AHEP 1531

Pediatric Hepatic Malignancy International Therapeutic Trial (PHITT)

A Phase 2/3 Study

An Intergroup Study by Société Internationale d'Oncologie Pédiatrique (SIOPEL) in collaboration with COG and the Japanese Children's Cancer Group (JCCG)

Coordinating Center: Cancer Research UK Clinical Trials Unit (CRCTU), University of Birmingham

JANUARY 31, 2022

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FOR NOW, FOR LIFE.

Background

The pediatric hepatic malignancies hepatoblastoma (HB) and hepatocellular carcinoma (HCC) account for 1% of malignant tumors in children with an incidence that has been increasing.

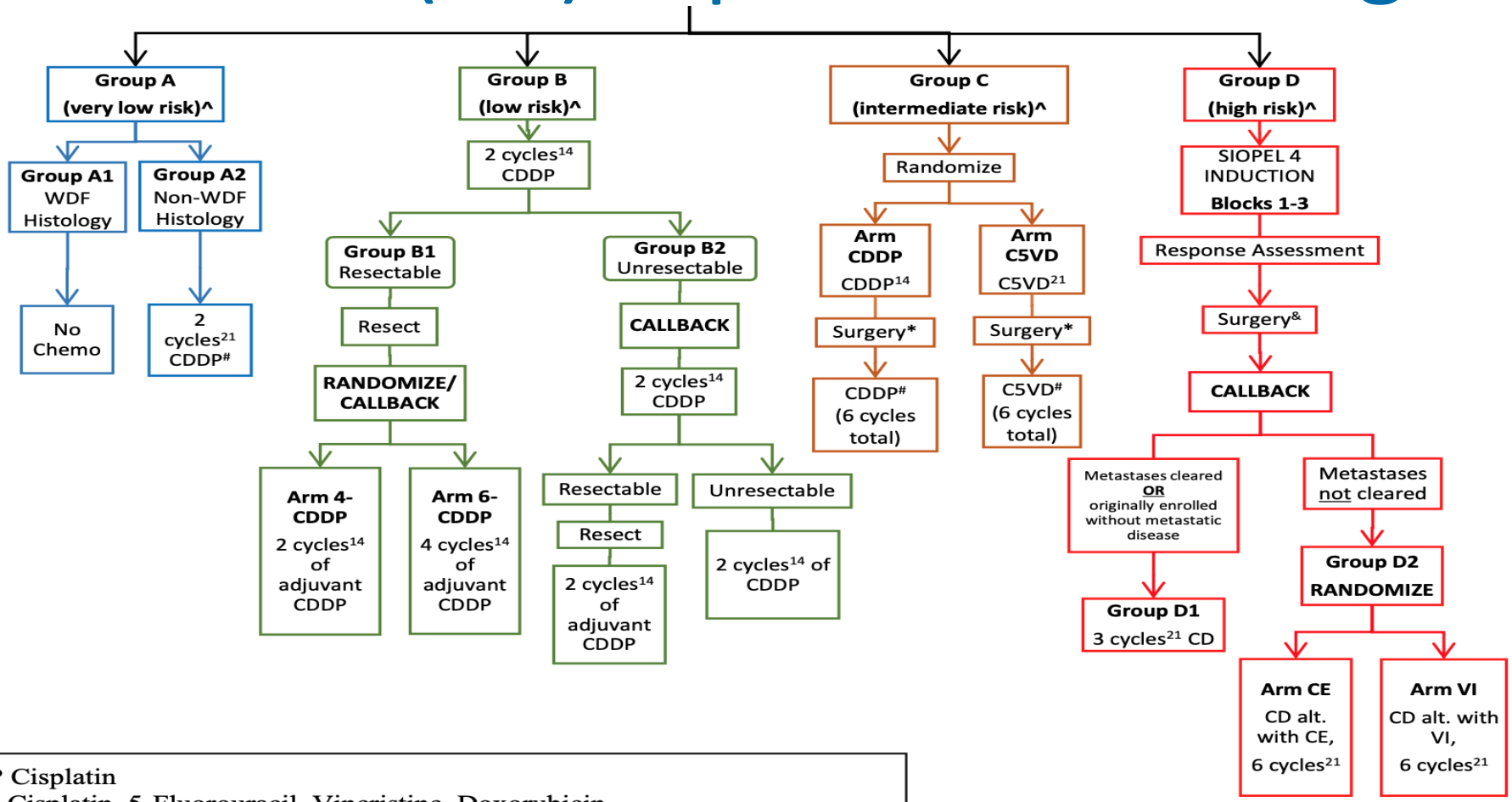
Depending on presentation and risk factors, the 5 year overall survival (OS) for children with HB ranges from 53-100%.

