

COG-AHEP1531: Pediatric Hepatic Malignancy International Therapeutic Trial (PHITT)

FAST FACTS

Eligibility Reviewed and Verified By

MD/DO/RN/LPN/CRA Date _____

MD/DO/RN/LPN/CRA Date _____

Consent Version Dated _____

PATIENT ELIGIBILITY:

Important note: The eligibility criteria listed below are interpreted literally and cannot be waived (per COG policy posted 5/11/01). All clinical and laboratory data required for determining eligibility of a patient enrolled on this trial must be available in the patient's medical research record which will serve as the source document for verification at the time of audit.

1. Pre-Enrollment Stratum Verification (Step 0)

In this trial, each patient will be assigned to the appropriate stratum centrally through a Step 0 mechanism. Institutions will first make a risk group determination locally, and patients may be enrolled in Step 0 once consent has been obtained and the institution has determined that the required data elements are available (refer to risk stratification tables in Section 3.2.4). Step 0 must be completed and confirmation of the appropriate stratum assignment MUST be obtained prior to enrollment on Step 1 and initiation of protocol therapy. If the stratum assignment obtained in Step 0 is different from the stratum anticipated by the institution, confirm all data entered for Step 0 is correct. The patient must meet all appropriate eligibility criteria (including any stratum-specific criteria) detailed in Section 3.2 prior to Step 1 enrollment, this may include providing consent again using the informed consent form for the assigned risk group.

2. Timing

Patients must be enrolled before treatment begins. The date protocol therapy is projected to start must be no later than 14 days from initial biopsy or 42 days (28 days preferred) from a definitive surgery, whichever occurs latest, except if therapy is started in an emergent situation (see Section 3.2.5 below). Investigators are strongly encouraged to enroll patients immediately following histological diagnosis and begin protocol therapy within 28 days of the initial surgical procedure.

3. All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated in the eligibility section below.

4. Randomization

When appropriate, randomization will take place at the time a patient is enrolled via OPEN (Groups C and F), or at a subsequent defined time point when relevant (Groups B (post Cycle 2 resection) and D (post induction for incomplete lung responders)). The treatment will be randomly assigned based on the statistical design of the trial.

5. Rapid Central Pathologic Review

Mandatory rapid (prospective) central pathologic review will be performed for the following cohorts to ensure histologic subtypes are appropriately stratified (see Section 14). This review will occur after enrollment but results must be available prior to starting therapy:

- Group A hepatoblastoma resection specimens (primary resections at diagnosis) to identify the subgroup with pure, well-differentiated fetal histology.
- All biopsy and/or resection specimens from patients suspected to have hepatoblastoma who are either ≥ 8 years of age or have an AFP ≤ 100 at diagnosis will be reviewed to identify non-HB/HCC liver tumors such as malignant rhabdoid tumor, allowing for correct protocol designation. (Note that specific AFP levels must be reported, see Section 10.2.2.3).

Note: In cases with biopsies in any of the above situations or any doubts of HB versus HCC, discussion with study pathologist is recommended prior to enrollment.

Review materials must be submitted within 72 hours of enrollment so that the review is completed within 14 days of enrollment (see Section 14.0 for complete details).

- ___6. **All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated. Laboratory values used to assess eligibility must be no older than seven (7) days at the start of therapy. Laboratory tests need not be repeated if therapy starts within seven (7) days of obtaining labs to assess eligibility. Exception: repeat AFP MUST be sent within 48 hours prior to starting chemotherapy and preferably on the same day that chemotherapy starts. However, the AFP result is NOT required prior to starting therapy.**

If a post-enrollment lab value is outside the limits of eligibility, or laboratory values are > 7 days old, then the following laboratory evaluations must be re-checked within 48 hours prior to initiating therapy: CBC with differential, bilirubin, ALT (SGPT) and serum creatinine. If the recheck is outside the limits of eligibility, the patient may not receive protocol therapy and will be considered off protocol therapy.

Imaging studies, if applicable, must be obtained within 2 weeks prior to start of protocol therapy (repeat the tumor imaging if necessary). If therapy is delayed beyond 28 days from surgery for patients with upfront resection, imaging must be repeated prior to starting therapy. (See Section 16.3 for timing of imaging studies.)

