFR should be estimated according to local practice.

[2] See Section 11.3 and Lab Manual for details. Tumour and non-tumour samples (representative HE slides; FFPE, fresh and snap-frozen specimens) are taken at surgery and at tumour recurrence (if appropriate). Blood samples for Biology are taken just before surgery, at EOT and at tumour recurrence (if appropriate). Blood samples for Toxicity are taken pre-infusion, mid-infusion, end-infusion and 2hr, 6hr, 24hr and 48hr post infusion of cisplatin, in two cycles of treatment. Urine samples for Toxicity are taken pre-infusion, 24hr and 48hr post infusion of cisplatin, in up to 3 cycles of treatment (including Cycle 1).

Table 23 Group F– PLADO Assessments

PROTOCOL ACTIVITY	Prior to Cycle 1	Prior to Cycle 2	Prior to Cycles 3-6	Post Cycle 3 / EOT
Physical exam, including weight, height and surface area	X	X	X	X
LABORATORY TESTS[1]				
Haematology, including Hb, WBC, differential cell count, neutrophils, lymphocytes, platelets	X	X	X	X
Biochemistry, including magnesium, potassium, calcium, urea, creatinine, total protein, albumin, bilirubin, ALP, GGT, LDH, ALT/AST,	X	X	X	X
AFP	X	X	X	X
GFR	X			X
RADIOLOGICAL ASSESSMENTS				
Tumour evaluation CT/MRI				X
OTHER ASSESSMENTS				
Audiogram	X		X[3]	X
Cardiology assessment	X			X
ECG	X	X[4]	X[4]	X
SAMPLING[2]				
Tumour tissue sample for Biology	X			
Non tumour tissue sample for Biology	X			
Blood sample for Biology	X			X
Blood sample for Toxicity	X	X		
Urine sample for Toxicity	X	X	X	

[1]Haematology should be performed weekly during trial treatment. Creatinine must be monitored carefully prior to each dose of cisplatin to monitor nephrotoxicity. If Creatinine is higher than normal range for age, formal GFR should be estimated according to local practice.

[2]See Section 11.3 and Lab Manual for details. Tumour and non-tumour samples (representative HE slides; FFPE, fresh and snap-frozen specimens) are taken at surgery (if appropriate). Blood samples for Biology are taken just before surgery and at EOT. Blood samples for Toxicity are taken pre-infusion, mid-infusion, end-infusion and 2hr, 6hr, 24hr and 48hr post infusion of cisplatin, in two cycles of treatment. Urine samples for toxicity analysis are taken pre-infusion, 24hr and 48hr post infusion of cisplatin, in up to 3 cycles of treatment (including Cycle 1 and cycle immediately prior to surgery)

[3] Mandatory for patients in France prior to Cycle 6 only. [4] Mandatory for patients in France only

Table 24 Group F- PLADO/GEMOX Assessments

PROTOCOL ACTIVITY	Prior to Cycle 1	Prior to Cycle 2	Prior to Cycles 3-7	Prior to Cycle 4 / 8	Post Cycle 4 / EOT
Physical exam, including weight, height and surface area	X	X	X	X	X
LABORATORY TESTS[1]					
Haematology, including Hb, WBC, differential cell count, neutrophils, lymphocytes, platelets	X	X	X	X	X
Biochemistry, including magnesium, potassium, calcium, urea, creatinine, total protein, albumin, bilirubin, ALP, GGT, LDH, ALT/AST,	X	X	X	X	X
AFP	X	X	X	X	X
GFR	X				X
RADIOLOGICAL ASSESSMENTS					
Tumour evaluation CT/MRI					X
OTHER ASSESSMENTS					
Audiogram	X				X
Cardiology assessment	X				X
ECG	X	X[3]	X[3]	X[3]	X
SAMPLING[2]					
Tumour tissue sample for Biology	X				
Non tumour tissue sample for Biology	X				
Blood for Biology	X				X
Blood for Toxicity	X	X			
Urine for Toxicity	X	X	X		

[1]Haematology should be performed weekly during trial treatment. Creatinine must be monitored carefully prior to each dose of cisplatin to monitor nephrotoxicity. If Creatinine is higher than normal range for age, formal GFR should be estimated according to local practice.

[2] See Section 11.3 and Lab Manual for details. Tumour and non-tumour samples (representative HE slides; FFPE, fresh and snap-frozen specimens) are taken at surgery (if appropriate). Blood samples for Biology are taken just before surgery and at EOT. Blood samples for Toxicity are taken pre-infusion, mid-infusion, end-infusion and 2hr, 6hr, 24hr and 48hr post infusion of cisplatin, in two cycles of treatment. Urine samples for toxicity analysis are taken pre-infusion, 24hr and 48hr post infusion of cisplatin, in up to 3 cycles of treatment (including Cycle 1 and cycle immediately prior to surgery)

[3] Mandatory for patients in France only. Additionally, an ECG must follow oxaliplatin infusion

12.3 Biological and Pathological Studies

12.3.1 Scientific Aims

The PHITT trial offers a unique opportunity to build a bridge between clinical and biological research through collaboration in validating diagnostic and prognostic biomarkers as well as decipher and increase the molecular knowledge of childhood liver cancer. To reach this, in parallel to the enrolment and treatment of paediatric patients with liver cancer within the PHITT trial, a large scale European biorepository of clinical and pathological-annotated biological samples from these patients will be created. This biorepository, named **Childhood Liver Cancer Network (CLCN) collection,** will include patient-derived xenografts and primary cell cultures and it is established to be the basis of future improvements of the treatment of these patients by facilitating translational investigation towards a more personalized medicine.

Within the European branch of the PHITT trial, the procedures and storage sites of biological samples are coordinated by Germans Trias i Pujol Research Institute (IGTP) in Badalona (Spain) and the Institute of Neuropathology at University Hospital of Bonn (Germany). These two centralized biorepositories are intended to function as the hubs of a large network of hospitals and multidisciplinary research groups.

To reach the secondary aims of the trial, it is crucial to collect a maximum number of samples at the highest quality from the majority of patients. To assure this, a PHITT Laboratory Manual and CLCN kits providing the material for sampling will be distributed at the time of PHITT initiation to the reference centres. Please refer to most recent version of PHITT Laboratory Manual before taking samples for protocol instructions, shipment addresses, contact details, etc.

The initial biological analyses of the ChiLTERN project that will be performed on the samples of the CLCN collection are listed in Table 25. Also, the research groups involved in this research are listed in Table 26.

In addition to the studies mentioned in this section, further research on collected biological samples will be carried out depending on initial findings, general advances in experimental techniques and our increasing knowledge of cancer. Importantly, the future aim of the CLCN collection is to be accessible to external non-profit research groups studying childhood liver cancer and in this way, continue to facilitate and contribute to research of this rare disease. In all circumstances, the conducted research will be evaluated by SIOPEL and CLCN Scientific Committees. Ongoing, planned and future studies using these samples will be always conducted according to legal and ethical rules, and their procedures will be subject to prior approval by the Research Ethics Committee at the national levels.

Table 25 Main studies planned for samples of the CLCN collection within the ChiLTERN project.

All obtained findings from these studies will be stored in the PHITT database and linked with the clinical data.

Study	Description	
Biomarker assessment	• In Europe, a panel of diagnostic and prognostic biomarkers based on the literature and recent research activities of European researchers will be analysed in HB and HCC patients. • Samples: tissue and plasma samples at diagnosis and surgery. • Biomarker panels: gene mutations (CTNNB1, NFE2L2, TERT by Sanger sequencing), gene hypermethylations (IGFBP3, RASSF1A by pyrosequencing), copy number variations (+2q24, +8q, +20 and -4q by OncoScan molecular inversion probe assays) as well as gene (16-gene signature, TERT, NQO1 by quantitative PCR) and protein (3-protein signature by immunohistochemistry and DKK1 by ELISA) expression signatures. This panel will be updated based on scientific publications that appear throughout the project and new biomarkers detected by our discovery approach. Validated biomarkers independently found in EU will be also cross-validated using biological samples from the independent US and Japan cohorts and vice versa.	
Exploratory studies	• Tumour Study of samples of patients stratified into the very high-risk group (low AFP, metastasis, ≥ 8 years of age), samples from recurrent tumours or paediatric • Samples: tissue samples at diagnosis and surgery • Techniques: Tumour and non-tumour samples will be analysed by using the latest omics and next-generation sequencing technologies. The three main techniques to study the genome, epigenome and proteome are summarized below. This does not exclude the use of new developed techniques that could appear during the ongoing study. If comparable newer platforms will become available, they will be used instead.	
	Next-generation sequencing	• High-depth DNA and RNA sequencing will be performed with the Illumina HiSeq 2500 system in tumour and corresponding non-tumour DNA and RNA samples. Matched germline DNA sequencing will also be done. • Expected results: identification of somatic alterations or damaging germline variants, which may be causally linked to the tumour. Also, transcriptome sequencing will provide a detailed gene expression profile useful for molecular tumour classification as well as allow the identification of new gene fusions and alternative splicing events.
	Methylation array analysis	• DNA methylation alterations will be studied using the Illumina Infinium Human Methylation 450k Beadchip array. • Expected results: identification of prognostic or predictive epigenetic markers.
	Proteomic profiling	• Protein profiling and the study of post-traductional changes (i.e. phosphorylome) will be studied by LC-MS label-free analysis (nanoAcquity-LTQ Orbitrap XL mass spectrometer, Thermo-Electron and/or in nanoAcquity-Synapt G2Si, Waters). Progenesis QI-MS software (Nonlinear Dynamics, Waters) will be used for the label-free differential protein expression analysis. • Expected results: identification of post-traductional changes of proteins that could be used as new targets for therapy.
Patient-derived xenograft (PDX) & Primary cell culture establishment	• **PDX establishment:** After surgery, fresh tumour fragments in culture media (MACS Tissue Storage Solution from Miltenyi or XenTech's transport medium) will be shipped by overnight courier to University of Padova in order to be grafted within the 24h post-surgery. Tumour samples will be grafted in NOD scid gamma (NSG) or athymic nude mice according to Nicolle et al [44]. • **Primary cell culture establishment:** Primary cell cultures will be isolated from PDXs but also from fresh samples directly obtained from surgical pieces in the IGTP.	

Table 26 Key centres, pathologists, clinic and basic researchers involved in the research studies (detailed in Table 27) with samples of the CLCN collection.

Institution	Destination	Contact details	Address
IGTP (CLCN repository)	Germans Trias i Pujol Research Institute	Carolina Armengol + 34 670799690 + 34 935543072 carmengol@igtp.cat	Germans Trias i Pujol Research Institute (IGTP) Ctra. de Can Ruti. Camí de les Escoles, s/n 08916 Badalona SPAIN
UKB (CLCN repository)	University Hospital of Bonn Institute of Neuropathology	Torsten Pietsch +49 22828716602 torsten.pietsch@ukb.uni-bonn.de	Sigmund-Freud-Strasse 25 53105 Bonn Germany
XenTECH (PDX models)	XenTECH	Stefano Cairo +33 160878982 stefano.cairo@xentech.eu	Rue Pierre Fontaine 4 91000 Evry FRANCE
UNIPD (PDX models)	University of Padova	Stefano Cairo stefano.cairo@xentech.eu Martina Pigazzi Tel. +39 049 8211471 martina.pigazzi@unipd.it	Universita Degli Studi Di Padova Department of Women's and Children's Health Via Giustiniani, 3 35128 Padova Italy
European Pathologist panel representative	University Medical Centre Utrecht Bambino Gesù Children's Hospital	Ronald de Krijger Tel: +31 88 7557701 r.r.dekrijger@umcutrecht.nl Rita Alaggio Tel. +39 06 68592818 Paola. FrancalanciTel. +39 06 68592817 paola.francalanci@opbg.net	Dept of Pathology, room H04.0221, Heidelberglaan 100 3584 CX Utrecht The Netherlands Unit of Pathology Bambino Gesu Children's Hospital Piazza Sant'Onofrio 4 00165 Rome
Central Pathology Review Centre	Contact details of the national reference pathologist for each country can be found in the PHITT Lab Manual.		

12.3.2 Pathology and Biology Sampling

Informed Consent must be obtained before any trial specific tissue is collected from the patient. Tissue may be collected as part of standard practice, part of generic tissue consent for research or using the PHITT trial consent.

Please refer to the PHITT Laboratory Manual before taking samples.

Blood and tumour tissue samples will be collected at diagnosis. Blood, tumour tissue and and non-tumour tissue will be collected at the point of surgery. Additional blood samples will also be taken pre-surgery and at end of treatment.

Table 27 Samples taken at Diagnosis

Sample	Preparation	Storage	Sent to
Tumour tissue sample	Representative HE slides and a representative FFPE block	RT	National / International Review Centre*
	2 FFPE blocks	RT	IGTP (CLCN repository)
	Snap-frozen sample(1-4 cores**)	-80°C	CLCN repository
Blood sample (3-6mL)	Few drops (Whatman paper)	RT	CLCN repository
	Plasma	-80°C	CLCN repository
	Peripheral Blood lymphocytes	-80°C	CLCN repository
	Whole Blood	-80°C	CLCN repository

*NB – For rapid central review, see section 7, samples should be sent to the International Review Centre within 5 days for real-time central pathology review. All other tumour tissue samples should be sent to the National Review Centre.