Among those cured, current treatment regimens have significant toxicities including cisplatin induced ototoxicity and renal toxicity and doxorubicin induced cardiomyopathy and secondary leukemia.

AHEP 1531: Primary Aim

- To reduce therapy associated toxicity for patients with non-metastic hepatoblastoma (HB) and hepatocellular carcinoma (HCC) without adversely affecting long term outcomes
- To improve the EFS of patients with High Risk HB (Group D) by treating them with interval compressed cisplatin and doxorubicin based induction regimen followed by response-adapted consolidation therapy
- To determine whether the addition of gemcitabine and oxaliplatin (GEMOX + sorafenib) to a cisplatin, doxorubicin and sorafenib backbone improves chemotherapy response, resectability and survival in patients diagnosed with unresectable/metastatic HCC (Group F)

Hepatoblastoma (HB) Experimental Design



CDDP Cisplatin
C5VD Cisplatin, 5-Fluorouracil, Vincristine, Doxorubicin
SIOPEL 4 Induction Cisplatin, Doxorubicin
CD Carboplatin/Doxorubicin
CE Carboplatin/Etoposide
VI Vincristine/Irinotecan
WDF Well-Differentiated Fetal histology

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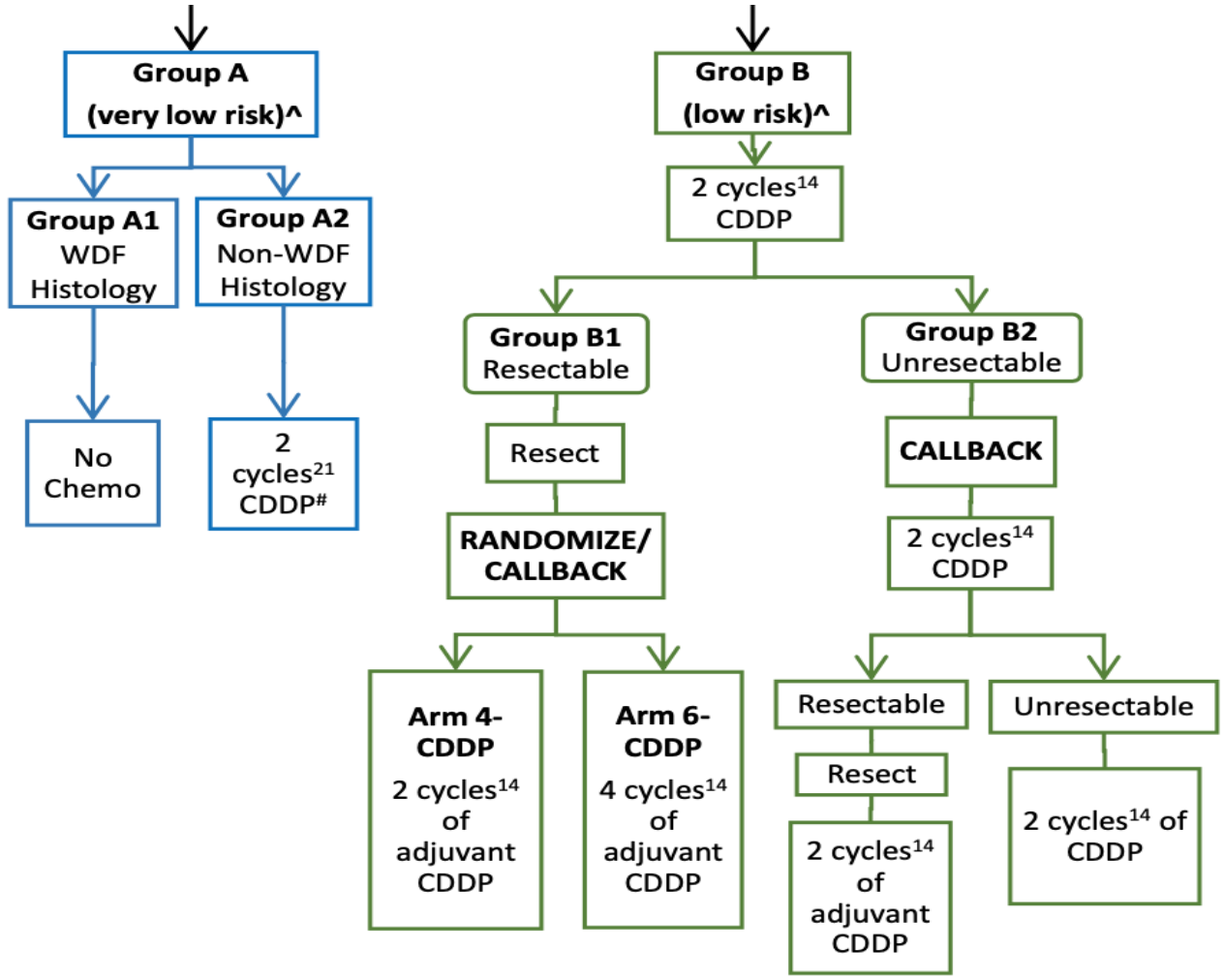
HB Design – Group A & B