See Section 7.2 for additional studies for consenting patients to be obtained prior to starting protocol therapy.

- ___7. Age
Patients must be ≤ 30 years of age at the time of diagnosis.
- ___8. Body Surface Area (BSA)
Patients in Group F must have a $BSA \geq 0.6 \text{ m}^2$.
- ___9. Performance Level
Patients must have a performance status corresponding to ECOG scores of 0, 1, or 2. Use Karnofsky for patients > 16 years of age and Lansky for patients ≤ 16 years of age.
Please refer to performance status scale on the COG website at:
https://www.cogmembers.org/_files/protocol/Standard/PerformanceStatusScalesScoring.pdf.
Patients who are unable to walk because of paralysis, but who are up in a wheelchair, will be considered ambulatory for the purpose of assessing the performance score.
- ___10. Diagnosis
Patients must be newly diagnosed with histologically-proven primary pediatric hepatic malignancies including hepatoblastoma or hepatocellular carcinoma, except as noted in Section 3.2.5 below. Please see the tables below for risk stratification of hepatoblastoma and hepatocellular carcinoma patients in this study. **Note that rapid central pathology review is required in some cases.**
Please note: All patients with histology as assessed by the institutional pathologist consistent with pure small cell undifferentiated (SCU) HB will be required to have testing for INI1/SMARCB1 by IHC according to the practices at the institution.
 - Patients with histology consistent with pure SCU must have positive INI1/SMARCB1 staining.
- ___11. Emergent Treatment for Hepatoblastoma
In emergency situations when a patient meets all other eligibility criteria and has had baseline required observations, but is too ill to undergo a biopsy safely, the patient may be enrolled without a biopsy.

Clinical situations in which emergent treatment may be indicated include, but are not limited to, the following circumstances:

- Anatomic or mechanical compromise of critical organ function by tumor (e.g., respiratory distress/failure, abdominal compartment syndrome, urinary obstruction, etc.).
- Uncorrectable coagulopathy.

For a patient to maintain eligibility for AHEP1531 when emergent treatment is given, the following must occur:

- The patient must have a clinical diagnosis of hepatoblastoma, including an elevated alphafetoprotein (AFP), and must meet all AHEP1531 eligibility criteria at the time of emergent treatment.
- Patient must be enrolled on AHEP1531 prior to initiating protocol therapy. Per protocol Section 3.2.8, a patient will be ineligible if any chemotherapy is administered prior to AHEP1531 enrollment.

Note: If the patient receives AHEP1531 chemotherapy emergently PRIOR to undergoing a diagnostic biopsy, pathologic review of material obtained in the future during either biopsy or surgical resection must either confirm the diagnosis of hepatoblastoma or not reveal another pathological diagnosis to be included in the analysis of the study aims.

___12. Prior Therapy

Patients may have had surgical resection of the hepatic malignancy prior to enrollment. All other anti-cancer therapy for the current liver lesion is prohibited.

Please see Section 4.1.7.4 for the concomitant therapy restrictions for patients during treatment.

___13. Organ Function Requirements

- Adequate renal function defined as:
 - Creatinine clearance or radioisotope GFR $\geq$ 70 mL/min/1.73 m² or
 - A serum creatinine based on age/gender as follows:

Age	Maximum Serum Creatinine (mg/dL)	
	Male	Female
1 month to < 6 months	0.4	0.4
6 months to < 1 year	0.5	0.5
1 to < 2 years	0.6	0.6
2 to < 6 years	0.8	0.8
6 to < 10 years	1	1
10 to < 13 years	1.2	1.2
13 to < 16 years	1.5	1.4
$\geq$ 16 years	1.7	1.4

The threshold creatinine values in this Table were derived from the Schwartz formula for estimating GFR (Schwartz et al. J. Peds, 106:522, 1985) utilizing child length and stature data published by the CDC.