**One third of the diagnostic material should not be fixed but reserved for biology.

Table 28 Samples taken just before surgery

Sample	Preparation	Storage	Sent to
Blood sample (3-6mL)	Plasma	-80°C	CLCN repository
	Peripheral Blood lymphocytes	-80°C	CLCN repository

Table 29 Samples taken at surgery of primary tumour

Sample	Preparation	Storage	Sent to
Tumour tissue sample	A representative HE stained slide from each relevant block and a representative FFPE block	RT	National / International Review Centre)**
	At least 1 representative FFPE blocks still containing at least half of the original material	RT	National / International Review Centre
	Snap-frozen sample (3 pieces)	-80°C	CLCN repository
	Fresh sample in culture media (1 piece; 2 pieces in Spain)	4°C	CLCN repository (IGTP) & PDX centre
	3 FFPE blocks	RT	CLCN repository
Non-tumour tissue sample	Relevant HE Slides and a representative FFPE block	RT	Central Pathology Review Centre

	At least 1 representative FFPE blocks still containing at least half of the original material	RT	National / International Review Centre
	Snap-frozen sample (3 tissue pieces)	-80°C	CLCN repository
	Fresh sample in culture media (1 piece)	4°C	CLCN repository (IGTP) Spain only
	3 FFPE blocks	RT	CLCN repository

* Sample processing should be within 30 minutes after specimen removal

**NB – For rapid central review, see section 7,samples should be sent to the International Review Centre within 5 days for real-time central pathology review. . All other tumour tissue samples should be sent to the National Review Centre.

Table 30 Samples taken at End of Treatment

Sample	Preparation	Storage	Sent to
Blood sample (3-6mL)	Plasma	-80°C	CLCN repository
	Peripheral Blood lymphocytes	-80°C	CLCN repository

Table 31 Samples taken at surgery of recurrent tumour

Sample*	Preparation	Storage	Sent to
Tumour tissue sample	A representative HE stained slide from each relevant block	RT	National Review Centre
	At least 3 representative FFPE blocks still containing at least half of the original material	RT	National Review Centre
	Snap-frozen sample (3 pieces)	-80°C	CLCN repository
	Fresh sample in culture media (2 pieces)	4°C	CLCN repository (IGTP) & PDX Centre
	3 FFPE blocks	RT	CLCN repository
Non-tumour tissue sample	Relevant HE Slides	RT	National Review Centre
	At least 1 representative FFPE blocks still containing at least half of the original material	RT	National Review Centre
	Snap-frozen sample (3 tissue pieces)	-80°	CLCN repository
	Fresh sample in culture media (1 piece)	4°C	CLCN repository (IGTP) Spain only
	3 FFPE blocks	RT	CLCN repository
Blood sample (3-6mL)	Plasma	-80°C	CLCN repository
	Peripheral Blood lymphocytes	-80°C	CLCN repository

*Sample processing should be within the 30 minutes after specimen removal

12.3.3 Toxicity Sampling

Blood and urine samples will be collected from all patients receiving cisplatin therapy to collect data on the relationships between cisplatin pharmacokinetics, pharmacogenetics and biomarkers of toxicity and the clinical efficacy and toxicity in patients.

- Blood for a Pharmacokinetics study will be taken pre-infusion, mid-infusion, end-infusion and 2hr, 6hr, 24hr and 48hr post end-infusion on 2 cycles of cisplatin treatment (preferably first and last cycles of treatment).
- Blood for a Cardiac toxicity biomarker study will be taken prior to treatment and at times of Cardiac assessment.
- Blood for a Pharmacogenetics study will be taken prior to treatment.
- Urine for a Kidney toxicity biomarker study will be taken pre-infusion, 24hr and 48hr post end-infusion on up to 3 cycles of cisplatin treatment (including 1st cycle and cycle immediately prior to surgery).

Table 32 Samples taken Pre-infusion (Day 1)

Sample	Preparation	Reason for sample	Storage	Sent to
Blood sample (3mL Heparin tube)	Plasma	Pharmacokinetics study	-20°C or -80°C	Newcastle
	Plasma ultrafiltrate	Pharmacokinetics study	-20°C or -80°C	Newcastle
Blood sample (5mL EDTA tube)*	Plasma	Cardiac toxicity biomarker study	-20°C or -80°C	Newcastle
Blood sample (5mL whole blood)	N/A	Pharmocogenetics study	-20°C or -80°C	Newcastle
Urine sample	N/A	Kidney toxicity biomarker study	-80°C	Newcastle

*Repeat sample at each Cardiac assessment.

Table 33 Samples taken Mid-infusion, End-infusion, 2hr post infusion and 6hr post infusion (Day 1)

Sample	Preparation	Reason for sample	Storage	Sent to
Blood sample (3mL Heparin tube)	Plasma	Pharmacokinetics study	-20°C or -80°C	Newcastle
	Plasma ultrafiltrate	Pharmacokinetics study	-20°C or -80°C	Newcastle

Table 34 Samples taken at 24hr post infusion (Day 2)

Sample	Preparation	Reason for sample	Storage	Sent to
Blood sample (3mL Heparin tube)	Plasma	Pharmacokinetics study	-20°C or -80°C	Newcastle
	Plasma ultrafiltrate	Pharmacokinetics study	-20°C or -80°C	Newcastle
Urine sample*	N/A	Kidney toxicity biomarker study	-80°C	Newcastle

* Blood sample for PK study need only be taken on 2 cycles (preferably first and last cycles of treatment).

** Urine sample should be taken on up to 3 cycles, including Cycle 1 and cycle immediately prior to surgery.

Table 35 Samples taken at 48hr post infusion (Day 3)

Sample	Preparation	Reason for sample	Storage	Sent to
Blood sample (3mL Heparin tube)*	Plasma	Pharmacokinetics study	-20°C or -80°C	Newcastle
	Plasma ultrafiltrate	Pharmacokinetics study	-20°C or -80°C	Newcastle
Urine sample**	N/A	Kidney toxicity biomarker study	-80°C	Newcastle

* Blood sample for PK study need only be taken on 2 cycles (preferably first and last cycles of treatment)

** Urine sample should be taken on up to 3 cycles, including Cycle 1 and cycle immediately prior to surgery

13. TREATMENT COMPLIANCE

Compliance for IMP treatment will be monitored by each NCC as specified in the International Monitoring Plan, Pharmacy Manual and by the CRF. The prescription and usage of the IMPs is recorded on the Treatment CRF. Local accountability processes must allow retrospective verification.

14. SUPPORTIVE TREATMENT

Cardioprotective agents

Dexrazoxane use for patients treated with doxorubicin is permitted at the discretion of the treating centre. Its use should be consistent where possible. Note: dexrazoxane is contraindicated in children aged between 0 and 18 years old receiving an anthracycline-based chemotherapy with scheduled cumulative doses of doxorubicin < 300mg/m^2 or with equivalent cumulative doses of other anthracyclines.

Hearing protective agents

Sodium thiosulfate (STS) is permitted to be used in Treatment Groups A, B and C at the discretion of the treating centre. SIOPEL6 study investigated the use of STS in patients receiving 6 cycles of

cisplatin monotherapy (cumulative dose 480mg/m^2). There is limited data available to support to use of STS in very low risk HB (Group A) treatment and in patients receiving less than 6 cycles of therapy in low risk HB (Group B). Investigators are advised to consider the risk-benefit assessment when recommending the use of STS to patients/parents. STS must not be used for patients in Groups D, E or F. Where STS is used, it should be used at all treatment cycles. STS should be given according to the guidelines provided in a separate Information Sheet. Strict adherence to scheduling of STS in relationship to the cisplatin infusion is vital.

Venous Access

A permanent indwelling venous access device is recommended. This is not a trial requirement.

Antiemetics

Patients should be treated with appropriate antiemetics according to local practice.

Neutropenia (Neutropenic fever)

Antibiotic coverage is at the discretion of the Investigator using broad spectrum cover. Use of G-CSF is at the discretion of the treating physician.

Blood products

Blood and platelet transfusions and the use of filtering and irradiating blood products may be done according to local practice. G-CSF may be used according to local practice.

Pneumocystis carinii infection prophylaxis

Pneumocystis carinii prophylaxis according to local guidance.

Hydration

Sufficient hydration (2-3L/m²/day) with appropriate electrolyte supplementation must be provided during chemotherapy. The application of diuretics may become necessary in case of oedema or hypertension. Avoid nephrotoxic drugs.

15. CONCOMITANT MEDICATION

The use of specific drugs which may interact with the trial IMPs must be avoided. These are listed below.

<u>All patient groups:</u>

-
- The use of live attenuated vaccines is prohibited.
- Any homeopathic or other agent delivered with anti-tumour intent is prohibited.
- Enrolment on a simultaneous clinical trial which administers an IMP is prohibited.

<u>Group F patients:</u>

The following drugs must not be taken by patients receiving sorafenib:

- CYP3A4 inducers (e.g. St John's Wort, dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, phenobarbital) due to their effect on QC prolongation.
- CYP3A4 inhibitors and CYP Isoform substrates (e.g. ketoconazole).
- CYP2B6 and CYP2C8 substrates (e.g. paclitaxel).
- Docetaxel.

- Fluorouracil/Leucovorin.
- Drugs which inhibit UGT1A1 and UGT1A9 metabolism (e.g. irinotecan).
- Drugs which interfere with GI flora (e.g. neomycin).

Concomitant medications will be recorded in the CRF as part of Serious Adverse Event (SAE) reporting only. Where concomitant medications are given in relation to standard clinical management, this information will not be recorded in the CRF.

16. PATIENT FOLLOW UP

Patients who received treatment must have follow-up assessments following trial entry for a minimum of 2 years. Patients who did not receive treatment will be followed up for disease progression and death only, for a minimum of 2 years.

3 monthly follow up visits should be carried out as per local practice and include:

- Physical examination at each visit
- AFP assessment
- Tumour assessment (ultrasound and/or MRI, with CT only if clinically appropriate)

Annual follow up visits should be carried out as per local practice and include:

- Audiology assessment
- Cardiology assessment (if abnormal at EOT)
- Creatinine clearance (if <80ml/min/1.73m^2 at EOT)

In case of tumour recurrence during follow-up, blood and tissue samples from these patients should be collected (see section 12.3 and refer to most recent version of PHITT Laboratory Manual before taking samples).

All patients will be followed up for progression and death until all trial objectives have been met.

17. TREATMENT DISCONTINUATION AND PATIENT WITHDRAWAL

17.1 Treatment Discontinuation

If a patient stops PHITT protocol treatment, the reason should be recorded in the patient's medical records and be reported on the appropriate CRF whether it is due to either the patient's, parent/legal guardian's or clinician's decision. Reasons for stopping protocol treatment may include, but are not limited to:

- The patient and/or patient's parent/guardian does not wish to continue with further trial treatment
- Unacceptable toxicity
- Disease progression whilst on therapy
- Pregnancy

PHITT will be analysed on an intention-to-treat (ITT) basis and all patients who stop randomised trial treatment will remain in the trial for follow-up unless the patient and/or parent/legal guardian explicitly withdraws consent for data collection (see Section 17.2).

17.2 Withdrawal of Consent to Data Collection

The patient and/or parent/legal guardian may withdraw consent at any time during the study. For the purposes of this trial, withdrawal is defined as:

- The patient would like to withdraw from trial medication and is not willing to be followed up for the purposes of the trial at any further visits (i.e. only data collected prior to the withdrawal of consent can be used in the trial analysis).

The details of withdrawal should be clearly documented in the patient's medical records. A Withdrawal of Consent Form should be completed.

A patient's wishes with respect to their data must be respected.

17.3 Loss to Follow-Up

If a patient is lost to follow-up, every effort should be made to contact the patient's primary physician (GP in the UK) to obtain information on the patient's status. Similarly, if a patient's care is transferred to another clinician, the applicable NCC should be informed and follow-up information be obtained.

18. ADVERSE EVENT REPORTING

The collection and reporting of Adverse Events (AEs) will be in accordance with EU Directive for Clinical Trials 2001/20/EC and the Detailed Guidance on the Collection, Verification and Presentation of Adverse Events/Reaction Reports Arising From Clinical Trials of Medicinal Products For Human Use ('CT-3'). Definitions of different types of AE are listed in Appendix 2 - Definition of Adverse Events.

The Investigator should assess the seriousness and causality (relatedness) of all AEs experienced by the patient (this should be documented in the patient's medical records - source data) with reference to the Summary of Product Characteristics.

18.1 Reporting Requirements

18.1.1 Adverse Events and Adverse Reactions

For definitions of Adverse Event (AEs) and Adverse Reactions (ARs) refer to Appendix 2 - Definition of Adverse Events.

As the safety profiles of the IMPs used in this trial are well characterised, only selected ARs experienced during treatment will be reported. The highest grade of AR experienced during each cycle of chemotherapy will be recorded only.

For patients on non-randomised arms (Groups A, B2, D1 and E) only chemotherapy-related cardiac, nephro- and oto- toxicity will be recorded.

An additional AE CRF will be completed for German patients on which all AEs not captured elsewhere must be reported.

18.1.2 Serious Adverse Events

Investigators should report AEs that meet the definition of an SAE (see Appendix 2 - Definition of Adverse Events for definition) and that are not excluded from the reporting process as described below.

18.1.2.1 Events that do not require reporting on a Serious Adverse Event Form

The following events should not be reported on an SAE Form:

- Hospitalisation's for:
  - Protocol defined treatment
  - Pre-planned elective procedures unless the condition worsens
  - Treatment for the symptoms of /progression of the patient's cancer

Progression or death as a result of the patient's cancer, as this information is captured elsewhere on the CRFs.

Hospitalisations for the following events should be reported on an **Expected SAR Form** rather than an SAE Form (unless the condition is life threatening or proves fatal):

- Fever
- Febrile neutropenia
- Infections
- Haematological toxicity:
    - Hemoglobin decreased
    - Lymphocyte count decreased
    - Neutrophil count decreased
    - Platelet count decreased
    - White blood cell decreased
- Gut toxicity:
    - Diarrhea
    - Nausea
    - Vomiting
    - Mucositis

Expected SAR Forms should be completed by sites as soon as possible once the event has resolved and sent via post or fax to the UK Coordinating Centre for data entry.

