CHILDREN'S ONCOLOGY GROUP

The world's childhood cancer experts

**Group Chair**
Peter C. Adamson, M.D.
adamson@email.chop.edu

**Group Statistician**
Todd Alonzo, Ph.D.
talonzo@childrensoncology group.org

**Group Vice Chair**
Susan Blaney, M.D.
smblaney@txch.org

**Chief Operating Officer**
Elizabeth O'Connor, M.P.H.
econnor@childrensoncology group.org

**Executive Director of Administration**
Deborah L. Crabtree, M.S.
crabtreed@email.chop.edu

**Group Chair's Office**
*The Children's Hospital of Philadelphia*
3501 Civic Center Blvd
CTRB 10060
Philadelphia, PA 19104

P 215 590 6359
F 215 590 7544

**Group Operations Center**
222 E. Huntington Drive
Suite 100
Monrovia, CA 91016

P 626 447 0064
F 626 445 4334

**Statistics & Data Center Headquarters**
222 E. Huntington Drive
Suite 100
Monrovia, CA 91016

P 626 447 0064
F 626 445 4334

**Gainesville Office**
6011 NW 1st Place
Gainesville, FL 32607

P 352 273 0556
F 352 392 8162

A National Cancer Institute-supported member group of the National Clinical Trials Network

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Martha Kruhm, MS, RAC
Head, Protocol and Information Office
Operations and Informatics Branch
Cancer Therapy Evaluation Program
Division of Cancer Treatment and Diagnosis
National Cancer Institute
Executive Plaza North Room 730
Bethesda, MD 20892

Dear Ms. Kruhm,

Enclosed please find Amendment #7 for protocol **AHEP0731**, *Treatment of Children with All Stages of Hepatoblastoma with Temsirolimus (NSC#683864) Added to High Risk Stratum Treatment*, for CTEP review.

This amendment is being submitted in response to a Request for Rapid Amendment (RRA) from Dr. L. Austin Doyle (doylela@mail.nih.gov), dated October 24, 2018. In this amendment, the revised CAEPR for temsirolimus (Version 2.6, August 19, 2018) has been inserted in the protocol, and the associated risk information in the informed consent document has been revised. Revisions to the protocol and consent documents are detailed in the pages below.

The AHEP0731 study team looks forward to approval of this amendment. Please contact me with any questions or concerns.

Sincerely,

Christine Wang, PhD, Protocol Coordinator (for)

Howard Katzenstein, MD, AHEP0731 Study Chair
Carlos Rodriguez-Galindo, MD, COG Rare Tumor Committee Chair
Peter Adamson, MD, Children's Oncology Group Chair

**SUMMARY OF CHANGES: PROTOCOL DOCUMENT**

In accordance with the above discussion, the following specific revisions have been made to the protocol.

| # | Section | Page(s) | Change |
|---|---|---|---|
| 1. | Title Page | 1 | Updated version date and amendment number. |
| 2. | 6.1 | 57-63 | Inserted revised CAEPR for temsirolimus (Version 2.6, August 19, 2018). Specific changes are as follows:<br>• The section below utilizes CTCAE 5.0 language unless otherwise noted.<br>• *Added New Risk:*<br>  • *Rare but Serious:* *Nephrotic syndrome*<br>• *Increase in Risk Attribution:*<br>  • Changed to Rare but Serious from Also Reported on Temsirolimus Trials But With Insufficient Evidence for Attribution: Proteinuria |

**SUMMARY OF CHANGES: INFORMED CONSENT DOCUMENTS**

In accordance with the above discussion, the following specific revisions have been made to the Informed Consent Documents.

**ICD-1:**

| # | Section | Page(s) | Change |
|---|---|---|---|
| 1. | General | All | Updated version date in the footer to match the protocol version date. No other changes have been made to this consent as the risks of temsirolimus are not applicable. |

**ICD-2:**

| # | Section | Page(s) | Change |
|---|---|---|---|
| 1. | General | All | Updated version date in the footer. |
| 2. | Possible Side Effects of Temsirolimus | 12-13 | • Provided Further Clarification:<br>  • Sore throat (under Occasional) is now reported as part of Sores in the mouth which may cause difficulty swallowing (under Common).<br>• Removed codename for temsirolimus (CCI-779) from the risk tables for consistency with the NCI supplied risk profile. |

**ICD-3:**

| # | Section | Page(s) | Change |
|---|---|---|---|
| 1. | General | All | Updated version date in the footer to match the protocol version date. No other changes have been made to this consent as the risks of temsirolimus are not applicable. |

Activated: September 14, 2009
Closed: July 20, 2018
Version Date: 11/07/18
Amendment: #7

# CHILDREN'S ONCOLOGY GROUP

## AHEP0731

## Treatment of Children with All Stages of Hepatoblastoma with Temsirolimus (NSC#683864) Added to High Risk Stratum Treatment

## A Phase III Study

## An Intergroup Study for Participation by COG and the Japanese Study Group for Pediatric Liver Tumors (JPLT)

| CTEP ID / JPLT Participating Institutions | Investigator | Investigator ID |
|---|---|---|
| 42067 / Fukushima Medical University Hospital | Dr. Atsushi Kikuta | 48577 |
| 42035 / Hiroshima University Hospital | Dr. Eiso Hiyama | 48669 |
| 42071 / Kagoshima University Medical and Dental Hospital | Dr. Yasuhiro Okamoto | 48673 |
| 42017 / National Cancer Center Hospital | Dr. Chitose Ogawa | 55762 |
| 42072 / Nihon University Itabashi Hospital | Dr. Tsugumichi Koshinaga | 55757 |
| 42063 / Shizuoka Cancer Center | Dr. Yuji Ishida | 48705 |

NCI Supplied Agent: Temsirolimus (NSC#683864)

IND sponsor for temsirolimus: DCTD, NCI

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**STUDY CHAIR**
Howard Katzenstein, MD
Nemours Children's Clinic – Jacksonville
Division of Hematology/Oncology
807 Children's Way
Jacksonville, FL 32207
Phone: (904) 697-3793
Fax: (904) 697-3792
E-mail: howard.katzenstein@nemours.org

ATTENTION JPLT SITES: Please refer to the JPLT group specific appendix (Appendix VII) for important JPLT site specific protocol information.