- Adequate liver function defined as:
 - Total bilirubin $\leq$ 5 x upper limit of normal (ULN) for age, and
 - SGOT (AST) or SGPT (ALT) < 10 x upper limit of normal (ULN) for age.
- Adequate cardiac function for patients on doxorubicin-containing regimens (Groups C, D, E, and F) defined as:
 - Shortening fraction of $\geq$ 27% by echocardiogram, or
 - Ejection fraction of $\geq$ 50% by radionuclide angiogram.
- Adequate pulmonary function defined as:
 - Normal pulmonary function tests (including DLCO) if there is clinical indication for determination (e.g. dyspnea at rest, known requirement for supplemental oxygen).

For patients who do not have respiratory symptoms or requirement for supplemental oxygen, PFTs are NOT required.

___14. **Note: There are additional consents required following evaluation time points.**

- Callback (Step 2 Registration) is **required** for:
 - All Group B patients after the first 2 cycles of protocol therapy
 - All Group D patients after Block 3 of induction therapy
- Callback must be completed even if the patient is not eligible for randomization
- Callback must be completed prior to any further protocol chemotherapy

EXCLUSION CRITERIA:

- ___1. Prior chemotherapy or tumor directed therapy except for surgical resection of the hepatic malignancy (i.e., radiation therapy, biologic agents, local therapy (embolization, radiofrequency ablation, and laser)). Therefore, patients with a pre-disposition syndrome who have a prior malignancy are not eligible.
- ___2. Patients who are currently receiving another investigational drug.
- ___3. Patients who are currently receiving other anticancer agents.
- ___4. Patients with uncontrolled infection.
- ___5. Patients who previously received a solid organ transplant.
- ___6. Pregnancy and Breast Feeding

These criteria apply ONLY to patients who will receive chemotherapy (all groups other than Group E1).

- Female patients who are pregnant, since fetal toxicities and teratogenic effects have been noted for several of the study drugs.

A pregnancy test is required for female patients of childbearing potential.

- Lactating females who plan to breastfeed their infants.
- Sexually active patients of reproductive potential who have not agreed to use an effective contraceptive method for the duration of their study participation.

Note for Group F: Patients of childbearing potential should use effective birth control during treatment with sorafenib and for at least 2 weeks after stopping treatment.

REQUIRED OBSERVATIONS:

GROUP A2 (very low risk)

- a. **Physical exam**, including blood pressure, weight, height and surface area. Prior to each cycle.
- b. **CBC, differential, platelets**. Weekly.
- c. **Creatinine**. Weekly. (If creatinine is outside normal range for age, either GFR or calculated creatinine clearance should be estimated according to local practice.)
- d. **Electrolytes**, including Na⁺, K⁺ Ca⁺⁺, PO₄, Mg⁺⁺. Prior to each cycle.
- e. **Total protein, albumin, bilirubin, ALT/AST**. Prior to each cycle.
- f. **AFP**. Prior to each cycle, preferably on Day 1 of chemotherapy. Result is not needed to start therapy. (Note that specific AFP levels must be reported, see Section 10.2.2.3).
- g. **Audiogram, GFR**. Prior to Cycle 1 only. See Appendix VII for GFR calculation.
- h. **Correlative studies sample**. See Section 7.2 for specimen requirements.

GROUP B (low risk), Cycles 1 & 2

- a. **Physical exam**, including blood pressure, weight, height and surface area. Prior to each cycle.
- b. **CBC, differential, platelets**. Weekly.
- c. **Creatinine**. Weekly. (If creatinine is outside normal range for age, either GFR or calculated creatinine clearance should be estimated according to local practice.)
- d. **Electrolytes**, including Na⁺, K⁺ Ca⁺⁺, PO₄, Mg⁺⁺. Prior to each cycle.
- e. **Total protein, albumin, bilirubin, ALT/AST**. Prior to each cycle.
- f. **AFP**. Prior to each cycle, preferably on Day 1 of chemotherapy. Result is not needed to start therapy. (Note that specific AFP levels must be reported, see Section 10.2.2.3).
- g. **Audiogram, GFR**. Prior to Cycle 1 only. See Appendix VII for GFR calculation.
- h. **Correlative studies sample**. See Section 7.2 for specimen requirements.
- i. **Primary tumor evaluation** (CT or MRI). End of Cycle 2 (see Section 16.3).