18.1.2.2 Monitoring pregnancies for potential Serious Adverse Events

It is important to monitor the outcome of pregnancies of patients in order to provide SAE data on congenital anomalies or birth defects.

In the event that a patient or their partner becomes pregnant during the SAE reporting period, complete a Pregnancy Notification Form (providing the patient's details). If it is the patient who is pregnant, outcome data should be provided on a follow-up Pregnancy Notification Form. Where the patient's partner is pregnant, consent must first be obtained and the patient should be given a Release of Medical Information Form to give to their partner. If the partner is happy to provide information on the outcome of their pregnancy, they should sign the Release of Medical Information Form. Once consent has been obtained, details of the outcome of the pregnancy should be provided on a follow-up Pregnancy Notification Form. If appropriate, an SAE Form should also be completed as detailed below.

18.1.3 Reporting period

Details of all ARs and SAEs (except those listed above) will be documented and reported from the date of commencement of protocol defined treatment until 30 days after the administration of the last treatment.

18.1.4 Post study SARs and SUSARs:

SAEs that are judged to be at least possibly related to the IMP(s) must still be reported in an expedited manner irrespective of how long after IMP administration the reaction occurred.

18.2 Reporting Procedure

18.2.1 Site

18.2.1.1 Adverse Reactions

ARs experienced during treatment should be recorded on the CRF. ARs will be reviewed using the Common Terminology Criteria for Adverse Events (CTCAE), version 4 (see Appendix 3 – Common Terminology Criteria for Adverse Events). Any ARs experienced by the patient but not included in the CTCAE should be graded by an Investigator and recorded on the AR Form using a scale of (1) mild, (2) moderate or (3) severe. For each sign/symptom, the highest grade observed since the last visit should be recorded.

18.2.1.2 Serious Adverse Events

For more detailed instructions on SAE reporting, refer to the SAE Form Completion Guidelines contained in the ISF.

AEs defined as serious and which require reporting as an SAE (excluding events listed in Section 18.1.2.1 above) should be reported on an SAE Form. When completing the form, the Investigator will be asked to define the causality and the severity of the AE which should be documented using the CTCAE version 4.

On becoming aware that a patient has experienced an SAE, the Investigator (or delegate) must complete, date and sign an SAE Form. The form should be faxed together with a SAE Fax Cover Sheet to the UK Coordinating Centre, based at the CRCTU, using one of the numbers listed below as soon as possible and no later than 24 hours after first becoming aware of the event:

To report an SAE, fax the SAE Form with an SAE Fax Cover Sheet to:

+44 (0) 121 414 9520 or +44 (0) 121 414 3700

Alternatively, email the SAE Form to **reg@trials.bham.ac.uk**

On receipt, the UK Coordinating Centre will allocate each SAE a unique reference number. This number will be transcribed onto the SAE Fax Cover Sheet which will then be faxed or emailed back to the site as proof of receipt. If confirmation of receipt is not received within 1 working day, please contact the UK Coordinating Centre. The SAE reference number should be quoted on all correspondence and follow-up reports regarding the SAE. The SAE Fax Cover Sheet completed by the UK Coordinating Centre should be filed with the SAE Form in the ISF.

For SAE Forms completed by someone other than the Investigator, the Investigator will be required to countersign the original SAE Form to confirm agreement with the causality and severity assessments. The form should then be returned to the UK Coordinating Centre in the post and a copy kept in the ISF.

Investigators should also report SAEs within their own institution in accordance with local practice.

18.2.1.3 Provision of follow-up information

Patients should be followed up until resolution or stabilisation of the event. Follow-up information should be provided on a new SAE Form (refer to the SAE Form Completion Guidelines for further information).

18.2.2 UK Coordinating Centre

On receipt of an SAE Form, seriousness and causality will be determined independently by a Clinical Coordinator. An SAE judged by the Investigator or Clinical Coordinator to have a causal relationship with the trial medication will be regarded as a Serious Adverse Reaction (SAR). The Clinical Coordinator will also assess all SARs for expectedness. If the event meets the definition of a SAR that

is unexpected (i.e. not defined in the Reference Safety Information), it will be classified as a Suspected Unexpected Serious Adverse Reaction (SUSAR).

18.2.3 Reporting to the Competent Authority and Research Ethics Committee

18.2.3.1 Suspected Unexpected Serious Adverse Reactions

The UK Coordinating Centre will report individual events categorised as SUSARs to the EudraVigilance Clinical Trial Module (EVCTM) and were required to the Competent Authority in all countries in which the trial has received regulatory approval. Events will be reported in accordance within the regulatory specified time frame:

- Fatal or life threatening SUSARs within a maximum of 7 days with a detailed follow-up report within an additional 8 days
- All other SUSARs within a maximum of 15 days

The UK Coordinating Centre will provide SUSARs reports to the NCCs who will report SUSARs to the relevant REC, within the time frame specified above, and Principal Investigators within their country. The UK Coordinating Centre will assume responsibility for reporting to these parties in the UK.

18.2.3.2 Development Safety Update Report

The UK Coordinating Centre will include details of all SAEs, SARs (including SUSARs) in a Development Safety Update Report (DSUR) produced annually from the date of the first Clinical Trial Authorisation received for the trial to the submission of the End of Trial Declaration. NCCs will be provided with a copy of this report and where contractually required to do so will forward this report to the relevant Competent Authority and REC.

18.2.3.3 Adverse Reactions

Details of all ARs will be reported to Competent Authorities on request.

18.2.3.4 Other safety issues identified during the course of the trial

The NCCs will notify the relevant Competent Authority and REC immediately if a significant safety issue is identified during the course of the trial. The UK Coordinating Centre will notify the MHRA and UK REC.

18.2.4 Investigators

Details of all SUSARs and any other safety issue which arises during the course of the trial will be reported to Principal Investigators. A copy of any such correspondence should be filed in the ISF.

18.2.5 Data Monitoring Committee

The independent Data Monitoring Committee (DMC) will review all SAEs.

19. DATA HANDLING AND RECORD KEEPING

19.1 Data Collection

This trial will use an eRDE system provided by CINECA which will be used for completion of the CRF. Access to the eRDE system will be granted to individuals via the UK Coordinating Centre.

SAE reporting will be entirely paper-based throughout the course of the trial.

If the eRDE system is unavailable for an extended period of time a paper based CRF should be completed and forms returned to the applicable NCC for data entry.

The CRF must be completed by an Investigator or an authorised member of the site research team (as delegated on the site signature and delegation log, or country specific equivalent) within the timeframe listed in the eRDE.

Entries on the paper CRF should be made in ballpoint pen, in blue or black ink, and must be legible. Any errors should be crossed out with a single stroke, the correction inserted and the change initialled and dated. If it is not obvious why a change has been made, an explanation should be written next to the change.

Data reported on each form should be consistent with the source data or the discrepancies should be explained. If information is not known, this must be indicated on the form. Missing and ambiguous data will be queried. All sections are to be completed before being submitted.

In all cases it remains the responsibility of the Investigator to ensure that the CRF has been completed correctly and that the data are accurate.

The CRF may be amended by the UK Coordinating Centre, as appropriate, throughout the duration of the trial. Whilst this will not constitute a protocol amendment, new versions of the form must be implemented by participating sites immediately on receipt, and acknowledgement of receipt and implementation should be sent to the applicable NCC if required.

19.2 Archiving

It is the responsibility of the Principal Investigator to ensure all essential trial documentation and source records (e.g. signed ICFs, ISF, Pharmacy Files, patients' medical records, copies of SAE forms, etc.) at their site are securely retained for at least 25 years after the end of the trial. NCCs will notify sites when documentation can be destroyed.

20. QUALITY MANAGEMENT

20.1 Site Set-up and Initiation

Sites will be set up and initiated in accordance by the applicable NCC. All sites will be required to sign a clinical study site agreement (or country specific equivalent) prior to participation. In addition, all participating Investigators will be asked to supply a current CV. All members of the site research team will also be required to sign the site signature and delegation log (or country specific equivalent).

Prior to commencing recruitment, all sites will undergo a process of initiation. It is anticipated that key members of the site research team will be required to attend either a meeting or a teleconference covering aspects of the trial design, protocol procedures, AE reporting, collection and reporting of data and record keeping.

It is anticipated that sites will be provided with an ISF and a Pharmacy File containing the documentation and instructions required for the conduct of the trial by the NCC. The applicable NCC must be informed immediately of any change in the site research team.

20.2 On-site Monitoring

Monitoring will be carried out as required following a risk assessment and as documented in the International Monitoring Plan.

Investigators will allow the PHITT trial research staff access to source documents as requested.

20.3 Central Monitoring

If allowed by country specific legislation/guidance and if the patient and/or parent/legal guardian has given explicit consent, sites are requested to send in copies of signed ICFs to the applicable NCC for in-house review.

Trial research staff will be in regular contact with the site research team to check on progress and address any queries that they may have. Trial research staff will check incoming data for compliance with the protocol, data consistency, missing data and timing. Sites will be sent requests for missing data or clarification of inconsistencies or discrepancies.

Sites may be suspended from further recruitment in the event of serious and persistent non-compliance with the protocol and/or Good Clinical Practice (GCP), and/or poor recruitment. Any major problems identified during monitoring may be reported to the Trial Management Group (TMG), Trial Steering Committee (TSC) and the relevant regulatory bodies. This includes reporting serious breaches of GCP and/or the trial protocol.

20.4 Audit and Inspection

The Investigator will permit trial-related monitoring, audits, ethical review, and regulatory inspections at their site, providing direct access to source data/documents.

Sites are also requested to notify the applicable NCC of any inspections by the relevant Competent Authority.

NCCs will notify the UK Coordinating Centre of any significant audit findings.

20.5 Notification of Serious Breaches

Country specific legislation may require the NCC to notify the Competent Authority and Ethics Committee in writing, within 7 days of becoming aware of any serious breach of:

- The conditions and principles of GCP in connection with the trial
- The protocol relating to the trial

A “serious breach” is a breach which is likely to affect to a significant degree:

- The safety or physical or mental integrity of the patients in the trial
- The scientific value of the trial

Sites are therefore requested to notify the applicable NCC of a suspected trial-related serious breach of GCP and/or the trial protocol. Where the applicable NCC is investigating whether or not a serious breach has occurred sites are also requested to cooperate with the applicable NCC in providing sufficient information to report the breach to the relevant regulatory authorities where required and in undertaking any corrective and/or preventive action.

Please note: persistent failure by sites to provide prompt and accurate information, particularly with regard to the reporting of SAEs, can be considered a serious breach.

The NCC will notify the UK Coordinating Centre of any serious breaches.

21. END OF TRIAL DEFINITION

The trial will remain open until the date of the last patient’s last visit. The applicable NCC will notify the relevant Competent Authority and Ethics Committee that the trial has ended at the appropriate time and will provide them with a summary of the clinical trial report within 12 months of the end of trial.

22. STATISTICAL CONSIDERATIONS

22.1 Trial Design

The study is viewed in the context of a long-term strategy for improving outcome in HB and HCC and it is important to investigate promising approaches in randomised trials. In some cases it is difficult to come up with plausible sample sizes and the cohort sizes that are available would be considered inadequate based on conventional criteria for Randomised Controlled Trials (RCTs) (e.g. alpha=0.05, beta=0.2). In the context of low-incidence paediatric cancer, frequent smaller trials will likely produce larger long-term gains in treatment efficacy [45]. Hence the study is driven by the objective of accumulating as much information as possible on the relative efficacies of the treatments using unbiased methods. Therefore alternative methods are considered which include Bayesian methods – based on probability distributions. This design will provide flexibility to make conclusions from all patients randomised without fixing the exact number which will be important given the recruitment from several collaborative groups. As a general principle, the approach that any randomised evidence is better than none is taken. A possible conclusion of the randomisations might be that there remains uncertainty as to which treatment is better and, therefore, that some of the randomisations could continue in the next trial.

22.2 Outcome Measures

The trial outcome measures are defined in Section 2.2. Table 1 specifies the outcome measures for each group.

22.3 Trial Sample Size Considerations

The sample size for each treatment groups was chosen based on the available number of patients across the three collaborative groups. The trial will aim to recruit the total number of patients across the three collaborative groups as specified in Table 1 for the main analysis, but the flexible design ensures that this analysis will be applicable for any number of patients, although operating characteristics may be different.

22.3.1 Randomised groups

For the randomised questions, specific decision guidelines were chosen based on the primary outcome in order to assist treatment selection decisions at the interim and main analysis. In general, a therapy may be chosen, based on the posterior probability at the main analysis if Pr(true therapy signal is < h, given observed data) > p, where h is the upper limit and p is the cut-off of the lower level of certainty (i.e. it is likely that the true signal in one of the therapy arms is greater than some clinically relevant value). The design parameters h and p were calibrated on the basis of the operating characteristics of the study design (and their clinical interpretation through discussion with the clinical community on clinically acceptable differences, and the level of certainty required in the decision making process) and were examined in simulation studies. The guidelines at an interim analysis were selected so that a randomisation will only stop when there is evidence of futility. Operating characteristics were calculated by simulating data for 1000 trials (or higher for a greater precision) under different possible underlying truths and decision guidelines and the number of trial stages. The results are given in the Statistical Analysis Plan. The guidelines for randomised questions are detailed in Table 36 and Table 37 for the interim and the main analysis respectively. Where a Bayesian probability based approach is adopted for survival outcomes, a Normal-Normal conjugate analysis for log Hazard Ratio (HR) was used to assess the design characteristics. The normal approximation for the log HR with variance 4/n is assumed, where n=total number of events in both arms [46]. Where a probability based approach is adopted for the response primary outcome, a Beta-Binomial conjugate analysis was used to assess the design characteristics. Non-informative priors were used. The posterior distributions were derived and from these, a distribution for the risk ratio (RR).