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## STUDY COMMITTEE

STUDY CHAIR
Howard Katzenstein, MD
Hematology/Oncology
Nemours Children's Clinic-Jacksonville
Hematology/Oncology
807 Children's Way
Jacksonville, FL 32207
Phone: (904) 697-3793
Fax: (904) 697-3792
E-mail: howard.katzenstein@nemours.org

STUDY VICE CHAIR
Marcio Malogolowkin, MD
Hematology/Oncology
University of California Davis Comprehensive Cancer Center
Pediatric Hematology/Oncology
2516 Stockton Blvd., 2nd Fl.
Sacramento. CA 95817
Phone: (916) 734-2781
Fax: (916) 451-3014
E-mail: mmalogolowkin@ucdavis.edu

STUDY STATISTICIAN
Mark Krailo, PhD
Statistics
Children's Oncology Group - Operations Center
222 E. Huntington Dr. Suite 100
Monrovia, CA 91016
Phone: (626) 241-1529
Fax: (626) 445-4334
E-mail: mkrailo@childrensoncologygroup.org

STUDY COMMITTEE MEMBERS
Rebecka Meyers, MD
Surgery
Primary Children's Medical Center
Division of Pediatric Surgery
100 North Mario Capecchi Drive, Suite 2600
Salt Lake City, UT 84113
Phone: (801) 662-2950
Fax: (801) 662-4707
E-mail: rebecka.meyers@hsc.utah.edu

Milton Finegold, MD
Pathology
Baylor College of Medicine
Texas Children's Hospital, MC1-2261
6621 Fannin Street
Houston, TX 77030-2399
Phone: (832) 824-1856
Fax: (832) 825-1032
E-mail: Mjfinego@TexasChildrens.org

STUDY COMMITTEE MEMBERS
Max Raymond Langham, MD
Surgery
St. Jude Children's Research Hospital
University of Tennessee Health Science Center, Surgery
777 Washington Ave, Suite P230
Memphis, TN 38106
Phone: (901) 289-6300
Fax: (901) 287-5191
E-mail: mlangham@uthsc.edu

Stephen P. Dunn, MD
Surgery
A.I. duPont Hospital for Children
Pediatric Surgery
1600 Rockland Road
Wilmington, DE 19803
Phone: (302) 651-5999
Fax: (302) 651-5990
E-mail: sdunn@nemours.org

Mary McCarville, MD
Diagnostic Imaging
St. Jude Children's Research Hospital
Radiological Sciences
262 Danny Thomas Place - MS 220
Memphis, TN 38105-3678
Phone: (901) 595-2399
Fax: (901) 595-3981
E-mail: beth.mccarville@stjude.org

Christie Powell, MSN, CPNP
Nursing
Children's Healthcare of Atlanta - Egleston
Aflac Center for Cancer and Blood Disorders
1405 Clifton Road NE
Atlanta, GA 30322
Phone: (404) 785-1743
Fax: (404) 785-6288
E-mail: christie.powell@choa.org

Alexander Justin Towbin, MD
Diagnostic Imaging
Cincinnati Children's Hospital Medical Center
Radiology
3333 Burnet Ave
Department of Radiology, ML 5031
Cincinnati, OH 45229
Phone: (513) 636-5896
Fax: (513) 636-1388
E-mail: Alexander.towbin@cchmc.org

STUDY COMMITTEE MEMBERS
Wayne Furman, MD
Hematology/Oncology
St. Jude Children's Research Hospital
Department of Oncology
262 Danny Thomas Place - MS 260
Memphis, TN 38105-3678
Phone: (901) 595-2403
Fax: (901) 521-9005
E-Mail: wayne.furman@stjude.org

Anne Warwick, MD, MPH
Hematology/Oncology
Walter Reed National Military Medical Center
Pediatric Hematology/Oncology
8901 Wisconsin Avenue
Bethesda, MD 20889-5600
Phone: (301) 400-1663
Fax: (301) 400-1662
E-mail: anne.warwick@usuhs.edu

Sarangarajan Ranganathan, MD
Pathology
Children's Hospital of Pittsburgh of UPMC
Division of Pediatric Pathology
One Children's Hospital Drive
4401 Penn Avenue
Pittsburgh, PA 15224
Phone: (412) 692-5879
Fax: (412) 692-6550
E-mail: Sarangarajan.Ranganathan@chp.edu

Eugene McGahren, MD
Surgery
University of Virginia
Department of Surgery/Division of Pediatric Surgery
University of Virginia Hospital
Box 800709
Charlottesville, VA 22908
Phone: (434) 924-5643
Fax: (434) 243-6129
E-mail: edm6k@virginia.edu

Arun Atreiya Rangaswami, MD
Hematology/Oncology
Lucile Packard Children's Hospital Stanford University
1000 Welch Road, Suite 300
Palo Alto, CA 94304-1812
Phone: (650) 723-5535
E-mail: atreiya@stanford.edu

STUDY COMMITTEE MEMBERS
Rhonda Crutcher, CCRP
Clinical Research Associate
Children's Hospital of Los Angeles
Hematology/Oncology
4650 Sunset Blvd. MS #54
Los Angeles, CA 90027
Phone: (323)361-8659
Fax: (323)361-1585
E-mail: rcrutcher@chla.usc.edu

Gregory Tiao, MD
Surgery
Cincinnati Children's Hospital Medical Center
3333 Burnet Avenue
MLC - 2023
Cincinnati, OH 45229
Phone: (513) 636-4371
Fax: (513) 636-7657
E-mail: Greg.Tiao@cchmc.org

Christopher Bertero Weldon, MD PhD
Surgery
Dana-Farber Cancer Institute
Surgery
Children's Hospital Boston
300 Longwood Avenue, Fegan 3
Boston, MA 02115
Phone: (617) 355-4503
Fax: (617) 730-0477
E-mail: Christopher.weldon@childrens.harvard.edu

PROTOCOL CONTACT
Christine Wang
Children's Oncology Group - Operations Center
Study Development Office
222 E. Huntington Drive, Suite 100
Monrovia, CA 91016
Phone: (626) 241-1626
Fax: (626) 445-4334
E-mail: cewang@childrensoncologygroup.org

RESEARCH COORDINATOR
Justin Davis
Children's Oncology Group - Operations Center
Statistics and Data Center
222 E. Huntington Drive, Suite 100
Monrovia, CA 91016
Phone: (626) 241-1509
Fax: (626) 445-4334
E-mail: jdavis@childrensoncologygroup.org