GROUP C, Arm CDDP (intermediate risk)

- a. **Physical exam**, including blood pressure, weight, height and surface area. Prior to each cycle.
- b. **CBC, differential, platelets**. Weekly.
- c. **Creatinine**. Weekly. (If creatinine is outside normal range for age, either GFR or calculated creatinine clearance should be estimated according to local practice.)
- d. **Electrolytes**, including Na⁺, K⁺ Ca⁺⁺, PO₄, Mg⁺⁺. Prior to each cycle.
- e. **Total protein, albumin, bilirubin, ALT/AST**. Prior to each cycle.
- f. **AFP**. Prior to each cycle, preferably on Day 1 of chemotherapy. Result is not needed to start therapy. (Note that specific AFP levels must be reported, see Section 10.2.2.3).
- g. **Audiogram, GFR**. Prior to Cycle 1 only. See Appendix VII for GFR calculation.
- h. **Correlative studies sample**. See Section 7.2 for specimen requirements.
- i. **Primary tumor evaluation** (CT or MRI). End of Cycle 2 and Cycle 4 (see Section 16.3).

GROUP C, Arm C5VD (intermediate risk)

- a. **Physical exam**, including blood pressure, weight, height and surface area. Prior to each cycle.
- b. **CBC, differential, platelets**. Weekly.
- c. **Creatinine**. Weekly. (If creatinine is outside normal range for age, either GFR or calculated creatinine clearance should be estimated according to local practice.)
- d. **Electrolytes**, including Na⁺, K⁺ Ca⁺⁺, PO₄, Mg⁺⁺. Prior to each cycle.
- e. **Total protein, albumin, bilirubin, ALT/AST**. Prior to each cycle.
- f. **AFP**. Prior to each cycle, preferably on Day 1 of chemotherapy. Result is not needed to start therapy. (Note that specific AFP levels must be reported, see Section 10.2.2.3).
- g. **Audiogram, GFR**. Prior to Cycle 1. See Appendix VII for GFR calculation.
- h. **ECHO or MUGA**. Prior to Cycle 1, 3, and 5 only.
- i. **Correlative studies sample**. See Section 7.2 for specimen requirements.
- j. **Primary tumor evaluation** (CT or MRI). End of Cycle 2 and Cycle 4 (see Section 16.3).

GROUP D Induction, Block 1 (high risk) (all Group D patients)

- a. **Physical exam**, including blood pressure, weight, height and surface area. Prior to chemotherapy and prior to surgery.
- b. **CBC, differential, platelets**. Weekly.
- c. **Creatinine**. Weekly. (If creatinine is outside normal range for age, either GFR or calculated creatinine clearance should be estimated according to local practice.)
- d. **Electrolytes**, including Na⁺, K⁺ Ca⁺⁺, PO₄, Mg⁺⁺.
- e. **Total protein, albumin, bilirubin, ALT/AST**.
- f. **AFP**. Prior to induction, preferably on Day 1 of chemotherapy. Result is not needed to start therapy. (Note that specific AFP levels must be reported, see Section 10.2.2.3).
- g. **Audiogram, GFR**. See Appendix VII for GFR calculation.
- h. **ECHO or MUGA**.
- i. **Correlative studies sample**. See Section 7.2 for specimen requirements.

GROUP E2 (HCC Resected at Diagnosis)

- a. **Physical exam**, including blood pressure, weight, height and surface area. Prior to each cycle.
- b. **CBC, differential, platelets**. Weekly.
- c. **Creatinine**. Weekly. (If creatinine is outside normal range for age, either GFR or calculated creatinine clearance should be estimated according to local practice.)
- d. **Electrolytes**, including Na⁺, K⁺ Ca⁺⁺, PO₄, Mg⁺⁺. Prior to each cycle.
- e. **Total protein, albumin, bilirubin, ALT/AST**. Prior to each cycle.
- f. **AFP**. Prior to each cycle, preferably on Day 1 of chemotherapy. Result is not needed to start therapy. (Note that specific AFP levels must be reported, see Section 10.2.2.3).
- g. **Audiogram, GFR**. Prior to Cycle 1 only. See Appendix VII for GFR calculation.
- h. **ECHO or MUGA**. Prior to Cycle 1 and 3.
- i. **Hepatitis B and C serology**. Prior to Cycle 1.
- j. **Correlative studies sample**. See Section 7.2 for specimen requirements.
- k. **Primary tumor evaluation** (CT or MRI). End of Cycle 2 only (see Section 16.3).