Table 36 Interim decision guidelines for randomised questions

Group	Baseline 3-year EFS (%)	Decision guideline
B1 - Low Risk HB Patients, Resected after 2 courses	87.5	Experimental treatment may be considered of futility if Pr(true HR<1.91|data)<20%
C - Intermediate Risk HB Patients	80	Experimental treatment may be considered of futility if Pr(true HR<1.6|data)<20%
D - High Risk HB Patients, Poor responders	60	No guideline
F – Un resected /metastatic HCC Patients, Not resected	40% response rate	Experimental treatment may be considered of futility if Pr(true RR<1|data)<20%

Table 37 Decision guidelines for randomised questions at the main analysis

Group	Decision guideline
B1 - Low Risk HB Patients, Resected after 2 courses	Experimental treatment may be accepted if Pr(trueHR<1.91|data)≥70%
C - Intermediate Risk HB Patients	Experimental treatment may be accepted if Pr(true HR<1.60|data)≥80% (for the C5VD and CPPD comparison)
D - High Risk HB Patients, Poor responders	A treatment may be accepted if Pr(true HR<1|data)≥50%
F – Un resected /metastatic HCC Patients, Not resected	Experimental treatment may be accepted if Pr(trueRR>1|data)>80%

22.3.1 Non-randomised groups

For the non-randomised groups, decision guidelines are planned to be used for safety monitoring purposes (treatment strategy may be reconsidered if outcomes reach an undesirable level; the decision guidelines were chosen based on a modified A'hern design and, if a certain number of failure events are observed, the treatment for a group may be reconsidered because of insufficient disease control, detailed in Table 38). The operating characteristics of the design are given in the Statistical Analysis Plan. There will be no comparison with historical data. The aim of data collection for these groups is for biological studies.

Table 38 Decision Guidelines for non-randomised questions

Group	Baseline long term EFS (%)	Decision guideline	
		at interim	at any time after interim
A1 - Well Differentiated foetal Histology	92.5	4 or more failure events occur	4 or more failure events occur
A2 - Not well differentiated foetal	85	Strategy may be reconsidered if 10 or more events are observed out of the 94 first patients	21 or more failure events occur
B2 - Not resected after 2 courses	Proportion of patients achieving resection is 90	Strategy may be reconsidered if 12 or more patients out of the 115 first fail to get resected	15 or more patients fail to get resected
D1 - Good responders	87.5	Strategy may be reconsidered if 4 or more failure events occur out of the 45 first patients	11 or more failure events occur
E1 - Fibrolamellar HCC	Not applicable	No guideline	No guideline
E2 - de novo non-fibrolamellar HCC	82.5	4 or more failure events occur	4 or more failure events occur

22.4 Analysis of Outcome Measures

For the randomised questions, the main analysis based on the primary outcome measure will result in a posterior probability distribution. The analysis will use non-informative priors. A decision on which therapy will be taken as the standard will be made at this stage, taking into account secondary outcome measures. To assist this decision, probabilities will be established on which therapy is truly better than the other by pre-specified clinically relevant value (i.e. decision guidelines specified in Section 22.2). Non-randomised groups will be summarised using descriptive statistics as these have no comparative questions. The analyses of all outcome measures will be performed according to the intention to treat principle. Further details of the planned statistical analysis are detailed in a separate Statistical Analysis Plan.

22.5 Planned Subgroup Analyses

Exploratory subgroup analyses will be performed for known prognostic factors. Given the well-known dangers of subgroup analyses, all analyses will be treated as hypothesis-generating.

22.6 Planned Interim Analysis

For all randomised groups, data will be analysed and reported at least annually to an independent DMC. The DMC may also recommend stopping or modifying the trial (or part of the trial) if any issues are identified which might compromise patient safety or for clear evidence of efficacy or because of poor accrual or data quality. Recruitment will not be stopped whilst the data is assessed by the DMC.

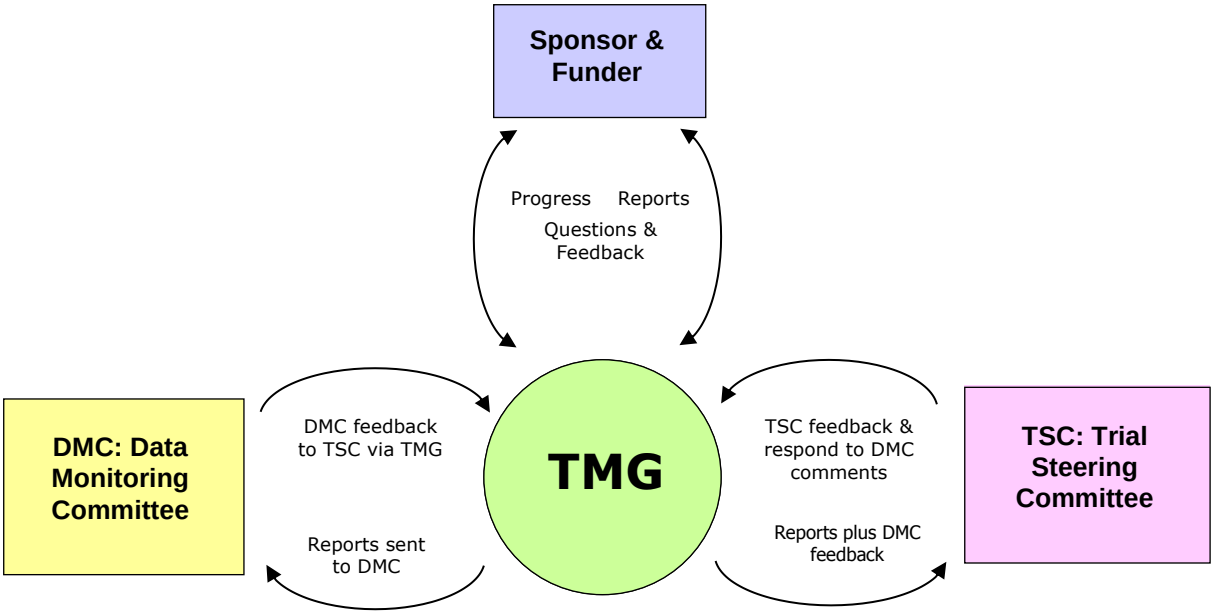
22.7 Planned Final Analyses

The first main analysis will be performed two years after recruitment of the last patient.

22.8 Stopping Guidelines

The ‘stopping’ and ‘taking forward’ decision guidelines at the interim and final analyses respectively are specified in the Section 22.2. The independent DMC will review the safety data and efficacy at regular intervals and will make recommendations to the TSC if they have concerns regarding any of the randomised cohorts.

23. TRIAL ORGANISATIONAL STRUCTURE



23.1 Coordinating Sponsor

The University of Birmingham is the Coordinating Sponsor. In addition, the University of Birmingham (UK Coordinating Centre) will undertake the responsibilities of NCC in the UK.

NCCs are responsible for the conduct of the trial within their own country.

23.2 National Coordinating Centres (NCCs)

The Coordinating Sponsor has delegated the set-up, management and analysis of the trial to the UK Coordinating Centre. The role of the UK Coordinating Centre is assumed by the CRCTU, University of Birmingham. The trial will be set-up, managed and analysed in the UK in accordance with CRCTU standard policy and procedures.

Each NCC (see the introductory pages for the list) will manage the trial in accordance with the trial protocol and their standard policy and procedures.

23.3 Trial Management Group

The TMG is composed of the Chief Investigator, co-investigators, representatives from each NCC, biology and pathology committee and the trial team at the CRCTU. The TMG is responsible for the day-to-day running and management of the trial and will meet by teleconference or in person at least every 3 months.

23.4 Trial Steering Committee

The TSC will provide oversight of the trial and provide advice through its independent chair. The TSC will include members of the ChiLTERN External Advisory Board, a patient representative and a sponsor's representative. The Chief Investigator will report to the TSC on behalf of the TMG. The TSC will assume responsibility for the oversight of the trial on behalf of the Coordinating Sponsor. The TSC will meet or hold teleconferences at least once a year during the treatment period, or more often if required.

23.5 Data Monitoring Committee

Analyses will be supplied in confidence by the trial statistician to an independent DMC. In the light of these analyses, and the results of any other relevant trials, the DMC will advise the TSC if, in their view, the randomised comparisons in the PHITT trial have provided **both** (i) "proof beyond reasonable doubt" that for all, or some specific types, of patient, any of the randomised treatments are clearly indicated or contraindicated in terms of a net difference in a major endpoint; **and** (ii) evidence that might be reasonably expected to influence materially the patient management of many clinicians who are already aware of the main results of any other trials. The DMC may also consider recommending stopping or modifying the trial, or part of the trial, if: any issues are identified which might compromise patient safety; the recruitment rate or data quality are unacceptable. The TSC can then decide whether to modify the trial, or to seek additional data. Unless this happens, the TSC, the TMG, the Principal investigators, the study participants and all trial staff (except those who provide the confidential analyses to the DMC) will remain blind to the interim results of the randomised questions.

The DMC will operate in accordance with a trial specific charter based upon the template created by the Damocles Group. The DMC will meet annually during the recruitment and treatment phases of the trial. Additional meetings may be called if recruitment is much faster than anticipated and the DMC may, at their discretion, request to meet more frequently or continue to meet following completion of recruitment. An emergency meeting may also be convened if a safety issue is identified.

The DMC will report to the TSC via the TMG. The TMG will also convey the findings of the DMC to the Coordinating Sponsor and funders, where applicable.

23.6 Finance

This is an investigator-initiated and investigator-led trial funded by European Union's Horizon 2020 research and innovation programme.
No payment will be made to investigators, patients or other third parties from this funding.

23.7 NIHR CRN Portfolio

The PHITT trial is a National Institute for Health Research (NIHR) Clinical Research Network (CRN) Portfolio study (UK).

24. ETHICAL CONSIDERATIONS

The accepted basis for the conduct of clinical trials in humans is founded on the protection of human rights and the dignity of human beings with regard to the application of biology and medicine, and requires compliance with the principles of GCP and detailed guidelines in line with those principles (Directive 2001/20/EC (2) and Directive 2005/28/EC (1)).

GCP is a set of internationally recognised ethical and scientific quality requirements which must be observed for designing, conducting, recording and reporting clinical trials that involve the participation of human subjects. Compliance with GCP provides assurance that the rights, safety and well-being of trial subjects are protected, and that the results of the clinical trials are credible (Article 1 (2) of Directive 2001/20/EC).

The NCCs and Investigators shall consider all relevant guidance with respect to commencing and conducting a clinical trial (Article 4 of Directive 2005/28/EC).

The conduct of the trial shall be based on the following international ethical and statutory sources:

- The **WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects**
- If the region has adopted the Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: **Convention on Human Rights and Biomedicine** (CETS No.: 164)
- **Directive 2001/20/EC** of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on

medicinal products for human use (Official Journal L21, 01/05/2001 P. 0034 – 0044) and detailed guidance.

- **Directive 2005/28/EC** of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products (Official Journal L 91, 09/04/2005 P. 0013 – 0019).
- **Directive 95/46/EC** of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data **(**Official Journal L 281 , 23/11/1995 P. 0031 – 0050).
- Scientific guidelines relating to the quality, safety and efficacy of medicinal products for human use, as agreed upon by the CHMP and published by the Agency, as well as the other pharmaceutical Community guidelines published by the Commission in the different volumes of the rules governing medicinal products in the European Community (Directive 2005/28/EC (9)).

It is the responsibility of the Principal Investigator to ensure that all subsequent amendments gain the necessary local site specific approval. This does not affect the individual clinicians' responsibility to take immediate action if thought necessary to protect the health and interest of individual patients.

25. CONFIDENTIALITY AND DATA PROTECTION

Personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the relevant data protection legislation in the member state. Patients will be identified using only their unique trial number in correspondence between the applicable NCC and participating sites. However, if local regulation/guidance permits patients are asked to give permission for the applicable NCC to be sent a copy of their signed ICF which will not be anonymised. This will be used to perform in-house monitoring of the consent process.

The Investigator must maintain documents not for submission to the applicable NCC (e.g. patient identification logs) in strict confidence. In the case of specific issues and/or queries from the regulatory authorities, it will be necessary to have access to the complete trial records, provided that patient confidentiality is protected.

The NCCs will maintain the confidentiality of all patients' data and will not disclose information by which patients may be identified to any third party other than those directly involved in the treatment of the patient and organisations for which the patient has given explicit consent for data transfer. Representatives of the PHITT trial research team may be required to have access to patients' medical records for quality assurance purposes but patients should be reassured that their confidentiality will be respected at all times.

26. INSURANCE AND INDEMNITY

University of Birmingham employees are indemnified by the University insurers for negligent harm caused by the design or co-ordination of the clinical trials they undertake whilst in the University's employment.

The University of Birmingham cannot offer indemnity for non-negligent harm. The University of Birmingham is independent of any pharmaceutical company and, as such, it is not covered by the Association of the British Pharmaceutical Industry (ABPI) guidelines for patient compensation.

27. PUBLICATION POLICY

Results of this trial will be submitted for publication in peer reviewed journals. The manuscripts will be prepared by the TMG and authorship will be determined by mutual agreement.