JPLT CONTACTS
Eiso Hiyama, MD, PhD
Oncology/Surgery
Hiroshima University Hospital
1-2-3 Kasumi, Minami-ku
Hiroshima 734-8551, Japan
Phone: 81 (82) 257-5951
Fax: 81 (82) 257-5416
Email: eiso@hiroshima-u.ac.jp

Eriko Aotani, RN, MSN
Director, Global Health Research Coordinating Center
Kanagawa Academy of Science and Technology (KAST)
KSP East 3F 309, 3-2-1, Sakado
Takatsu-ku, Kawasaki-shi
Kanagawa, 213-0012 Japan
Phone: 81 (44) 850-1731
Fax: 81 (44) 850-1732
Email: ahep0731@newkast.or.jp

| AGENT | NSC#'s | IND# |
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| FLUOROURACIL | 19893 | Exempt |
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| DEXRAZOXANE | 169780 | Exempt |
| DOXORUBICIN | 123127 | Exempt |
| IRINOTECAN | 616348 | Exempt |
| VINCRISTINE | 67574 | Exempt |
| TEMSIROLIMUS | 683864 | |

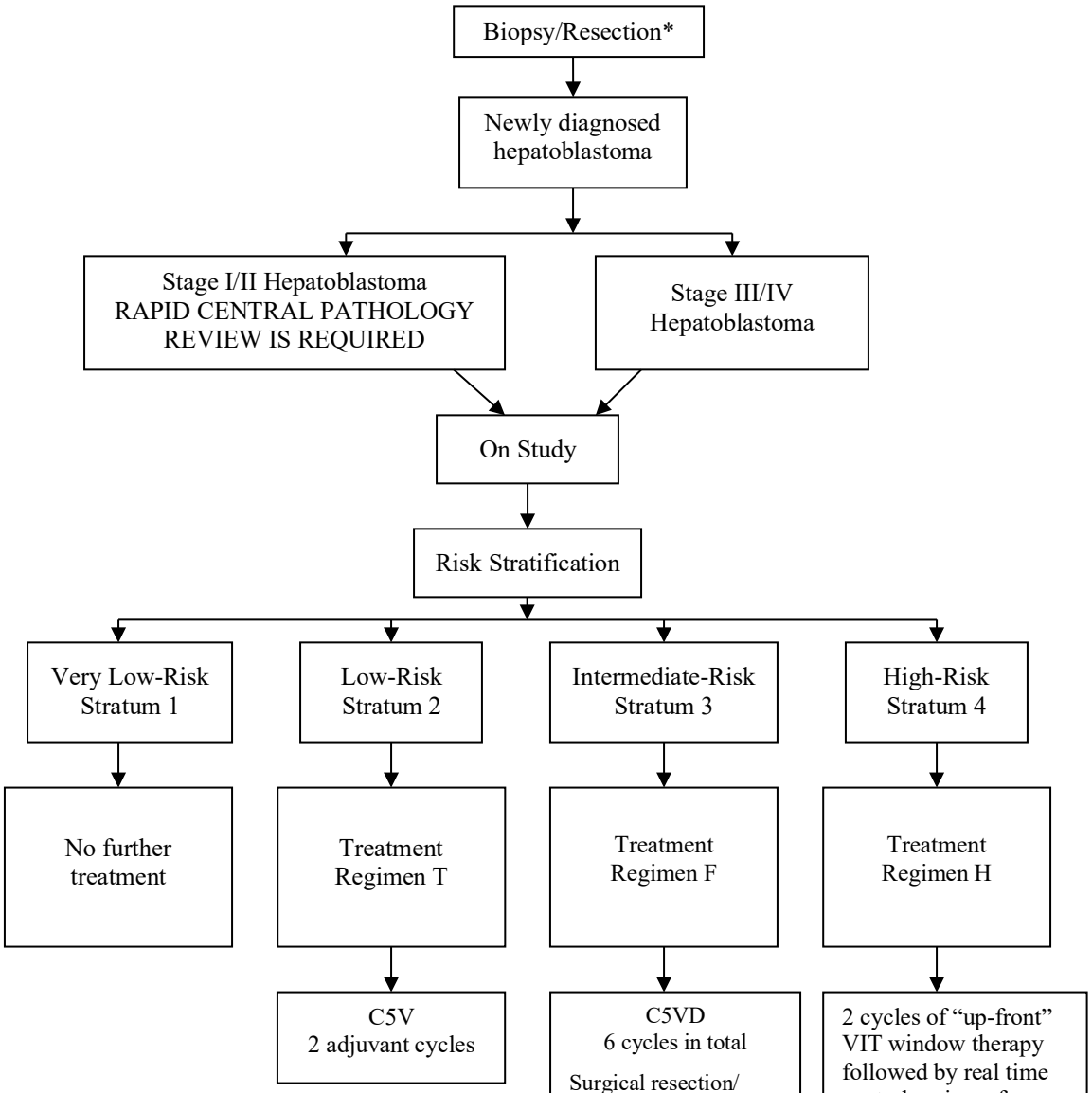
**SEE SECTIONS 14.0 AND 15.0 FOR SHIPPING ADDRESSES**