GROUP F (HCC Unresectable) Arm PLADO

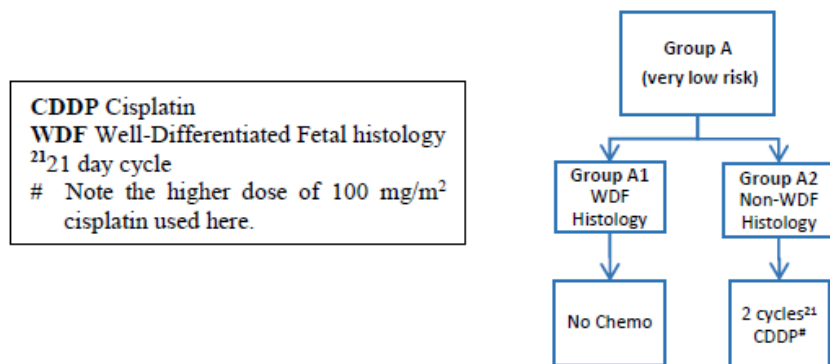
- a. **Physical exam**, including blood pressure, weight, height and surface area. Prior to each cycle.
- b. **CBC, differential, platelets**. Weekly.
- c. **Creatinine**. Weekly. (If creatinine is outside normal range for age, either GFR or calculated creatinine clearance should be estimated according to local practice.)
- d. **Electrolytes**, including Na⁺, K⁺ Ca⁺⁺, PO₄, Mg⁺⁺. Prior to each cycle.
- e. **Total protein, albumin, bilirubin, ALT/AST**. Prior to each cycle.
- f. **AFP**. Prior to each cycle, preferably on Day 1 of chemotherapy. Result is not needed to start therapy. (Note that specific AFP levels must be reported, see Section 10.2.2.3).
- g. **Audiogram**. Prior to Cycle 1 only.
- h. **GFR**. Prior to Cycle 1 of both Course 1 and Course 2 (if continuing therapy). See Appendix VII for GFR calculation.
- i. **ECHO or MUGA, and EKG**. Prior to Cycle 1 of both Course 1 and Course 2 (if continuing therapy).
- j. **Hepatitis B and C serology**. Prior to Cycle 1.
- k. **Correlative studies sample**. See Section 7.2 for specimen requirements.
- l. **Primary tumor evaluation** (CT or MRI). End of Cycle 3 (see Section 16.3).
- m. **Metastatic tumor evaluation** (CT chest). End of Cycle 3 (see Section 16.3).

GROUP F (HCC Unresectable) Arm P/GEMOX, Cycles 1 & 3

- a. **Physical exam**, including blood pressure, weight, height and surface area. Prior to each cycle.
- b. **CBC, differential, platelets**. Weekly.
- c. **Creatinine**. Weekly. (If creatinine is outside normal range for age, either GFR or calculated creatinine clearance should be estimated according to local practice.)
- d. **Electrolytes**, including Na⁺, K⁺ Ca⁺⁺, PO₄, Mg⁺⁺. Prior to each cycle.
- e. **Total protein, albumin, bilirubin, ALT/AST**. Prior to each cycle.
- f. **AFP**. Prior to each cycle, preferably on Day 1 of chemotherapy. Result is not needed to start therapy. (Note that specific AFP levels must be reported, see Section 10.2.2.3).
- g. **Audiogram**. Prior to Cycle 1 only.
- h. **GFR**. Prior to Cycle 1 of both Course 1 and Course 2 (if continuing therapy). See Appendix VII for GFR calculation.
- i. **ECHO or MUGA, and EKG**. Prior to Cycle 1 of both Course 1 and Course 2 (if continuing therapy).
- j. **Hepatitis B and C serology**. Prior to Cycle 1.
- k. **Correlative studies sample**. See Section 7.2 for specimen requirements