The first publication of the results of this study shall be made as a joint multi-centre publication under the lead of the UK Coordinating Centre at the CRCTU and the Chief Investigator. Any secondary publications and presentations prepared by Investigators must be reviewed and approved by the TMG. Manuscripts must be submitted to the TMG in a timely fashion and in advance of being submitted for publication to allow time for review, resolution of any outstanding issues and approval. Authors must acknowledge that the trial was performed with the support of the University of Birmingham and where applicable other NCCs. Intellectual property rights will be addressed in the agreements between the NCCs and the clinical study site agreement (or country specific equivalent) between the NCCs and sites.

Individual NCCs will be allowed to publish their efficacy results. However, the publication of efficacy results from the whole trial will precede efficacy result publications of individual countries, unless the TMG decides otherwise.

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APPENDIX 1 - WMA DECLARATION OF HELSINKI

Please refer to:
www.wma.net/en/20activities/10ethics/10helsinki/index.html

APPENDIX 2 - DEFINITION OF ADVERSE EVENTS

Adverse Event (AE)

Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

Comment:

An AE can therefore be any unfavourable and unintended sign (including abnormal laboratory findings), symptom or disease temporally associated with the use of an investigational medicinal product, whether or not related to the investigational medicinal product.

Adverse Reaction (AR)

All untoward and unintended responses to an IMP related to any dose administered.

Comment:

An AE judged by either the reporting Investigator or Sponsor as having causal relationship to the IMP qualifies as an AR. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

Serious Adverse Event (SAE)

Any untoward medical occurrence or effect that at any dose:

- Results in death
- Is life-threatening*
- Requires hospitalisation** or prolongation of existing inpatients' hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly/birth defect
- Or is otherwise considered medically significant by the Investigator***

Comments:

The term severe is often used to describe the intensity (severity) of a specific event. This is not the same as serious, which is based on patients/event outcome or action criteria.

* Life threatening in the definition of an SAE refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

**Hospitalisation is defined as an unplanned, formal inpatient admission, even if the hospitalisation is a precautionary measure for continued observation. Thus, hospitalisation for protocol treatment (e.g. line insertion), elective procedures (unless brought forward because of worsening symptoms), or for social reasons (e.g. respite care), are not regarded as an SAE.

*** Medical judgment should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should be considered serious.

Serious Adverse Reaction (SAR)

An Adverse Reaction which also meets the definition of a Serious Adverse Event.

Suspected Unexpected Serious Adverse Reaction (SUSAR)

A SAR that is unexpected i.e. the nature, or severity of the event is not consistent with the Reference Safety Information.

A SUSAR should meet the definition of an AR, UAR and SAR.

Unexpected Adverse Reaction (UAR)

An AR, the nature or severity of which is not consistent with the Reference Safety Information.

When the outcome of an AR is not consistent with the Reference Safety Information the AR should be considered unexpected.

APPENDIX 3 – COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS

Toxicities will be recorded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4. The full CTCAE document is available on the National Cancer Institute (NCI) website, the following address was correct when this version of the protocol was approved:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

APPENDIX 4 – PRETEXT

For full paper see 2017 PRETEXT: radiologic staging system for primary hepatic malignancies of childhood revised for the Paediatric Hepatic International Tumour Trial (PHITT)[47].

The PRETEXT system was initially designed by the International Childhood Liver Tumour Strategy Group (SIOPEL) for staging and risk stratification in liver tumours. The intention was to develop a system that could be used to describe tumour extent based upon radiographic imaging, before any therapy (Aronson 2005, Roebuck 2007, Meyers 2014). The PRETEXT Groups (I, II, III, and IV) have not changed over time. The group assignment is dependent upon an understanding of hepatic segmental anatomy and defines the number of contiguous tumour free sections. A POST-TEXT group assignment defines the number of contiguous tumour free sections after chemotherapy and before surgical resection. Unlike the group assignment, the PRETEXT annotation factors define caudate and extraparenchymal tumour involvement. Initially just V, P, E, M, these annotation factors have evolved over time and in the PHITT study will include V, P, E, F, R, C, N, M. Definitions are described in detail below.

Hepatic Segmental Anatomy

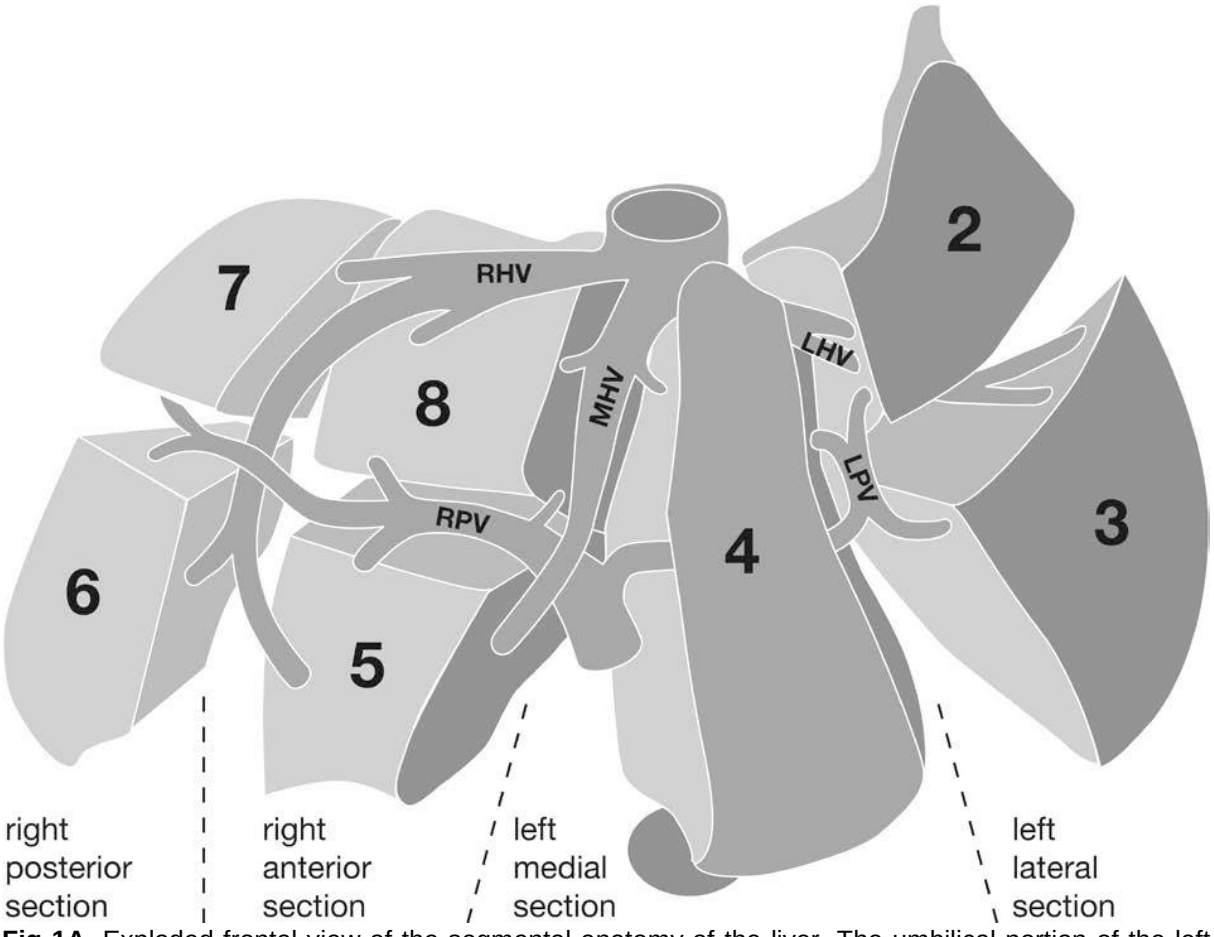


Fig 1A. Exploded frontal view of the segmental anatomy of the liver. The umbilical portion of the left portal vein (LPV) separates the left medial section (LMS) from the left lateral section (LLS). Segment 1 is obscured in this view. Couinaud segments are denoted 1-8; Sections as left lateral, left medial, right anterior and right posterior. Hemiliver as either right or left.

The Brisbane nomenclature of segmental hepatic anatomy denotes a hierarchy of Hemi-Liver > Liver Sections > Couinaud segments. (Strasburg 2005) The eight Couinaud *segments* are grouped into four liver *sections* as follows: segments 2 and 3 (left lateral section), segments 4a and 4b (left medial section), segments 5 and 8 (right anterior section) and segments 6 and 7 (right posterior section).

(Figure 1A). Caudate (segment 1) involvement when present is denoted as an annotation factor "C" discussed below. The traditional approach to radiological segmentation of the liver, based on the paths of the hepatic veins, is an oversimplification. This is partly due to the variability of hepatic venous anatomy (Roebuck 2007). For PRETEXT group determination, the hepatic veins and portal veins divide the liver into its four sections: left lateral (Couinaud segments 2 and 3), left medial (segments 4a and 4b), right anterior (segments 5 and 8), and right posterior (segments 6 and 7). The hepatic sections are delineated in the following manner:

• Left lateral/left medial section – The left hepatic sections are delineated by the plane that extends along the hepatic fissure and the umbilical portion of the left portal vein. It should be noted that the left hepatic vein is not used in determining involved sections. Instead, the left hepatic vein separates Couinaud segments 2 and 3.

• Left medial/right anterior section – The right and left lobes are separated by the plane drawn between the middle hepatic vein and the middle of the gall bladder fossa (also referred to as Cantlie's line).

• Right anterior/right posterior section – The right hepatic sections are separated by the course of the right hepatic vein.**(Figure 1B).**

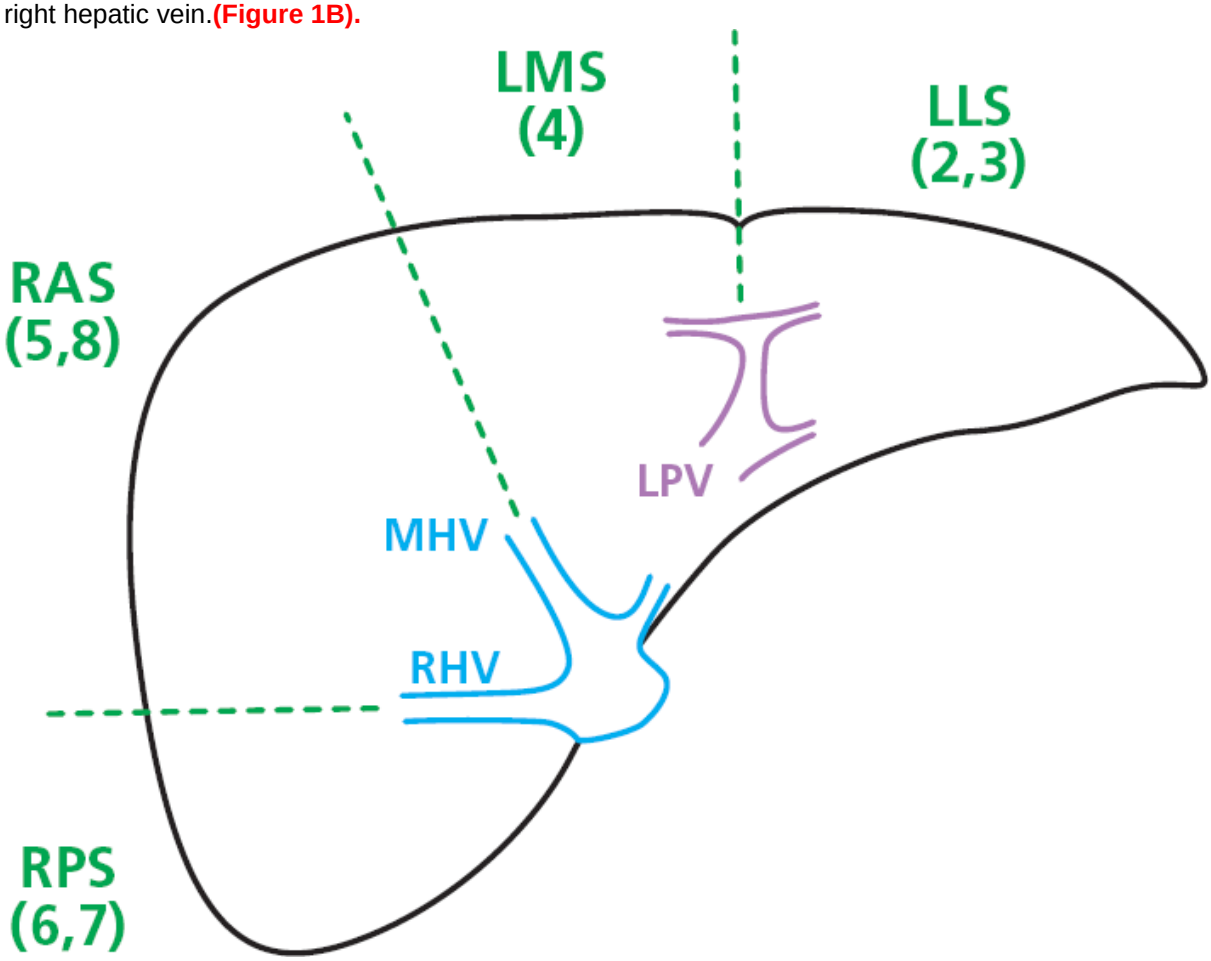


Fig 1B. Transverse section of the liver showing the planes of the major venous structures used to determine the PRETEXT number. The hepatic (blue) and portal (purple) veins define the sections of the liver (Coinaud numerals in parentheses). This schematic diagram shows how the right hepatic (RHV) and middle hepatic (MHV) veins indicate borders of the right posterior (RPS), right anterior (RAS), and left medial (LMS) sections. Note that the left portal vein (LPV) actually lies caudal to the confluence of the hepatic veins and is not seen in the same transverse section on imaging studies. The left hepatic vein (LHV) runs between segments 2 and 3 and is not used to determine the PRETEXT number.