Group A: Very Low Risk
- Resected without pre-treatment chemotherapy
- Group A1 with WDF receives no chemotherapy
- Group A2 with Non-WDF will receive 2 cycles of cisplatin chemotherapy (CDDP)

Group B: Low Risk
- All patients will receive 2 cycles of cisplatin
- For patients with resectable disease (Group B1), they will be randomized to receive 2 vs 4 post op cycles of cisplatin
- For patients whose tumors are not resectable (Group B2), a total of 6 cycles of cisplatin will be administered with resection after the fourth cycle

Satellite Clinics can support weekly CBC/Lytes.



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HB Design – Group C & D

Group C: Intermediate Risk

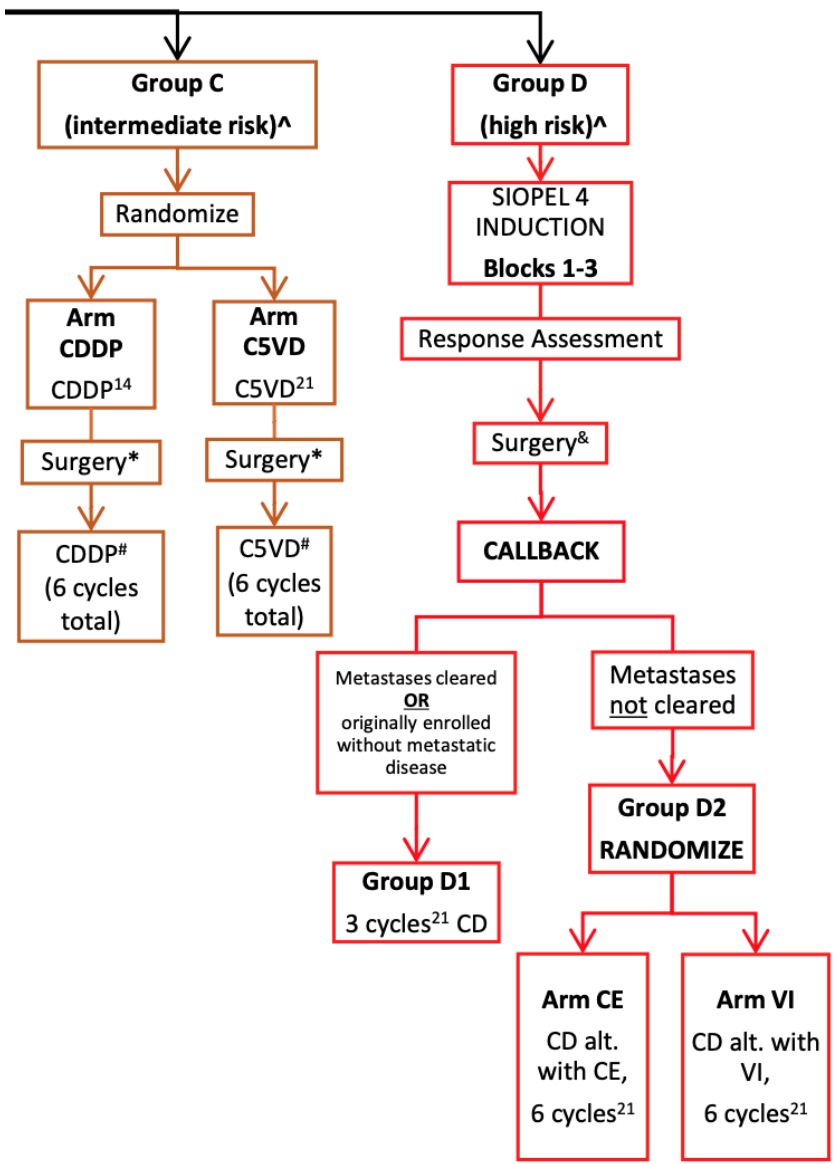
- Patients with locally advanced, non-metastatic tumours will be randomized to one of 2 chemotherapy arms:
  - Arm C5VD – Cisplatin, 5-fluorouracil, Vincristine, Doxorubicin
  - Arm CDDP – interval compressed Cisplatin monotherapy