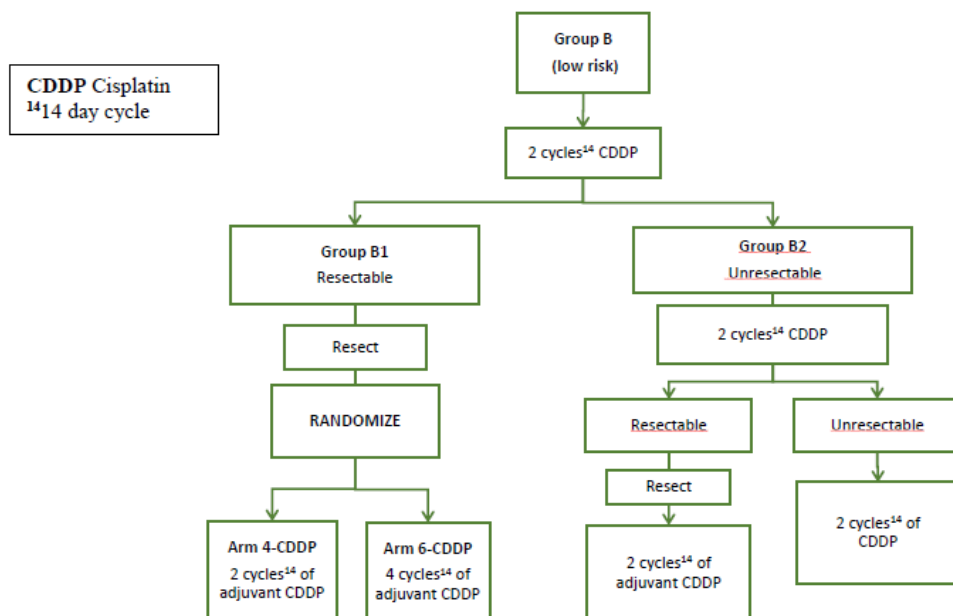
TREATMENT PLAN:

See Section 4

Treatment for Group A: Very Low Risk HB

These patients will have a primary resection of their tumor. 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 Group B of the protocol and receive preoperative chemotherapy. The treating institution is encouraged to discuss any questions regarding the timing of surgical resection with the surgical members of the study committee (see Section 13.1 for Surgical Resection Guidelines).

Following surgical resection, all Group A patients **MUST** have rapid central review of their pathology with submission of materials within 72 hours and an expected central review response within 14 days of enrollment (see Section 14) to determine stratification. Patients with completely resected, margin-negative, Well Differentiated Fetal (WDF) histology that is confirmed by central review (**Group A1**) will receive no adjuvant chemotherapy. All non-WDF patients (and grossly resected, margin-positive WDF cases) (**Group A2**) will receive 2 cycles of cisplatin chemotherapy (CDDP) (see Section 4.2).