PRETEXT/ POST-TEXT Groups (I, II, III, IV)

When the assessment is completed at diagnosis it is termed PRETEXT (pretreatment extent of tumour). When the assessment is completed after chemotherapy it is termed POST-TEXT (post-

treatment extent of tumour). A summary diagram of PRETEXT, POST-TEXT, Groups, and Annotation Factors (V, P, E, F, R, C, N, M) is shown in **(Figure 2).**

PRETEXT I
PRETEXT I tumors are uncommon and are typically small. By definition, three contiguous hepatic sections must be free of tumor. Therefore, PRETEXT I tumors can only involve either the left lateral or right posterior section.
PRETEXT II
Almost all PRETEXT II tumors are limited either to the right lobe or the left lobe of the liver. They may involve either one or two sections of the liver. If a tumor involves either the left medial or right anterior section only, it is considered a PRETEXT II tumor as either a left or right hepatectomy must be performed in order to resect the mass.
Tumors that only involve the caudate lobe are considered to be PRETEXT II. If the tumor involves other section(s) in addition to the caudate, the PRETEXT determination can be made by accounting for all of the other sections involved with tumor.
PRETEXT III
PRETEXT III tumors involve portions of both the right and left lobes. These tumors involve either two or three sections with only one contiguous section that is tumor free. Central tumors that involve only the left medial AND right anterior section have only one contiguous tumor free section and are considered PRETEXT III by convention.
PRETEXT IV
PRETEXT IV tumor are almost always multifocal or infiltrative. Because it is unlikely for a single mass to affect all four sections, careful assessment should be made before assigning the stage in the absence of the multifocal or infiltrative pattern. Often, in cases where there is an extremely large tumor, one or more sections is being severely compressed. This may be best assessed in the coronal plane.

Figure 2. PRETEXT Groups (I, II, III, IV) and PRETEXT Annotation Factors (V,P,E,F,R,C,N,M)
I

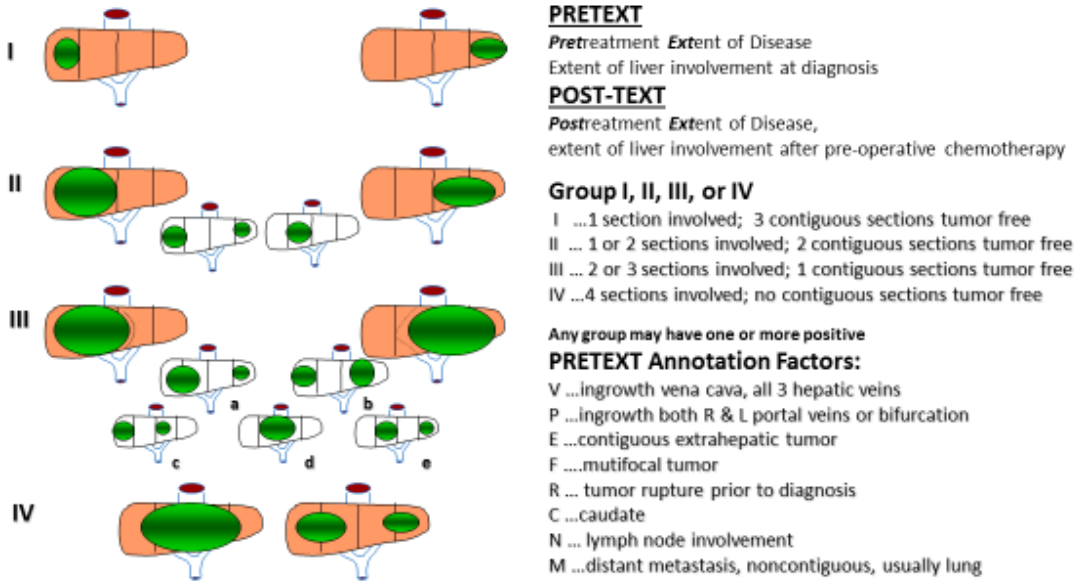


Table 1. PRETEXT group assignments based on the hepatic sections containing tumor. An x in a cell below means that that section of the liver contains tumor. Table 1 can be used as a guide to determine PRETEXT grouping based on the liver sections or Couinaud segments that contain tumor.

Sections affected by tumor					
C	RP	RA	LM	LL	PRETEXT
	x				1
				x	1
	x	x			2
		x			2
			x		2
			x	x	2
x					2
x	x				2
x		x			2
x	x	x			2
x			x		2
x			x	x	2
x				x	2
	x			x	2
	x	x	x		3
		x	x		3
		x	x	x	3
x	x	x	x		3
x		x	x		3
x		x	x	x	3
		x		x	3
	x		x		3
	x		x	x	3
	x	x		x	3
x		x		x	3
x	x			x	3
x	x		x		3
x	x		x	x	3
x	x	x		x	3
x	x	x	x	x	4
	x	x	x	x	4

Section name	Sections	Segment
Caudate	C	1
Left lateral	LL	2
Left lateral	LL	3
Left medial	LM	4a
Left medial	LM	4b
Right anterior	RA	5
Right anterior	RA	8
Right posterior	RP	6
Right posterior	RP	7

PRETEXT Annotatation Factors

The PRETEXT Annotation Factors have been updated for this trial. The new definitions are below. Tumors are considered either V-positive or V-negative. A tumor is said to be V-positive if it meets any of the following criteria:

1. The tumor obliterates (meaning that the lumen is no longer visible) all three first order hepatic veins or the intrahepatic inferior vena cava. It is recognized that failure to identify the lumen on cross-sectional imaging does not imply functional obstruction of the inferior vena cava and the presence of enlarged collateral venous pathways (azygos and/or hemiazygos veins) or clinical signs (e.g. lower body edema) are not required to confirm this finding.
2. The tumor encases (by more than 180 degrees) all three first order hepatic veins or the intrahepatic inferior vena caval.
3. There is tumor thrombus in any one (or more) first order hepatic vein or the intrahepatic inferior vena cava.

If the tumor does not meet any of these criteria, it should be assigned a V-negative.

The following definitions are important to help assess hepatic venous/inferior vena cava involvement:

1. First order hepatic vein – the portion of hepatic vein between its confluence with the inferior vena cava and its most central branch

2. Intrahepatic inferior vena cava – the inferior vena cava is said to be intrahepatic if it is surrounded by >180 degrees by liver parenchyma. Typically, this occurs between the right atrium and the inferior aspect of the caudate.
3. Tumor thrombus – for the purpose of PRETEXT classification, any type of thrombus within a first order hepatic vein or the inferior vena cava should be considered tumor thrombus. Generally, tumor thrombus appears as an expansile, enhancing mass within a vessel on CT or MRI. Color Doppler ultrasound may reveal the presence of small vessels within the thrombus.
Hepatic Vein, IVC, involvement, "V". For the purposes of the treatment assignment as a VPEFR positive or negative tumour, a "Vpositive" tumour will be if all three striped cells are selected or if any one solid-coloured cell is selected (see Figure 3).

Extent of hepatic venous involvement	Right hepatic vien	Middle hepatic vein	Left hepatic vein	Intrahepatic inferior vena cava
Tumour obliterating vein(s) or encasing ≥180 degrees				
Intravascular tumour thrombus				

Portal Vein involvement, "P".
Tumors are either considered either P-negative or P-positive. A tumor is said to be P-positive if it meets any of the following criteria:
1. The tumor obliterates (meaning that the lumen is no longer visible) both first order portal veins or the main portal vein.
2. The tumor encases (by more than 180 degrees) both first order portal veins or the main portal vein.
3. There is tumor thrombus in either or both the right or left portal veins or the main portal vein.
If the tumor does not meet any of these criteria, it should be assigned a P-negative.
The following definitions are important to help assess portal venous involvement:
1. First order portal vein – a portal vein is said to be involved by tumor if the tumor is affecting the vessel between the bifurcation of the main portal vein and the first major branch of the vein.
2. Tumor thrombus – for the purpose of PRETEXT classification, any type of thrombus within either the right or left portal vein or the main portal vein should be considered tumor thrombus. Cavernous transformation should be considered as evidence of tumor thrombus.
Table 3. Portal vein involvement (P). A tumor is considered P-positive if both striped cells are selected or if any one solid-colored cell is selected.

Extent of portal venous involvement	Right portal vien	Left portal vein	Main portal vein
Tumour obliterating vein(s) or encasing ≥180 degrees			
Intravascular tumour thrombus			

Contiguous Extrahepatic Tumor, "E".
Diagnosis of contiguous extrahepatic disease remains difficult. Frequently, a large tumor is seen to abut the diaphragm or abdominal wall causing a loss of the plane between the affected structure and the tumor. Therefore, for extrahepatic disease to be present, one of the following criteria must be met:
1. Tumor is seen to cross boundaries/tissue planes – i.e. tumor is seen both above and below the diaphragm or extending through the abdominal wall.
2. Tumor is seen to be surrounded by normal tissue by > 180 degrees.

3. Peritoneal nodules (not lymph nodes) are present so that there is at least one nodule measuring ≥ 10 mm or two or more nodules measuring ≥ 5 mm.
The following factors are important in the assessment of extrahepatic disease:
1. Ascites – ascites is relatively common in the setting of liver tumors. Simple ascites is not considered extrahepatic disease.
2. Biopsy tracks – it is often difficult to assess for tumor within a biopsy track. In this instance, tumor should not be considered as present unless there is a discreet tumor nodule.

Tumor Multifocality "F"
Tumor multifocality (F) is defined as two or more discrete hepatic tumors with normal liver intervening. At times, this distinction can be difficult. This is most pronounced when there are multiple tumor nodules in close proximity. With tumor shrinkage in the setting of neoadjuvant chemotherapy, it is thus possible for a unifocal tumor to "become multifocal." In this instance the PRETEXT annotation may be unifocal and the POSTTEXT annotation multifocal.

Tumor rupture or intraperitoneal hemorrhage "R".
The new PHITT trial defines tumor rupture (R) as free fluid in the abdomen or pelvis at diagnosis with one or more of the following findings of hemorrhage (Figs 15-16).
1. Internal complexity/septations within fluid.
2. High density fluid on CT (> 25 Hounsfield units).
3. Imaging characteristics of blood or blood degradation products on MRI.
4. Heterogeneous fluid on ultrasound with echogenic debris.
5. Visible rupture/hepatic capsular defect on imaging.
It should be noted that while tumor rupture is most commonly diagnosed via imaging, it can also be diagnosed after laparotomy/laparoscopy or paracentesis. It should be noted that while tumor rupture can be diagnosed at pathology, the timing of this rupture cannot be determined. Therefore, it cannot be assigned as a PRETEXT factor unless upfront surgery is performed (before initiation of chemotherapy). Instead, rupture identified at resection after chemotherapy would be considered a POSTTEXT factor.
The following factors are important in the assessment of tumor rupture:
Biopsy – Hemorrhage related to tumor biopsy is not considered tumor rupture for the purposes of PRETEXT classification.
1. Surgical rupture – surgical rupture is not considered as tumor rupture for the purposes of PRETEXT classification.
2. Ascites – simple (i.e. non-hemorrhagic) ascites is common in the setting of hepatoblastoma and hepatocellular carcinoma. This type of peritoneal free fluid is not considered tumor rupture.
3. Subcapsular fluid – fluid collections beneath the liver capsule, even if hemorrhagic, are not considered to represent tumor rupture.

Caudate lobe tumors "C".
In order to determine if the caudate is truly involved with tumor, it is important to understand the boundaries of the caudate. For the purpose of PRETEXT staging, the caudate is defined as the part of the liver that extends along the posterior surface of the liver between the portal vein and intrahepatic inferior vena cava. The following are used as the borders of the caudate.
1. Right margin – right lateral border of the inferior vena cava.
2. Left margin – ligamentum venosum.
3. Anterior margin – porta hepatis and ligamentum teres.
4. Superior margin – dome of liver.
5. Inferior margin – as liver passes between main portal vein and inferior vena cava.

Lymph node metastases "N".
In young children, traditional diameter-based cutoffs may be problematic as there are no agreed upon standards. Therefore for PRETEXT staging, nodal metastases are considered to be present if one of the following criteria are met (Fig 18):
1. Lymph node with a short axis diameter of > 1 cm or a portocaval lymph node with short axis diameter > 1.5 cm
2. Spherical lymph node shape with loss of fatty hilum.
It should be noted that prior studies have shown that morphologic criteria, such as in criterion 2, are less sensitive for detection of metastases. Therefore, this criterion should be used with some caution. Definitive involvement of lymph nodes is confirmed at histologic examination.

Distant metastases "M".

The lungs are far and away the most common site of distant metastases in patients with hepatoblastoma and hepatocellular carcinoma. Pulmonary metastases are present in 17% of children with hepatoblastoma at diagnosis.1 CT is the imaging modality of choice to diagnose pulmonary metastases and should be performed in all pediatric patients with a liver tumor at the time of diagnosis. The use of intravenous contrast is controversial in this setting. However, many pediatric practices recommend performing at least the first CT with intravenous contrast to better demonstrate hilar vessels and pleural or perihilar nodules. In addition to administering intravenous contrast, the following reconstructed images are recommended in order to improve nodule detection: thin slices (1 mm or less), sliding maximum intensity projection images, and coronal plane images.

In order to qualify as M-positive, a patient must have least one non-calcified pulmonary nodule greater than or equal to 5 mm in diameter; or two or more non-calcified pulmonary nodules, each greater than or equal to 3 mm in diameter. Like tumor rupture, metastases can be diagnosed via pathology. While patients with characteristic imaging findings of pulmonary metastatic disease do not require biopsy, patients with equivocal findings may require biopsy as this finding significantly changes therapy.