## ABSTRACT

Hepatoblastoma is the most common malignant liver neoplasm in children. Although surgical resection is the mainstay of curative therapy for children with hepatoblastoma, only one-third to one-half of newly diagnosed patients with hepatoblastoma can be expected to have resectable disease at presentation. Patients who undergo a primary complete resection of their tumor have an excellent prognosis (90% event-free survival [EFS]). The use of chemotherapy has improved survival in patients with unresectable hepatoblastoma by increasing the number of patients whose tumors can be resected. However, more recent trials over the last decade have failed to significantly improve survival numbers. Therefore, the current EFS for the entire group of patients with non-metastatic, unresectable hepatoblastoma at diagnosis remains suboptimal (< 70%) and warrants novel treatment approaches. The survival of patients with metastatic disease at diagnosis remains poor (20-30%) and also requires consideration of novel therapeutic strategies. AHEP0731 builds on the results of the last 20 years of hepatoblastoma clinical trials and seeks to diminish toxicity in the approximately 30% of low-risk patients, increase survival in intermediate-risk patients and identify new agents(s) that may be used in high-risk and recurrent patients. Patients will be staged for risk classification and treatment at diagnosis using COG staging guidelines (see Appendix III). Study enrollment for patients with Stage I and II tumors is contingent on rapid central pathologic review of tumor specimens. All patients with Stage I pure fetal histology (PFH) hepatoblastoma will be classified as very low-risk and will be treated with surgery only. Patients with Stage I non-PFH, non-small cell undifferentiated (SCU) hepatoblastoma or with Stage II non-SCU hepatoblastoma will be classified as low-risk and will be treated on Regimen T with 2 adjuvant cycles of cisplatin, 5-flouorouracil, and vincristine (C5V), a reduction from the standard 4 cycles of chemotherapy used in previous COG trials. Patients with Stage I SCU, Stage II SCU, or any Stage III hepatoblastoma will be classified as intermediate-risk and will be treated with Regimen F (intermediate risk, stratum 3, has been closed to accrual as of 03/12/12). This treatment regimen is based on previous COG trials which administered 6 cycles of C5V therapy plus surgical resection of the tumor. However, to improve resection and survival rates, doxorubicin, an agent with proven efficacy will be added to the C5V therapy (C5VD). Surgical resection is necessary for cure and surgical resection whether by primary resection or orthotopic liver transplant (OLT) is intended after 4 cycles of intermediate-risk therapy. This trial will assess the feasibility in a cooperative group setting of timely referral (by the completion of Cycle 2) for OLT in children with hepatoblastoma designated as potentially unresectable following central surgical review and staging according to the PRETEXT (Pretreatment Extent of Disease) grouping system. AHEP0731 also aims to determine if PRETEXT grouping can predict tumor resectability and to assess if institutional assessment of PRETEXT grouping is reliable by comparing to PRETEXT grouping as performed by central review. All patients with any Stage IV hepatoblastoma as well as patients with any stage of hepatoblastoma and initial AFP <100 ng/mL will be classified as high-risk and will be treated with the novel combination of vincristine, irinotecan and temsirolimus in Regimen H in order to estimate the response rate of this new combination of agents. This regimen includes 2 cycles of "up-front" vincristine, irinotecan and temsirolimus in the initial 6 weeks of therapy. Patients who respond to vincristine/irinotecan/temsirolimus (VIT) will continue to receive this combination. Responding patients

will receive a total of 6 cycles of C5VD therapy with 2 more cycles of VIT (total of 4). Non-responding patients will only receive the 6 cycles of C5VD following the "up-front" window therapy. The primary goal of AHEP0731 is to show that a risk-based treatment approach will maintain or improve EFS, decrease acute and long-term chemotherapy toxicity, and identify new agents for the treatment of children with hepatoblastoma.

**EXPERIMENTAL DESIGN SCHEMA**




**Very Low-Risk:** Stage I PFH hepatoblastoma
**Low-Risk:** Stage I non-PFH, non-SCU or Stage II non-SCU hepatoblastoma
**Intermediate-Risk:** Stage I SCU, Stage II SCU, or any Stage III hepatoblastoma
**High-Risk:** Any Stage IV or any stage hepatoblastoma with initial AFP < 100 ng/mL hepatoblastoma

**C5V:** Cisplatin 5-Fluorouracil, Vincristine
**VIT:** Vincristine, Irinotecan, Temsirolimus
**C5VD:** Cisplatin, 5-Fluorouracil, Vincristine, Doxorubicin

* Biopsy or complete tumor resection if deemed feasible at diagnosis

# 1.0 GOALS AND OBJECTIVES (SCIENTIFIC AIMS)

## 1.1 Hypotheses

1.1.1
A risk-based treatment approach will maintain or improve event-free survival (EFS), decrease acute and long-term chemotherapy toxicity, and identify new agents in the treatment of children with hepatoblastoma.

1.1.2
Stage I hepatoblastoma (non-pure fetal histology [PFH]), non-small cell undifferentiated [SCU]) and Stage II (non-SCU) is a highly curable disease with 2 cycles of adjuvant cisplatin, 5-fluorouracil, and vincristine (C5V).

1.1.3
The addition of doxorubicin to the chemotherapy regimen of C5V for children with intermediate-risk hepatoblastoma will be feasible and associated with acceptable levels of toxicity.

1.1.4
The use of vincristine, irinotecan and temsirolimus in an upfront window for children with high-risk, metastatic hepatoblastoma will improve the response rate in this group of children.

1.1.5
Referral for orthotopic liver transplant (OLT) is feasible in a cooperative group setting in children with hepatoblastoma designated as potentially unresectable following central surgical review and staging according to the PRETEXT (Pretreatment Extent of Disease) grouping system.

## 1.2 Primary Aims

1.2.1
To estimate the EFS in children with Stage I (non-PFH, non-SCU) and Stage II (non-SCU) hepatoblastoma treated with surgical resection followed by 2 cycles of C5V.

1.2.2
To determine the feasibility and toxicity of adding doxorubicin to the chemotherapy regimen of C5V for children with intermediate-risk hepatoblastoma.

1.2.3
To estimate the response rate to vincristine, irinotecan and temsirolimus in previously untreated children with high-risk, metastatic hepatoblastoma.

1.2.4
To determine whether timely (between diagnosis and end of second cycle of chemotherapy) consultation with a treatment center with surgical expertise in major pediatric liver resection and transplant can be achieved in 70% of patients with potentially unresectable hepatoblastoma.

1.2.5
To foster the collection of tumor tissue and biologic samples to facilitate translational research and to provide data that may aid in risk-adapted approaches for subsequent clinical trials.

### 1.3 Secondary Aims

1.3.1
To estimate the EFS of patients with Stage I PFH treated with surgery alone.

1.3.2
To determine whether OLT can be accomplished after successful referral and completion of 4 cycles of initial chemotherapy.

1.3.3
To estimate the 2-year EFS for patients once identified as candidates for possible OLT, the 2-year EFS for patients referred to a transplant center that are resected without OLT, and the 2-year EFS for patients referred to a transplant center who receive OLT.

1.3.4
To register children with hepatoblastoma who receive OLT with PLUTO (Pediatric Liver Unresectable Tumor Observatory), an international cooperative registry for children transplanted for liver tumors.

1.3.5
To determine if PRETEXT grouping can predict tumor resectability.

1.3.6
To monitor the concordance between institutional assessment of PRETEXT grouping and PRETEXT grouping as performed by expert panel review.