Group D: High Risk

- Patients receive SIOPEL 4 induction (Cisplatin/Doxorubicin)
- Favourable responders (Group D1) will receive 3 cycles of Carboplatin/Doxorubicin
- Unfavourable responders (Group D2) will be randomized to:
  Arm CE – Carboplatin/Doxorubcin & Carboplatin/Etoposide
  or Arm VI – Carboplatin/Doxorubin & Vincristine/Irinotecan

Satellite Clinics may support

- weekly CBC/Lytes,
- Vincristine and Irinotecan (VI)
- Carboplatin and Doxorubicin (with Dexrazoxane)
- Caroboplatin and Etoposide (CE)



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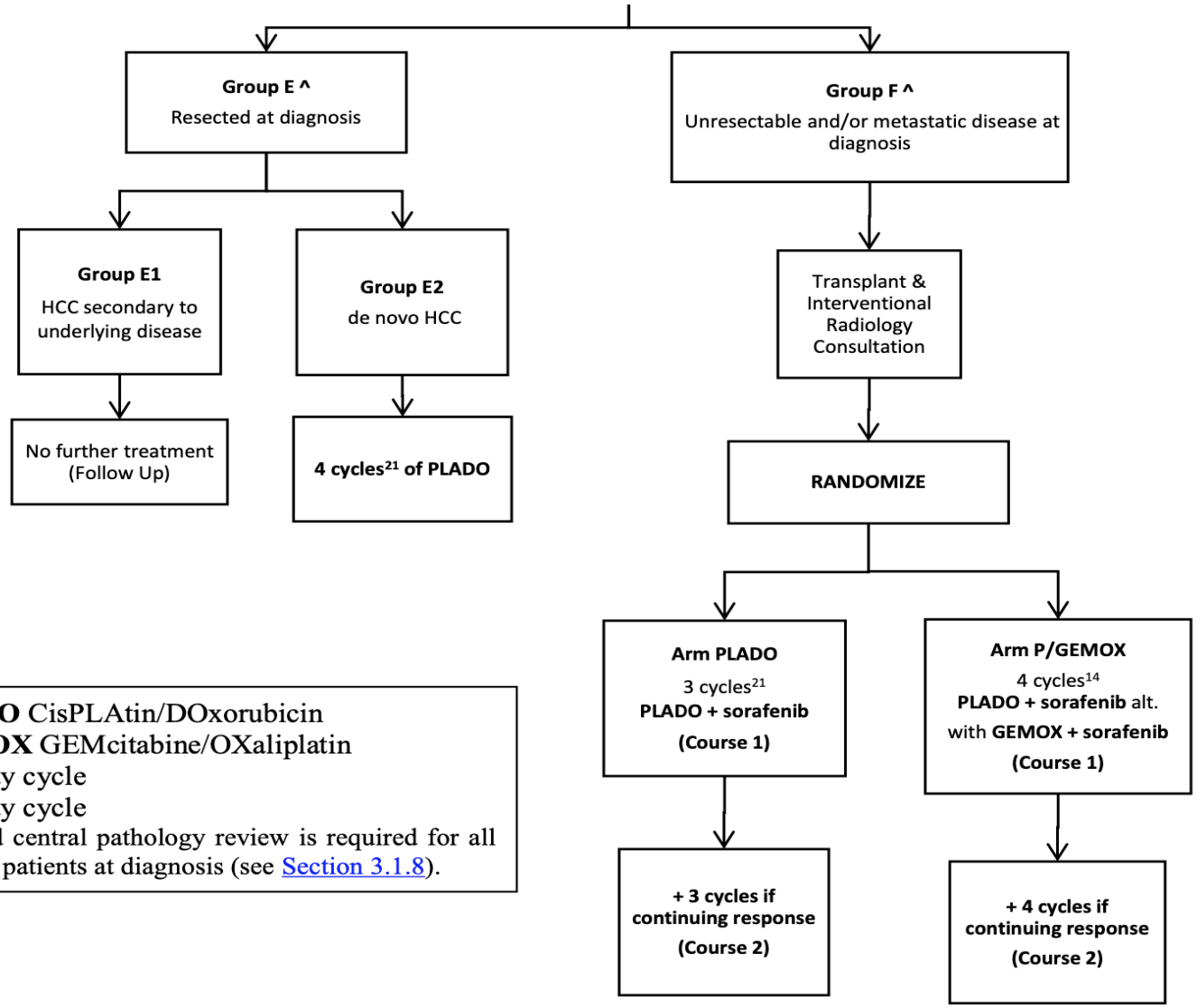
Hepatocellular Carcinoma (HCC) Experimental Design