Treatment for Group B: Low Risk HB

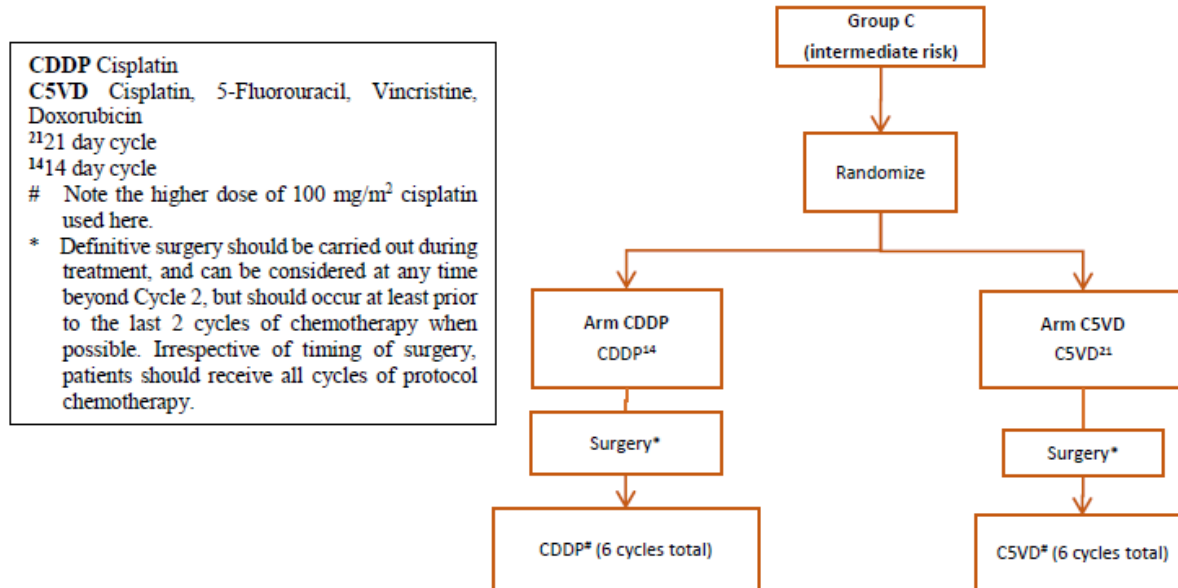
These patients will have tumors deemed unresectable at diagnosis but no other adverse features (localized PRETEXT I-III tumors without positive VPEFR annotation factors). Following completion of 2 cycles of chemotherapy (see Section 4.3), patients will be evaluated for resectability. Those patients deemed resectable will be assigned to Group B1 and those patients deemed unresectable will be assigned to Group B2.

Callback Requirement

After completion of 2 cycles of protocol therapy, Callback (Step 2 Registration) must be completed. The institutional investigator will identify whether the patient is to be randomized or will not be randomized. The date of complete tumor resection will be required to complete the randomization process. For patients who will not be randomized, the reason for non-randomization must be provided.

Patients who receive systemic chemotherapy after the completion of Cycle 2 but before accomplishing the treatment assignment Callback will be considered off protocol therapy on the first day of administration of such treatment.

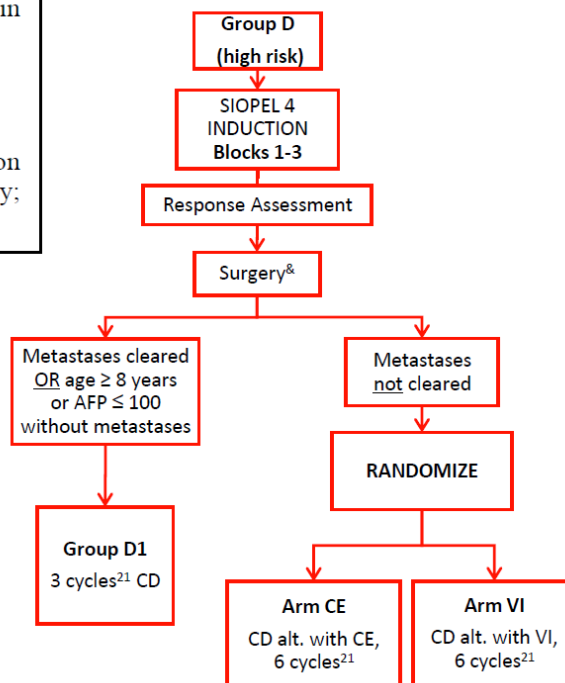
Treatment for Group C: Intermediate Risk HB



Patients in Group C will have locally advanced tumors including PRETEXT I-III tumors with a positive VPEFR annotation factor and all PRETEXT IV tumors. Early referral (at the time of diagnosis) to a transplant center is encouraged so that sufficient time can be allowed for the surgical planning and/or transplant workup to take place.

Treatment for Group D: High Risk HB

SIOPEL 4 Induction Cisplatin, Doxorubicin
CD Carboplatin/Doxorubicin
CE Carboplatin/Etoposide
VI Vincristine/Irinotecan
²¹21 day cycle
 & Surgery may be performed after induction therapy or during consolidation therapy; timing may vary.