1.3.7
To estimate the proportion of Stage IV patients who have surgical resection of metastatic pulmonary lesions.

1.3.8
To determine the proportion and estimate the EFS of patients with potentially poor prognostic factors including AFP < 100 ng/mL at diagnosis, microscopic positive surgical margins, surgical complications, multifocal tumors, microscopic vascular invasion, macrotrabecular histologic subtype, and SCU histologic subtype.

## 2.0 BACKGROUND

### 2.1 Treatment Considerations

Hepatoblastoma is the most common malignant liver neoplasm in children. Although surgical resection is the mainstay of curative therapy for children with hepatoblastoma, only one-third to one-half of newly diagnosed patients with hepatoblastoma can be expected to have resectable disease at presentation.[1,2] The main determinants of clinical outcome in patients with hepatoblastoma are the presence or absence of metastatic disease, and tumor resectability.[3] In addition, unique histologic variants of hepatoblastoma, such as SCU histology, have also been shown to adversely affect survival.[4,5]

Patients who undergo a primary complete resection of their tumor have an excellent prognosis (90% EFS) in several series.[3,6,7] The use of chemotherapy has improved survival in patients with unresectable hepatoblastoma by increasing the number of patients whose tumors can be resected.[6,8] Cisplatin (CDDP) has been identified as the most active agent for the treatment of hepatoblastoma.[9,10] Doxorubicin (DOXO) appears to be the next most active agent. There is relatively little information on the efficacy of other single agents such as ifosfamide (IFOS), etoposide (ETOP), vincristine (VCR), 5-fluorouracil (FU),

cyclophosphamide (CPM), and carboplatin (CARBO) in the treatment of hepatoblastoma as most of these agents have been used in combination.[2,11,12] Over the last 2 decades, the chemotherapeutic regimen CDDP/5-FU/VCR (C5V) has been utilized and studied within Children's Oncology Group (COG) trials and has been adopted as the standard treatment regimen by COG because of its similar activity and favorable toxicity profile when compared to doxorubicin-containing regimens.

Cooperative group studies from around the world performed in the late 1980s and early 1990s demonstrated the effectiveness of chemotherapy in increasing rates of surgical resection and survival in initially unresectable patients.[13,14] However, more recent trials over the last decade have failed to significantly improve survival numbers. Therefore, the current EFS for the entire group of patients with non-metastatic, unresectable hepatoblastoma at diagnosis remains suboptimal (< 70%) and warrants novel treatment approaches. The survival of patients with metastatic disease at diagnosis remains poor (20-30%) and also requires consideration of novel therapeutic strategies.[2,15]

For patients without metastatic disease, delayed tumor resection has been associated with survival rates comparable to the survival rates observed in patients who undergo a primary resection at the time of diagnosis.[2] However, only approximately two-thirds of patients with unresectable tumors at diagnosis become resectable with chemotherapy[2] leaving too many children with gross residual disease. There is no good marker or method to predict which tumors initially considered unresectable will eventually become amenable to resection. OLT is sometimes the only option that may result in complete tumor removal and increased chance for cure.

In addition, biologic factors may be able to help predict tumor phenotype. These biologic variables may help to result in better identification of disease risk and therefore yield additional refinement criteria to risk-stratified therapy. This could decrease toxicity for the most favorable groups by limiting therapy and maximize therapeutic options for the most aggressive tumor phenotypes. Hepatoblastoma has been characterized by several genetic markers, including chromosomal numerical and structural aberrations, in particular specific trisomies of chromosome 2, 8, and 20 and translocations with breakpoints at chromosome 1q12.[16-19] The correlation of these genetic markers in response to treatment and outcome has been only minimally studied. It has recently been determined that translocation of the *NOTCH2* gene on chromosome 1 may be an important component to the development of some cases of hepatoblastoma.[20] As systematic evaluation of tumor biology may allow for refining risk stratification and for developing more targeted therapy for this childhood cancer, a goal for AHEP0731 is to characterize these genetic markers with respect to their association with outcome.

### 2.2 Pathologic Considerations

The presence of SCU components in the resection specimen is an unfavorable histologic variant and has been previously associated with a trend towards an increased risk for an adverse event ($P = 0.15$). However, the number of patients with SCU tumors reported in the literature is relatively small.[5] In the largest previous report, Haas and colleagues described the presence of SCU elements in 16 patients with Stage I tumors. A much higher than expected relapse rate for Stage I patients was observed in this cohort with recurrences in 10 of the 16 patients.[5] Relapses and death were seen even in patients with a small focus of SCU, including 1 patient who ultimately died from disease and had only 1 microscopic SCU focus among 8 slides examined. These observations warrant further study. The adverse prognostic impact of SCU in the reported cases warrants that the presence of any SCU elements must be considered as significant. In an analysis of data from CCG trial CCG-881, survival was 70% in Stage I patients without SCU (n = 30) vs. 50% in Stage I patients with SCU (n = 4). In a similar analysis of the INT-0098 study, recurrence was observed in 9% of non-SCU, non-PFH Stage I patients (n = 35) compared to a 38% recurrence rate in Stage I patients with SCU (n = 8). The presence of SCU elements has also been recently identified and correlated with the presence of a low alphafetoprotein (AFP) level (< 100 ng/mL), another poor prognostic variable, and has

been observed in all stages of hepatoblastoma[21]. Previous cytogenetic reports have demonstrated that SCU hepatoblastomas have chromosome aberrations involving chromosome 22q11.[22,23] A deletion of the rhabdoid associated gene, hSNF5/INI1 gene, has been observed in tumor tissue from 1 patient with SCU histology studied in the hepatoblastoma biology study POG 9346. A recent report summarizes similar findings in 11 patients with Stage III and IV disease with elements of SCU histology who often had low AFP and responded poorly to therapy. These patients clearly require novel therapeutic approaches.[24]

## 2.3 Risk-Stratified Treatment

### 2.3.1 Very Low-Risk Patients

Very low-risk patients will include those patients who have grossly resected tumors (Stage I) with PFH AND have an elevated AFP level > 100 ng/mL.