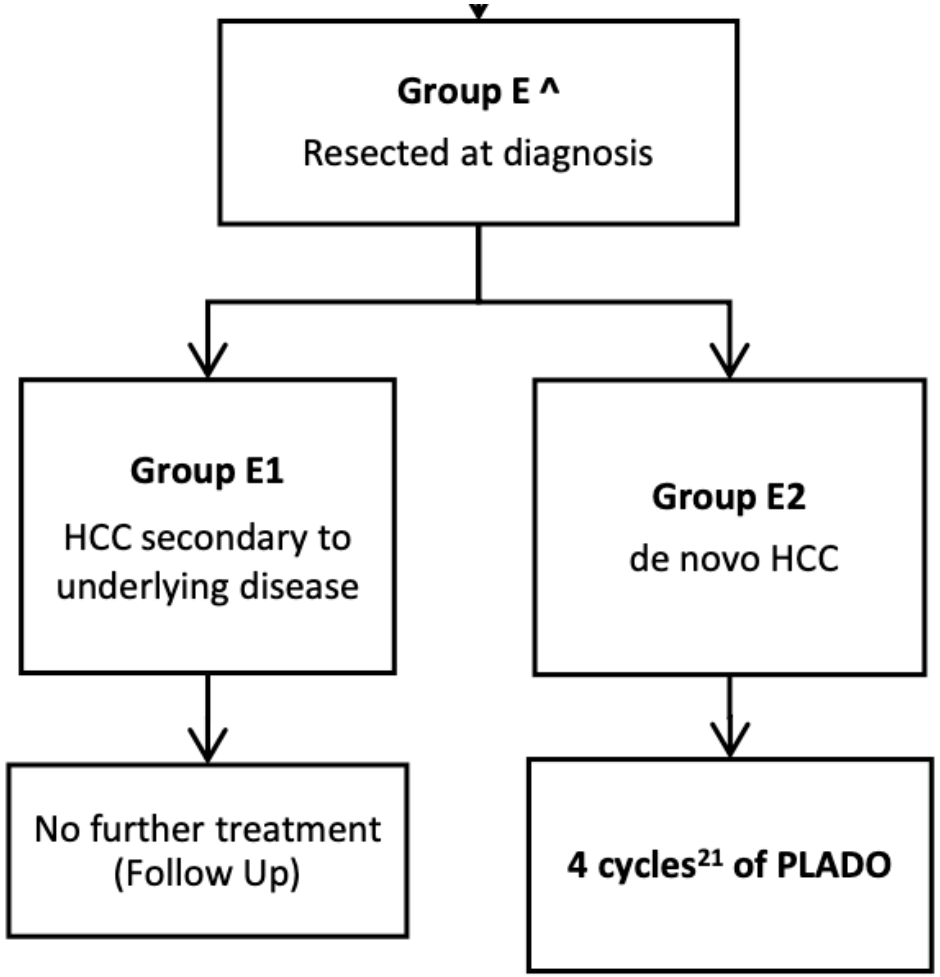
PLADO CisPLAtin/DOxorubicin
GEMOX GEMcitabine/OXaliplatin
[21]21 day cycle
[14]14 day cycle
^ Rapid central pathology review is required for all HCC patients at diagnosis (see Section 3.1.8).