While the lungs are far and away the most common site of metastasis in the setting of hepatoblastoma, metastases to other locations can occur. Because these other sites (such as brain or bone) of disease are uncommon, routine imaging beyond chest CT should not be performed in attempt to identify distant metastases. Prior SIOPEL and COG protocols have recommended studies such as bone scan or brain MRI. These imaging studies are no longer recommended unless the patient is symptomatic or there is an unexplained rise in the serum alpha-fetoprotein level.

Table 5

PRETEXT annotation factors E, F, R, C, N and M

Factor	Annotation	Positive definition
Extrahepatic spread of disease	E	Any one of the following criteria is met: 1. Tumor crosses boundaries/tissue planes 2. Tumor is surrounded by normal tissue more than 180° 3. Peritoneal nodules (not lymph nodes) are present so that there is at least 1 nodule measuring 10 mm or larger or at least 2 nodules measuring 5 mm or larger
Multifocality	F	Two or more discrete hepatic tumors with normal intervening liver tissue

Factor	Annotation	Positive definition
Tumor rupture	R	Free fluid in the abdomen or pelvis with one or more of the following findings of hemorrhage 1. Internal complexity/septations within fluid 2. High-density fluid on CT (>25 HU) 3. Imaging characteristics of blood or blood degradation products on MRI 4. Heterogeneous fluid on ultrasound with echogenic debris 5. Visible defect in tumor capsule -OR- Tumor cells are present within the peritoneal fluid -OR- Rupture diagnosed pathologically in patients who have received an upfront resection
Caudate involvement	C	Tumor involving the caudate
Lymph node metastases	N	Any one of the following criteria is met: 1. Lymph node with short-axis diameter of >1 cm 2. Portocaval lymph node with short-axis diameter >1.5 cm 3. Spherical lymph node shape with loss of fatty hilum
Distant metastases	M	Any one of the following criteria is met: 1. One non-calcified pulmonary nodule greater than or equal to 5 mm in diameter 2. Two or more non-calcified pulmonary nodules, each greater than or equal to 3 mm in diameter 3. Pathologically proven metastatic disease

APPENDIX 5 –CHIC-HEPATOBLASTOMA STRATIFICATION

While the COG historically used a surgical based staging system in its trials INT - 0098 and P9645 this evolved into a hybrid risk stratification schema for its current trial, AHEP0731 (Table 2). The SIOPEL, GPOH, and JPLT research consortia have increasingly utilized the Pretreatment Extent of disease (PRETEXT) system for risk stratification. The PRETEXT group assignment (I, II, III, IV) is based on the number of hepatic sections involved by tumour at diagnosis. The group assignment is then further annotated with a V, P, E, M, C, F, R, N depending upon extension of tumour beyond the hepatic parenchyma (Figure 1). Because of the differing systems, direct comparison of results between cooperative group specific trials has been very difficult. To address this issue, the **C**hildhood **H**epatic tumour **I**nternational **C**onsortium (CHIC) group sought to create a dataset of sufficient size to empower robust statistical analysis as a foundation for an internationally cooperative risk stratification system.

Table 1. Post-Surgical based staging system (Evans) used in INT-0098 and COG P9645

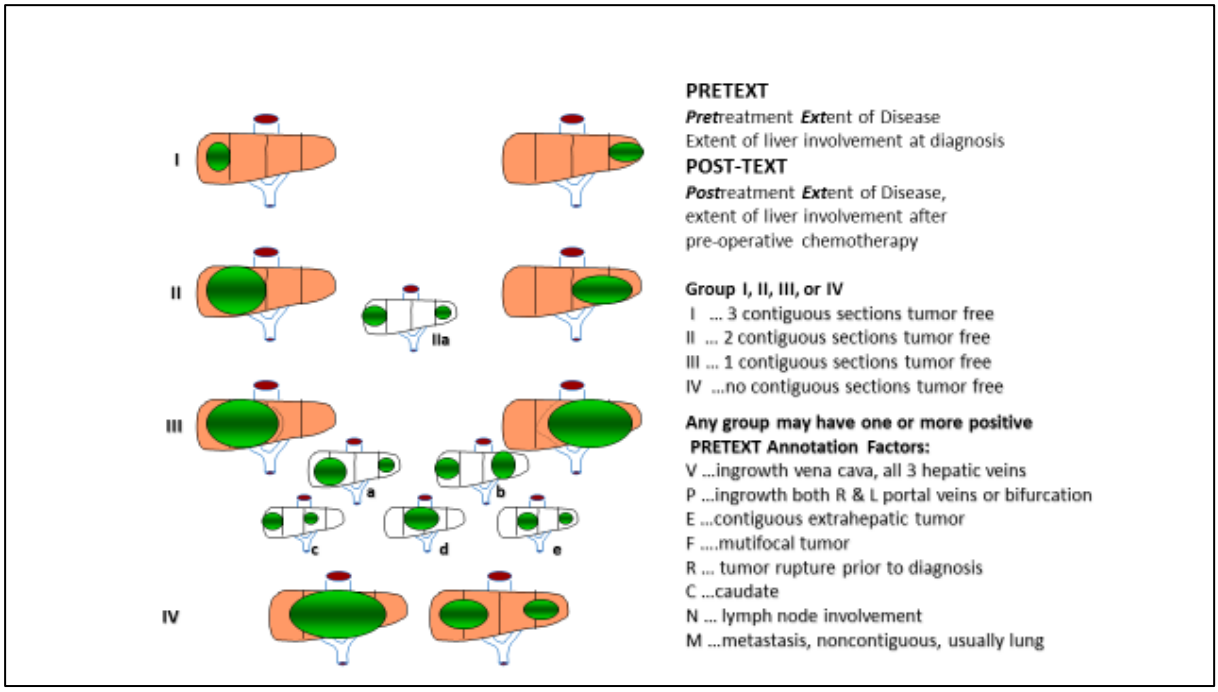
Stage	Surgical Procedure
I	Tumour resected at diagnosis, margins negative
II	Tumour resected at diagnosis, margins microscopic positive
III	Biopsy at diagnosis or gross residual disease after attempted resection
IV	Metastatic disease

Table 2. Hybrid risk stratification based staging system used in COG AHEP-0731

Risk Group	Definition
Very Low risk	Stage I pure fetal histology
Low Risk	Stage I non pure PFH or Stage II non-small cell undifferentiated
Intermediate risk	Stage I or II with small cell undifferentiated or Stage III
High Risk	Stage IV or any stage +initial AFP<100ng/mL

PRETEXT group (Figure 1) has been a robust predictor of outcome in all prior investigations of risk factors, while other risk factors, including the various PRETEXT Annotation Factors, have achieved significance in certain cooperative group studies, while remaining non-significant in others. (Fuchs 2002, Aronson 2005, Meyers 2009, Maibach 2012). Other potential risk factors were postulated, but due to low patient numbers, never achieved statistical significance (Meyers 2009, Maibach 2012). CHIC was created to specifically address this challenge by collecting and combining the data of all four groups in order to gain a dataset with enough statistical power to identify reliable risk factors in HB. The following trials conducted between 1989 and 2008 were included in this database: SIOPEL 2 and 3 from SIOPEL, INT0098 and P9645 from COG, HB 89 and HB 99 from GPOH, JPLT 1 and 2 from JPLT[4-6, 8, 10-15]. Ongoing trials and trials where follow-up was not yet mature, including SIOPEL 4, SIOPEL 6, and COG AHEP0731, could not be included and it is our hope that in the future the results of these most recent trials will be added and interrogated as a validation set of the findings.

Figure 1. Pretreatment Extent of disease (PRETEXT) system



As shown in Table3, several analyses were performed to test the reliability and coherence of the CHIC database. They included analysis per every individual trial registered in the database, as well as per treatment period, to exclude any potential treatment era related bias. Additionally, patients were analyzed according to whether or not a central pathology review was performed as an integral component of the parent study in order to control for the potential influence of an incorrect histopathological diagnosis on outcome. Neither treatment time-period nor central pathologic review appeared to significantly confound our ability to include the data in analysis of the event-free survival (EFS) of other potential prognostic variables.

Table 3: CHIC collaborative dataset - Patient demographics, event status and follow-up

	Reference	N=	Enrollment (mm/yyyy)		Event Status				Median Follow Up[1] (Range; Years)	Number Alive at Last Contact
			Start	End	No Event	Disease	SMN	Death		
HB 89	Von Schweinitz 1995	72	3/1988	10/1993	53	12	0	7	4.7 (1.6-5.7)	56
HB 99	Haeberle 2012	141	1/1999	12/2008	103	28	2	8	5.4 (1.5-10.6)	110
INT 0098	Ortega 2000	170	8/1989	12/1992	108	53	1	8	10.3 (0.9-19.2)	120
JPLT 1	Sasaki 2002	106	12/1990	11/1997	72	27	0	7	5.7 (0.9-16.8)	79
JPLT 2	Hishiki 2011	298	4/1999	12/2010	212	65	3	18	4.0 (0.2-12.5)	243
P9645	Malogolowkin 2006; Katzenstein 2009	277	4/1999	11/2006	190	78	0	9	7.9 (0-11.7)	219
SIOPEL 2	Perilongo 2004	135	11/1995	5/1998	97	26	0	12	7.4 (0.2-9.4)	100
SIOPEL 3	Perilongo 2009	406	7/1998	12/2006	319	75	0	12	5.0 (0.2-10.9)	334
Overall		1605	3/1988	12/2010	1154	364	6	81	5.9 (0-19.2)	1271

[1] For patients without an EFS event.

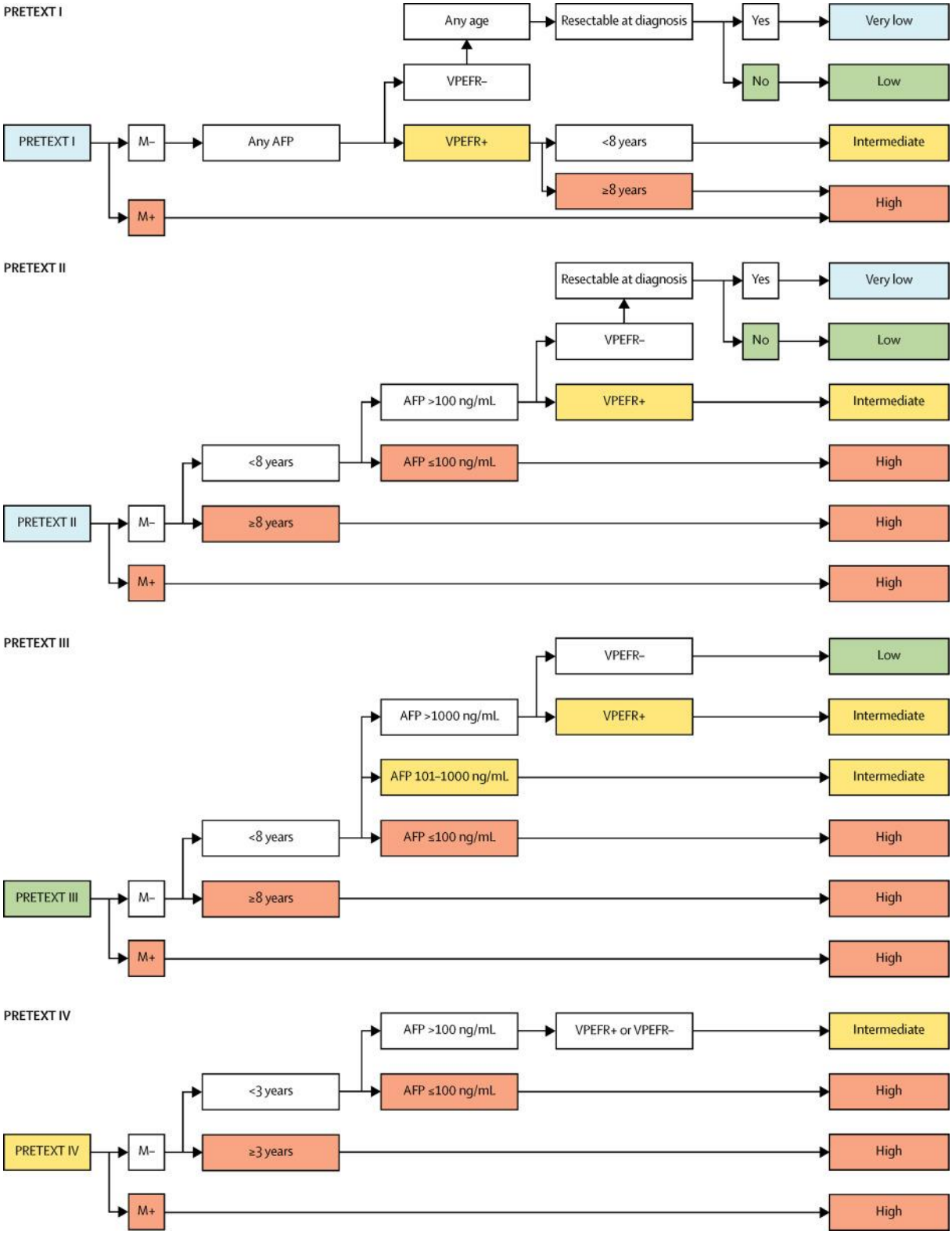
Univariate analysis showed EFS was adversely correlated with advanced PRETEXT group, involvement of the major hepatic inflow (portal vein) and outflow vessels (hepatic veins) (+V and +P), contiguous extrahepatic disease (+E), tumour multifocality (+F), and tumour rupture (+R). Higher age, low AFP and metastatic disease were also associated with inferior outcome. Lower age was associated with superior outcomes and this relationship between age and outcome is an important new finding for this tumour which will be the focus of ongoing analysis of the database.
Initial multivariate analysis using a backwards elimination technique of those factors most significant in the univariate analysis is shown in Table 4. This led to selection of a risk backbone based upon PRETEXT I/II, PRETEXT III, PRETEXT IV, AFP <100, and metastatic disease. Within each of these backbone groups, the presence or absence of the remaining risk factors were further stratified by multivariate estimates of events to determine those constellations of risk factors that were most predictive of event free survival. The results of the initial multivariate analysis had varying breakpoints for different age groups, AFP values, and number of positive PRETEXT annotation factors (V, P, E, F, R). In search of robust simplicity we repeated the backwards elimination analysis using more stringent p-values and confidence intervals. This led to the condensation of meaningful age categories, and simple presence or absence any V, P, E, F, R.