Patients with Stage I PFH hepatoblastoma have been considered as a "favorable" subtype and have been treated with surgical resection without adjuvant chemotherapy on the COG P9645 study. The rationale for this approach was based upon reports of selected patients who fared well with surgery alone.[25] Stopping rules for the failure of this hypothesis have not been met on the current P9645 study and no events have been observed in the 18 patients enrolled on the study to date.[26] All 18 patients enrolled onto P9645 study were alive and free of disease at the time of last contact, at a mean post-resection interval of 3.7 years (personal communication, Mark Krailo, PhD). This suggests that surgical resection alone provides adequate therapy for this selected subset of children with hepatoblastoma. Utilization of this approach limits unnecessary and harmful exposure to various chemotherapeutic regimens, such as cisplatin, vincristine, 5-fluorouracil, and doxorubicin in the approximately 4% of all children with Stage I PFH hepatoblastoma.

### 2.3.2 Low-Risk Patients

Low-risk patients will include those patients who have grossly resected tumors (Stages I and II) AND lack any unfavorable biologic feature (ie, any SCU elements or a low diagnostic AFP level < 100 ng/mL).

Approximately 20-30% of children with hepatoblastoma can be expected to be classified as low-risk. In the POG 8696/8697, INT-0098, and P9645 studies, these patients received 4 adjuvant cycles of C5V. The 5-year EFS was 84% and survival was 96% in patients treated with this approach.[6] This approach has used the most active compound, cisplatin, as the integral component of therapy while avoiding exposure to anthracyclines and ifosfamide and their associated short- and long-term toxicities for the 15-30% of low-risk patients diagnosed with hepatoblastoma and treated on COG studies. The 5-year EFS for Stage I patients with non-PFH is 91% and survival is 98% in patients treated with this approach.[6] Cumulative Grade 3-4 toxicities associated with 4 cycles of this regimen on P9645 include: anemia (45%), neutropenia (75%), thrombocytopenia (11%), anorexia (10%), vomiting (14%), febrile neutropenia (16%), and stomatitis (2%). Noticeable hearing loss (> 40 dB at any frequency from 3-5 kHz or > 20 but ≤ 40 dB at 2 kHz) as a measure of ototoxicity occurred in 2 of 21 evaluable patients (10%). This therapy has a significant impact on both the short-term and long-term quality of life in these children. Therefore, the history of the successful use of the C5V regimen within COG studies over the last 20 years has led to the point where a reduction in chemotherapy appears justified in the subset of patients with non-PFH, non-SCU hepatoblastoma who have an excellent prognosis. In addition, the successful reduction in therapy for Stage I PFH patients treated with surgery alone helps to justify the reduction in therapy for this group of Stage I non-PFH, non-SCU patients who comprise about 20-25% of all hepatoblastoma patients. Strict monitoring criteria and stopping rules will be utilized to ensure patient safety and maintain excellent EFS.

While cisplatin has been the backbone of hepatoblastoma therapy, the additional agents used in combination with cisplatin have differed among the various cooperative groups. It is somewhat difficult to compare the results of COG studies with that of international groups as different staging criteria have been used and therefore comparison groups are not necessarily equivalent. COG and the German Cooperative Pediatric Liver Tumor Studies have used a surgical staging system. SIOPEL (International Childhood Liver Tumour Strategy Group) has classified patients using radiographic criteria as part of the PRETEXT (Pretreatment Extent of Disease) system and has categorized standard-risk patients as those with tumors that are either PRETEXT 1, 2, or 3.[3] This standard-risk group is fairly similar to the Stage I and II COG patients classified in this trial as low-risk. The most recent published results of SIOPEL-2 have focused on the use of cisplatin monotherapy for these standard-risk patients who received a total of 6 cycles of cisplatin at 80 mg/m$^2$ for a cumulative dose of 480 mg/m$^2$.[3] This is more than the total cumulative dose given during the 4 cycles of cisplatin at 100 mg/m$^2$ used for resected Stage I and II patients on COG studies such as P9645. In the German Cooperative Group HB studies, resected patients received 2 to 3 cycles of doxorubicin (60 mg/m$^2$) and ifosfamide (3500 mg/m$^2$) in addition to cisplatin (20mg/m$^2$ x 5) exposing these patients to much more toxic chemotherapy than in resected Stage I and II COG patients.[7,27] The further reduction in this study to 2 cycles of cisplatin for low-risk patients should reduce both associated toxicity and medical costs. A comparison of survival rates in several recent studies is summarized in Table 1. Survival rates among COG and SIOPEL groups are comparable with SIOPEL-2 standard-risk patients having a 3-year progression-free survival (PFS) of 89 ±7% compared to 88 ±6% for low-risk COG patients treated with C5V on INT-0098 and 86 ±6% for COG patients treated with C5V without amifostine on P9645.[3] However, results of the SIOPEL-2 trial must be interpreted with caution for several reasons: 1) the study uses any tumor shrinkage or decrease in AFP as a response, which is far less stringent than the 50% decrease in tumor size used as response criteria on COG studies; 2) of the 77 patients who were classified as standard-risk, 23 (30%) were not treated according to protocol and received additional, more intense therapy with doxorubicin and carboplatin, making the SIOPEL-2 results difficult to interpret. When chemotherapy administration in violation of protocol was considered as an event in the SIOPEL-2 study, the 3-year EFS was substantially inferior to COG studies at only 73 ± 11% for the standard-risk patients.[3]

Table 1. Treatment and Survival of Resectable and Non-Metastatic Hepatoblastoma Patients in Recent Studies

| Study | Treatment | Number of Patients | Stage | EFS (%) | S (%) |
|---|---|---|---|---|---|
| P9645[26] | CDDP/5-FU/VCR | 55 | I/II | 84* | 96* |
| INT-0098[6] | CDDP/5-FU/VCR<br>CDDP/DOXO | 26<br>24 | I/II<br>I/II | 88*<br>96* | 100*<br>96* |
| SIOPEL-2[3] | CDDP | 6<br>36<br>25 | I/II/III<br>(PRETEXT) | 73# | 91# |
| SIOPEL-1[14] | CDDP/DOXO | 6<br>52<br>45 | I<br>II<br>III<br>(PRETEXT) | 100&<br>83&<br>56& | 100&<br>91&<br>68& |
| HB-94[7] | CDDP/DOXO/IFOS | 27<br>3 | I<br>II | 89<br>100 | 96<br>100 |
| HB-89[27] | CDDP/DOXO/IFOS | 21<br>6 | I<br>II | 100<br>50 | Not provided |

* = 4-year EFS or S; & = 5-year EFS and S; # = 3-year EFS and S

While the roles of vincristine and 5-fluorouracil used in COG studies are not entirely clear, indirect evidence suggests that these 2 agents are active against hepatoblastoma and may be synergistic with cisplatin. COG results compare favorably with those reported in the SIOPEL studies using the PLADO regimen (CDDP and DOXO) and with the 3 drug IPA regimen (IFOS, CDDP, DOXO) used in the HB (German Cooperative