HCC Design – Group E

Group E are those patients with HCC resected at diagnosis.

- Group E1 are patients who have an underlying predisposition to HCC will receive no adjuvant chemotherapy

- Group E2 are patients with de novo HCC. This group will receive 4 cycles of PLADO chemotherapy



PLADO CisPLAtin/DOxorubicin
GEMOX GEMcitabine/OXaliplatin

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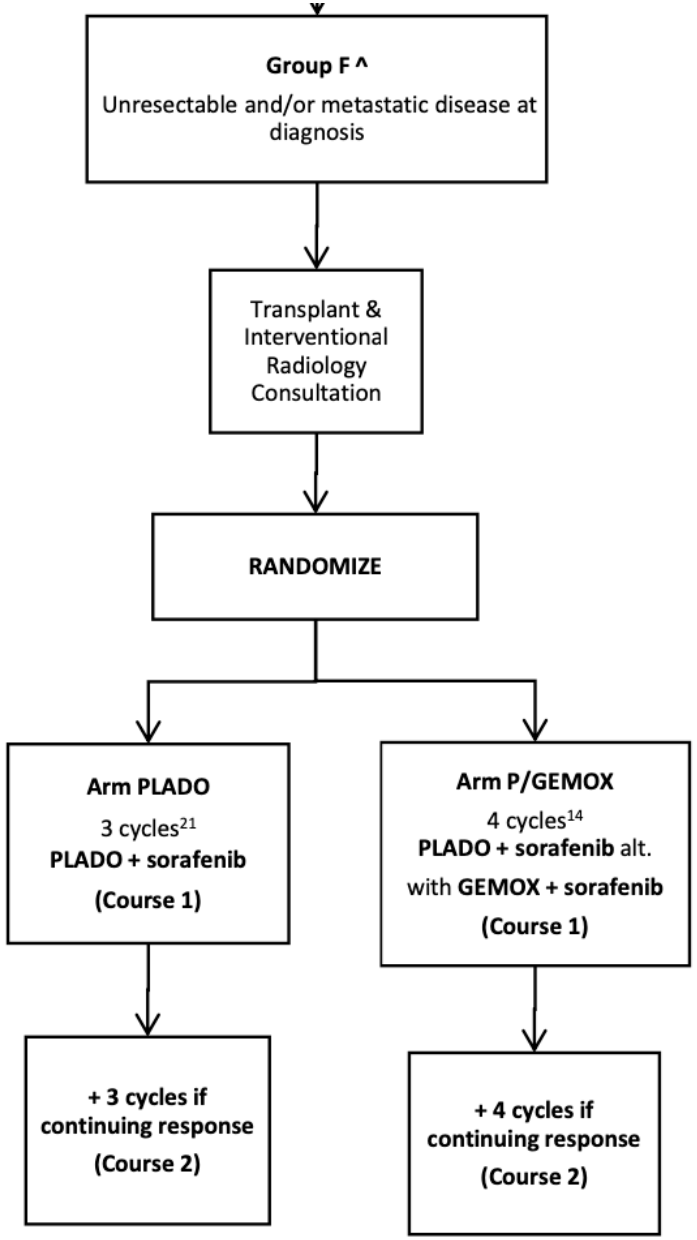
HCC Design – Group F

Patients with unresected and/or metastatic HCC at diagnosis are randomized to the following groups:

Group F, Arm PLADO
- PLADO + sorafenib every 21 days

Group F, Arm P/GEMOX
- PLADO + sorafenib alternating with GEMOX + sorafenib every 14 days

Satellite Clinics can support
- weekly CBC/Lytes and supportive care
- Primary assessment of sorafenib toxicity



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Sorafenib

- Sorafenib is a multikinase enzyme inhibitor that decreases cell proliferation in vitro
- Used in Pediatric AML (FLT3 ITD Variant) and HCC
- It blocks Raf kinase and inhibits tumour angiogenesis by blocking activation of involved receptor tyrosine kinases
- (https://www.cancercareontario.ca/en/drugformulary/drugs/SORAfenib)