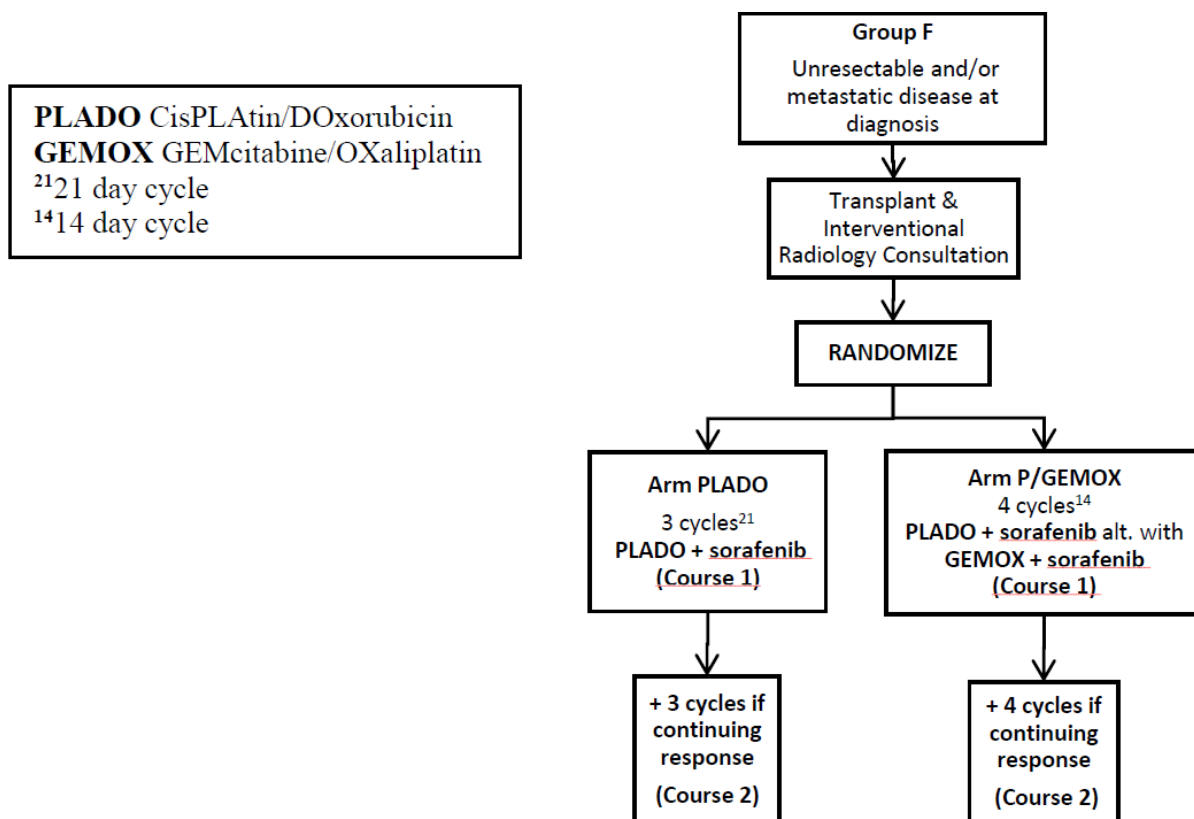
Nearly all of these patients will have pulmonary metastatic disease. Often patients will also have challenging primary tumors and a significant number may be considered suitable for transplantation (assuming a lung CR can be achieved). We would encourage early referral (at the time of diagnosis) to a transplant center (as above for Group C) 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.

Group D will also include suspected HB patients who are ≥ 8 years of age or have an $\text{AFP} \leq 100$ at diagnosis. These patients are required to have rapid central review of their pathology with submission of materials within 72 hours and an expected central review response within 14 days of enrollment (see Section 14).

Treatment for Group E: Resected HCC

These patients have completely resected HCC at diagnosis with negative margins. In borderline cases (i.e. uncertainty regarding margins) we would recommend patients enter Group F of the protocol.

Treatment for Group F: Unresected and/or Metastatic HCC



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

TOXICITIES AND DOSAGE MODIFICATIONS:

See Section 5

SPECIMEN REQUIREMENTS:

See Section 14

BIOLOGY REQUIREMENTS:

See Section 15