Pediatric Liver Tumor) studies. If vincristine and 5-fluorouracil were entirely inactive, then it would be expected that both the PLADO and IPA regimens should be superior to C5V. However, the results of SIOPEL and HB trials have been either equivalent or inferior to COG studies (see Table 1) despite more intense chemotherapy exposure in the international studies. In addition, in the most recent COG study, P9645, the experimental arm of intensified platinum-based therapy with cisplatin and carboplatin that was administered to advanced-stage patients proved to be inferior to the C5V regimen, suggesting that the addition of vincristine and 5-fluorouracil may add to the activity of single-agent cisplatin. Since cisplatin is the main cause of chemotherapy-related toxicity in low-risk patients, the best strategy to decrease toxicity may be to decrease the total dose of cisplatin that is administered. The continued use of vincristine and 5-fluorouracil and their potential synergy with cisplatin may be a significant contributor to the safe reduction in the total cumulative dose of cisplatin delivered to low-risk patients. The toxicity associated with vincristine and 5-fluorouracil is mild with little to no expected long-term toxicity as compared to the significant short- and long-term toxicities often associated with doxorubicin, ifosfamide, or etoposide.

These data demonstrate that low-risk COG patients (Stage I non-PFH, Stage II patients) have:

- excellent survival with the current COG standard therapy C5V,
- equivalent, if not better, survival with C5V when compared to other cooperative group regimens;
- potential for diminished toxicity when using regimen C5V compared with other regimens by avoiding the use of anthracyclines and ifosfamide; and
- potential for salvage in the event of relapse with the administration of doxorubicin when it is excluded from initial treatment.

For these reasons, C5V is the optimal treatment for the 20-25% of patients with non-PFH, low-risk disease.

2.3.3 Intermediate-Risk Patients

Enrollment to stratum 3 was suspended on 12 March 2012 at the completion of the required number of patients to address study aim 1.1.3. Enrollment to this particular stratum will not reopen.

Intermediate-risk patients will include those patients with: 1) gross residual disease/unresectable disease; or 2) grossly-resected disease with any SCU elements but who do not have metastatic disease and do not have a low diagnostic AFP level < 100 ng/mL.

The Pediatric Intergroup Study INT-0098 randomized patients with hepatoblastoma to receive treatment with either C5V [cisplatin (90 mg/m$^2$), 5-fluorouracil (600 mg/m$^2$), and vincristine (1.5 mg/m$^2$)], or CD [cisplatin and doxorubicin (80 mg/m$^2$)]. Resected patients received 4 cycles whereas initially unresected patients received 6 or 8 cycles to a maximum total of 720 mg/m$^2$ of cisplatin and 640 mg/m$^2$ of doxorubicin.[6] Three patients treated with CD developed congestive heart failure, 2 of whom died. No significant renal toxicity was reported and information on ototoxicity was not specifically measured or reported. Five-year EFS was 64% for 83 Stage III patients and 25% for 40 Stage IV patients. Survival for children with localized hepatoblastoma was approximately 70%, while for those with metastatic disease at diagnosis, survival was approximately 35%. Although there was no significant difference in outcome between the 2 treatment arms, they differed with regards to the types of events observed. Tumor progression accounted for 86% of the events among patients treated with C5V, but only 50% of the events for those treated with CD. Consequently, COG adopted treatment with C5V as the standard for the treatment of patients with hepatoblastoma. While the doxorubicin arm was associated with a greater number of toxic events and deaths, these results do suggest some improved tumor response for patients receiving doxorubicin. AHEP0731 will evaluate whether the addition of doxorubicin can improve EFS in children with intermediate- and high-risk disease. In patients with unresectable and metastatic disease at diagnosis, no published treatment regimen has demonstrated clearly superior results (see Table 2). Therefore, it is reasonable to consider the use of C5VD as a novel therapeutic strategy to improve EFS for intermediate-

and high-risk patients. The addition of doxorubicin to the C5V regimen in this trial will intensify the regimen in an attempt to improve the outcome for intermediate-risk patients. A goal of AHEP0731 is to determine the feasibility and toxicity of adding doxorubicin to the chemotherapy regimen of C5V for children with intermediate-risk hepatoblastoma.

The administration of doxorubicin in the majority of previous trials has been by continuous infusion.[6,14,27] However, there are no data that establish continuous infusion doxorubicin as more efficacious than bolus administration. Prolonged administration of doxorubicin requires hospitalization and results in more mucositis and myelosuppression. Additionally, there is no documented evidence that continuous infusion doxorubicin results in diminished cardiac toxicity.[28-30] The incidence of significant cardiac toxicity in INT-0098 was relatively small with 3 patients (4%) developing congestive heart failure among 81 patients who were intended to receive either 320 mg/m$^2$ (n = 24) or 640 mg/m$^2$ (n = 57) of doxorubicin.[6] In an older study, CCG-823F, > 400 mg/m$^2$ of doxorubicin was given to 30 patients with no cardiac dysfunction reported.[13] Cisplatin was also given in that study at 100 mg/m$^2$ for a total of 4 or 8 courses depending upon the timing of resection. Magnesium wasting occurred in 13% of patients but no other permanent renal dysfunction was reported. Since the EFS in patients with Stages III and IV disease is less than desirable at 64% and 25% respectively,[6] the relatively small risk of cardiac toxicity with a maximum cumulative dose of 360 mg/m$^2$ is reasonable. No data have been established to suggest that the administration of dexrazoxane (DXRZ) has impaired survival in pediatric malignancies. Therefore, the cardioprotectant dexrazoxane will be incorporated into AHEP0731 treatment postoperatively for all patients (when the doxorubicin dose has exceeded 240 mg/m$^2$). In this trial, doxorubicin will be administered over 15 minutes on 2 consecutive days.