Sorafenib toxicities

Common (>20% of patients)	Occasional (4-20% of patients)	Rare
• Anemia • Pain • Diarrhea • Nausea • Tiredness • Bruising, bleeding • Weight loss, loss of appetite • Infection • Hair loss, **rash** • **Redness, pain or peeling of palms and soles**	• **High blood pressure** • Chest pain • Ascites • Constipation, vomiting • Bleeding from multiple sites • Internal bleeding • Sores in the mouth • Swelling of arms, legs • Fever • Dizziness, headache • Difficulty sleeping • Kidney damage • Cough, shortness of breath • Changes in voice • Dry skin, itching	• Heart failure • Liver damage • Allergic Reaction • Non-healing surgical site • Change in the heart rhythm • Bleeding in the brain • Brain damage • Gastrointestinal perforation • Blood clot • Severe skin rash

Sorafenib – When to Administer

- Sorafenib will be administered BID on Days 3-21 (Arm PLADO) or Days 3-14 (Arm P/GEMOX).
  - It is administered on an empty stomach (1 hour before or 2 hours after eating)
  - Drinking grapefruit juice or eating grapefruits should be avoided for the duration of treatment
- If patients are admitted for Fever and Neutropenia or other complications of therapy, sorafenib should be generally continued (in discussion with referring centre)
- Please discuss all toxicities including rash, hypertension and laboratory abnormalities with referring centre!

Gemcitabine

- Gemcitabine is a deoxycytidine that is cell phase specific, primarily killing cells undergoing DNA synthesis (S-phase) and also blocking the progression of cells through the G1/S-phase boundary
- The cytotoxic effects of gemcitabine result in the inhibition of DNA synthesis and induction of apoptosis.
- (https://www.cancercareontario.ca/en/drugformulary/drugs/gemcitabine)

Gemcitabine toxicities

Common (>20% of patients)	Occasional (4-20% of patients)	Rare
• **Flu-like symptoms** • Nausea, vomiting • Hair loss • Infection • Bruising, bleeding • Anemia • Muscle weakness • Blood in urine • **Numbness/tingling of the arms and legs** • Tiredness • Difficulty sleeping • Swelling of arms and legs	• Swelling and redness of the area of radiation • Blisters on the skin • Diarrhea • Constipation • Sores in the mouth • Liver damage • Allergic Reaction • Scarring of the lungs • Shortness of breath • Fluid in the organs which may cause low blood pressure, shortness of breath, swelling of ankles	• Brain damage • Severe blood infection • Kidney problems • Blood clot • Blockage of the airway

Oxaliplatin

- Oxaliplatin is a platinum alkylating agent, which contains platinum complexed to oxalate and diaminocyclohexane (DACH) complex
- Platinum complexes are formed intracellularly and bind to DNA, forming cross-links which inhibit DNA replication and transcription, leading to cytotoxic and antitumor effects
- (https://www.cancercareontario.ca/en/drugformulary/drugs/oxaliplatin)

Oxaliplatin toxicities

Common (>20% of patients)	Occasional (4-20% of patients)	Rare
• Anemia • Nausea, vomiting • Diarrhea • Constipation • Loss of appetite • Tiredness • Bruising, bleeding • Infection • **Numbness/tingling of upper and lower extremities** • Pain • Fever, cough	• Blood clot • Severe blood infection • Hearing loss • Changes in taste • Kidney damage • Liver damage • Mouth sores • Muscle damage/weakness • Hair loss • Allergic reaction	• Scarring of lungs • Brain damage

Summary

- Satellite Clinic involvement will vary based on which Group the patient is registered in, but will primarily be to provide supportive care, collect bloodwork, and administer satellite-friendly chemotherapy.
- While hepatoblastoma patients are regularly seen in satellite centres, Hepatocellular Carcinoma is a rare pediatric entity and satellite practitioners should be aware of specific toxicities of less commonly seen agents such as sorafenib
- All adverse events should be documented and reported to the specialized childhood cancer program with which the patient is affiliated.

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Upon receiving your Certificate of Completion, POGO notifies your affiliated specialized childhood cancer program that your training for AHEP1531 is complete.

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