Table 4. EFS Kaplan Meier estimates in risk categories defined by statistical analysis within Hepatoblastoma CHIC database backbone groups

Backbone group	# pts in subgroup	Factor	observed 5 year EFS and 95% conf.int.
1. PRETEXT I/II	365	Age 0-<3	91% (87-93%)
	56	Age 3-7	72% (57-83%)
	19	Age ≥8	40% (18-61%)
2. PRETEXT III	260	AFP>1000, negative VPEFR	89% (85-92%)
	109	AFP>1000, positive VPEFR	73% (64-80%)
	28	AFP≤1000, **+ / -** VPEFR	61% (40-76%)
3. PRETEXT IV	51	Age<3, negative VPEFR	84% (70-92%)
	76	Age<3, positive VPEFR	56% (44-67%)
	20	age3-7, **+ / -** VPEFR	40% (19-61%)
	14	Age ≥8, **+ / -** VPEFR	31% (10-65%)
4. Metastatic	183	AFP>1000	47% (40-55%)
	17	100<AFP≤1000	18% (4-38%)
5. AFP≤100	65	---	35% (24-47%)

Validation was done utilizing a statistical “bootstrapping” technique (Frazier 2015). This process was based on merging aspects of clinical relevance and statistical significance and took place in a series of discussions between clinicians and statisticians. We took into account not only statistical significance, but also the need to guide treatment in a clinically feasible way, the potential ease of application by clinicians of all backgrounds, and the need to create treatment groups of a size that are amenable to study in clinical trials. The results of these discussions yield a PRETEXT based series of four classification trees shown in Figure 2.

Figure 2 - Risk stratification trees for the Children's Hepatic tumors International Collaboration—Hepatoblastoma Stratification (CHIC-HS)



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APPENDIX 6 – BOSTON OTOTOXICITY SCALE

Platinum-Induced Ototoxicity in Children: A Consensus Review on Mechanisms, Predisposition, and Protection, Including a New International Society of Pediatric Oncology Boston Ototoxicity Scale

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Purpose
The platinum chemotherapy agents cisplatin and carboplatin are widely used in the treatment of adult and pediatric cancers. Cisplatin causes hearing loss in at least 60% of pediatric patients. Reducing cisplatin and high-dose carboplatin ototoxicity without reducing efficacy is important.

Patients and Methods
This review summarizes recommendations made at the 42nd Congress of the International Society of Pediatric Oncology (SIOP) in Boston, October 21-24, 2010, reflecting input from international basic scientists, pediatric oncologists, otolaryngologists, oncology nurses, audiologists, and neurosurgeons to develop and advance research and clinical trials for otoprotection.

Results
Platinum initially impairs hearing in the high frequencies and progresses to lower frequencies with increasing cumulative dose. Genes involved in drug transport, metabolism, and DNA repair regulate platinum toxicities. Otoprotection can be achieved by acting on several these pathways and generally involves antioxidant thiol agents. Otoprotection is a strategy being explored to decrease hearing loss while maintaining dose intensity or allowing dose escalation, but it has the potential to interfere with tumoricidal effects. Route of administration and optimal timing relative to platinum therapy are critical issues. In addition, international standards for grading and comparing ototoxicity are essential to the success of prospective pediatric trials aimed at reducing platinum-induced hearing loss.

Conclusion
Collaborative prospective basic and clinical trial research is needed to reduce the incidence of irreversible platinum-induced hearing loss, and optimize cancer control. Wide use of the new internationally agreed-on SIOP Boston ototoxicity scale in current and future otoprotection trials should help facilitate this goal.

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Ototoxicity Grades and Classification

Numerous ototoxicity criteria or grading systems have been developed and used to classify hearing loss in children, but in the clinical trial setting, uniformity is essential. There are currently two main types of ototoxicity assessment criteria: (1) those that rely on change of hearing from baseline, including WHO Common Toxicity Criteria,[69] National Cancer Institute Common Toxicity Criteria for Adverse Events (CTCAE),[70] protocol criteria from Children's Cancer Group A9961 (CCG-A9961; phase III intergroup average-risk medulloblastoma protocol[71]), and the Children's Hospital Boston (CHB) scale[72]), and (2) those specifically written for children that measure absolute hearing levels, including Brock et al[7] and Chang and Chinosornvatana[73] (hereafter Brock and Chang), and the new SIOP Boston scale proposed in this article. The new scale detailed in Table 2, which all participants agreed on, combines the best elements from all the assessment criteria. This new scale will make it possible to compare clinical trial outcomes world-wide.

Classification of ototoxicity in children should be objective, sensitive, reliable, valid, functionally relevant, applicable to results obtained at any age, and simple to understand and describe. The primary intent of any scale will depend on whether its purpose is to guide treatment decisions, identify ototoxicity at the soonest possible opportunity during treatment, or report the incidence and severity of acquired hearing loss in children at the completion of treatment for comparison of clinical trials. The SIOP scale is intended to be used for patients at the end of treatment on a clinical trial (Table 2). It is sensitive to high-frequency hearing losses that result in reduced audibility of the average speech spectrum, and it uses the criteria that correspond to functional outcomes, including the need for audiologic interventions such as hearing aids and other assistive technologies.

Table 2. SIOP Boston Ototoxicity Scale

Grade	Parameters
0	≤ 20 dB HL at all frequencies
1	> 20 dB HL (ie, 25 dB HL or greater) SNHL above 4,000 Hz (ie, 6 or 8 kHz)
2	> 20 dB HL SNHL at 4,000 Hz and above
3	> 20 dB HL SNHL at 2,000 Hz or 3,000 Hz and above
4	> 40 dB HL (ie, 45 dB HL or more) SNHL at 2,000 Hz and above

NOTE. Scale is based on sensorineural hearing thresholds in dB hearing level (HL; bone conduction or air conduction with a normal tympanogram). Bone conduction thresholds are used to determine the grade in the case of abnormal tympanometry and/or suspected conductive or mixed hearing loss. Even when the tympanogram is normal, bone conduction is strongly recommended at the single frequency that is determining the ototoxicity grade to fully confirm that the hearing loss at that frequency is sensorineural. Temporary, fluctuating conductive hearing loss due to middle ear dysfunction or cerumen impaction is common in the pediatric population, and decreases in hearing thresholds that include conductive hearing losses do not reflect ototoxicity to the cochlea.

Abbreviations: SIOP, International Society of Pediatric Oncology; SNHL, sensorineural hearing loss.

The scale was based on a modification of the CHB functional scale,[72] which classifies hearing loss as grade 1, 2, or 3 on the basis of change in hearing threshold of 20 dB or more compared with baseline measures.
The CHB scale was validated by using the Brock scale which, in a multivariate analysis, showed that cisplatin dose was a significant predictor of hearing loss. The CHB scale was favored for its simplicity and objectivity, but two main modifications were recommended. The first was to use absolute hearing levels similar to those of Brock and Chang. The second was to add a grade 4 that was equivalent to Brock and Chang grade 3.
The reason for opting for absolute hearing levels is that, although baseline evaluation is the gold standard for ototoxicity monitoring and obtaining a baseline is recommended for all children who are treated with cisplatin, it has been recognized for many years that a complete and reliable baseline evaluation is not always possible in young children with cancer. Children are often quite sick, they may be fearful in the clinical setting, and attention or cooperation may be limited. When grading is based on change from baseline, audiograms from children without a baseline are not gradable. Furthermore, absolute hearing threshold levels after cessation of treatment, rather than change from baseline, determine whether an individual child has sufficient acoustic access to all of the speech sounds for everyday listening situations, including distance hearing and the ability to understand speech in a noisy environment.
Grade 4 was added, equivalent to Brock and Chang grade 3, to distinguish children who acquire moderate or greater ototoxic hearing loss from those with milder impairment, since there are important functional and clinical differences as the degree of hearing loss increases. A minor modification was to expand grade 3 to include hearing loss greater than 20 dB at 2,000 or 3,000 Hz, since audibility at both 2,000 and 3,000 Hz is critical for speech intelligibility, and loss at either of these frequencies is commonly used as the indication for hearing aids in children.
The SIOP Boston ototoxicity scale is being validated on existing data that include international multicenter audiologic results in very young children treated with cisplatin. Results will be directly compared with existing scales (CTCAE versions 3 and 4; Brock and Chang) to determine whether the SIOP scale better correlates with functional outcomes and offers improved simplicity and inter-rater reliability.
Results will be submitted for future publication and the SIOP scale will be recommended if the study outcomes are positive.

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APPENDIX 7 – RECIST CRITERIA 1.1

The following contains excerpts from the RECIST criteria.
For more information regarding RECIST and a full copy of criteria, go to http://www.eortc.org [49].

Definitions for the modified response evaluation criteria in solid tumours

Measurable lesions

Tumour lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10mm by CT scan (CT scan slice thickness no greater than 5 mm)
- 10mm calliper measurement by clinical exam (lesions which cannot be accurately measured with callipers should be recorded as non-measurable)
- 20mm by chest X-ray

Malignant lymph nodes: To be considered pathologically enlarged *and* measurable, a lymph node must be≥15mm in *short* axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5mm). At baseline and in follow up, only the *short* axis will be measured and followed.

Non-measurable lesions

All other lesions, including small lesions (longest diameter < 10mm or pathological lymph nodes with P10 to < 15mm short axis), as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly, identified by physical exam that is not measurable by reproducible imaging techniques.

Target lesions

When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means in instances where patients have only one or two organ sites involved a maximum of two and four lesions respectively will be recorded). Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

Non-target lesions

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as ‘present’, ‘absent’, or in rare cases ‘unequivocal progression’ (more details to follow). In addition, it is possible to record multiple non target lesions involving the same organ as a single item on the case record form (e.g. ‘multiple enlarged pelvic lymph nodes’ or ‘multiple liver metastases’).

Evaluation of target lesions

- Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
- Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Evaluation of non-target lesions

While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

- Complete Response (CR): Disappearance of all non-target lesions and normalisation of tumour marker level. All lymph nodes must be non-pathological in size (< 10mm short axis).
- Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumour marker level above the normal limits.
- Progressive Disease (PD): Unequivocal progression (see comments below) of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

Evaluation of best overall response

Best response determination in trials where confirmation of complete or partial response IS NOT required: Best response in these trials is defined as the best response across all time points (for example, a patient who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR). When SD is believed to be best response, it must also meet the protocol specified minimum time from baseline.

If the minimum time is not met when SD is otherwise the best time point response, the patient's best response depends on the subsequent assessments. For example, a patient who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same patient lost to follow-up after the first SD assessment would be considered inevaluable.

Time point response: patients with target (+/- non target) disease:

Target lesions	***Non-target lesions***	***New lesions***	***Overall response***
CR	CR	No	CR
CR	Non CR/non PD	No	PR
CR	Not evaluated	No	PR
PR	Non PD or not all evaluated	No	PR
SD	Non PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Time point response: patients with non target disease only:

Non target lesions	*New lesions*	*Overall response*
CR	No	CR
Non CR/non PD	No	Non CR/non PD
Not all evaluated	No	NE
Unequivocal PD	Yes or no	PD
Any	Yes	PD

CR (complete response), PD (progressive disease) and NE (inevaluable). A ‘non CR/non PD’ is preferred over ‘stable disease’ for non target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

APPENDIX 8 – HEPATOBLASTOMA RESPONSE CRITERIA

CRITERIA FOR ASSESSMENT OF TUMOUR RESPONSE IN HEPATOBLASTOMA

Complete response (CR): As definition in RECIST 1.1 criteria (Appendix 7) and normal serum AFP value (for age).

Partial response (PR): As definition in RECIST 1.1 criteria (Appendix 7) and a decreasing serum AFP value, > 1 log (90% reduction) below the original measurement, or no radiological evidence of disease (CR) but abnormal serum AFP value (for age).

Stable disease (SD): As definition in RECIST 1.1 criteria (Appendix 7) or a decreasing serum AFP value, < 1 log (90% reduction), even without clinical (physical and/or radiological) evidence of tumour re-growth.

Progressive disease (PD): As definition in RECIST 1.1 criteria (Appendix 7) or an increase of the serum AFP concentration (three successive 1-2 weekly determinations) even without clinical (physical and/or radiological) evidence of tumour re-growth.

Please note:

- Bear in mind that "no change" or even an increase in "tumour" volume, especially during the first few weeks of chemotherapy, may be the consequence of intra-tumoural haemorrhage/oedema. If serum AFP is falling, continue the same chemotherapy for at least one more course.
- “Tumour lysis syndrome" may lead to an initial rise in AFP before the level falls.
- Sometimes the actual tumour volume does not change in response to therapy, but the AFP decreases; this would not necessarily require a change of therapy.
- The rate of decline of AFP has not been shown to be of prognostic value

APPENDIX 9 – SURGICAL IMAGING GUIDELINES

Please refer to www.siopel.org for the current advice.