The HB studies from the German Cooperative Pediatric Liver Group have used a slightly different treatment strategy and have incorporated ifosfamide and etoposide along with cisplatin and carboplatin. In HB-89, patients were treated with ifosfamide (3500 mg/m$^2$), doxorubicin (60 mg/m$^2$), and cisplatin (20 mg/m$^2$ x 5) per cycle. Twenty-one Stage I patients received 3 cycles and had 100% disease-free survival (DFS) while 6 Stage II patients received 4 cycles and had only 50% DFS. DFS was 71% in 38 Stage III patients and only 9% for the 7 Stage IV patients.[27] A separate report from the HB-89 study reported on a total of 37 patients with unresectable or metastatic disease. However, the number of chemotherapy courses was not standardized as 21 patients received 2 courses, 5 patients received 3 courses, 7 patients received 4 courses, 3 patients received 5 courses, and 1 patient received 6 courses.[31] Thus, the efficacy of the IPA regimen in inducing resectability and survival is not assessable because it was not administered in a consistent manner. In HB-94, a total of 69 patients with hepatoblastoma were treated according to a complex treatment schema with CDDP/DOXO/IFOS and with additional carboplatin and etoposide administered to 46% of patients with poor response. Again, it is difficult to discern the number of cycles different patients received, but EFS was 89% for 27 Stage I patients, 100% for 3 Stage II patients, 68% for 25 Stage III patients, and 21% for 14 Stage IV patients. These results are no different and no better than that observed in COG studies.[7]

A summary review of the results from the most recent COG, SIOPEL, and HB studies is shown in Table 2. These results demonstrate that there is no clearly superior regimen when comparing the largest international trials. Overall survival for patients treated on P9645 was greater than that observed in SIOPEL-2 and may reflect the ability to salvage patients with the use of doxorubicin.

Table 2. Treatment and Survival of Unresectable and Metastatic Hepatoblastoma Patients in Recent Studies

| Study | Treatment | Number of Patients | Stage | EFS (%) | S (%) |
|---|---|---|---|---|---|
| P9645[26] | CDDP/5-FU/VCR | 38<br>10 | III<br>IV | 63*<br>50# | 88*<br>67# |
| INT-0098[6] | CDDP/5-FU/VCR<br><br>CDDP/DOXO | 45<br>21<br>38<br>19 | III<br>IV<br>III<br>IV | 60*<br>14*<br>68*<br>37* | 68*<br>33*<br>71*<br>42* |
| SIOPEL-2[3] | CDDP/DOXO/CARBO | 21<br>25 | IV<br>Metastatic (PRETEXT) | 48#<br>(combined) | 61#<br>44# |
| SIOPEL-1[14] | CDDP/DOXO/IFOS | 39<br>31 | IV<br>Metastatic (PRETEXT) | 46&<br>28& | 57&<br>57& |
| HB-94[7] | CDDP/DOXO/IFOS<br>VP/CARBO | 25<br>14 | III<br>IV | 68<br>21 | 76<br>36 |
| HB-89[27] | CDDP/DOXO/IFOS | 38<br>7 | III<br>IV | 71<br>29 | Not provided |
| SIOPEL-3HR[32] | CDDP/DOXO/CARBO | 70 | IV | 56# | 62# |
| SIOPEL-4 | CDDP/DOXO/CARBO | 39 | M+/IV | 77# (95% CI 63-90) | 79# |

* = 4-year EFS or S; & = 5-year EFS and S; # = 3-year EFS and S

Xenograft studies have been performed using doxorubicin, cisplatin, carboplatin, etoposide, and ifosfamide.[32] Reduction in tumor size and declines in AFP values were only seen following cisplatin and doxorubicin. Ifosfamide, carboplatin, and etoposide caused a slightly lower rate of tumor growth when compared to controls. Based on this xenograft study it was concluded that as single agents, cisplatin and doxorubicin are most effective, ifosfamide is effective in some, carboplatin is moderately effective, and etoposide is ineffective. This xenograft report followed the completion of HB-94 which incorporated all of these agents. Previous phase 2 studies have evaluated the response of ifosfamide in 3 patients with hepatoma. None of the 3 patients showed a response.

### 2.3.4 High-Risk Patients

High-risk patients include: 1) any patient with metastatic disease; 2) any patient with a low diagnostic AFP level < 100 ng/mL, regardless of stage (see Section 7.1).

Based on multiple cooperative group studies, the 40-70% EFS for unresectable patients and 20-40% EFS for metastatic patients remain suboptimal (see Table 2). The optimal dose of cisplatin to administer to patients with unresectable and metastatic disease is unclear. However, as cisplatin is the most active agent for hepatoblastoma, intensification of cisplatin therapy may be beneficial. The dose of cisplatin proposed for intermediate- and high-risk patients in this trial exceeds doses used in other trials. SIOPEL administers an additional 3 grams of platin-based therapy with carboplatin to patients who receive 320 mg/m$^2$ of cisplatin. SIOPEL-4, the current study for high-risk patients includes cisplatin (570 mg/m$^2$), doxorubicin (300-350 mg/m$^2$) and 2-3 courses of carboplatin. The HB studies administer 12,000 mg/m$^2$ of ifosfamide. Table 3 provides a dose comparison of the cumulative chemotherapy dosing for intermediate- and high-risk patients being used in current studies.

Table 3. Cumulative Dosage* of Chemotherapy in Advanced-Stage Patients According to Treatment Regimen

| Study | CDDP | DOXO | IFOS | CARBO | VCR | FU |
|---|---|---|---|---|---|---|
| **AHEP0731** | 600 | 360 | 0 | 0 | 33-39 | 3600 |
| **P9645** | 600 | 0 | 0 | 0 | 0 | 0 |
| **SIOPEL-2** | 320 | 360 | 0 | 3000 | 0 | 0 |
| **SIOPEL-4** | 570 | 300-350 | 0 | 2-3 courses | 0 | 0 |
| **HB-GPOH** | 400 | 240 | 12000 | 0 | 0 | 0 |

*Chemotherapy dosing is mg/m$^2$

Chemotherapy is an important part of the treatment for patients with hepatoblastoma. However, since the introduction of platinum agents as part of the chemotherapy for hepatoblastoma, no new agents with significant activity have been identified. As most pediatric phase 1 and 2 studies usually include less than 2 patients with liver tumors, identification of new effective agents against these tumors has been and will continue to be a challenge. Children with metastatic hepatoblastoma account for 25% of all cases of this disease. The outcome for these patients over the last 30 years has remained poor, despite intensive chemotherapy with the best available agents including cisplatin and doxorubicin (PLADO) as given by SIOPEL or COG, or with C5V as developed by POG and compared in INT-0098.[6] All of these studies show similar unacceptable outcomes with < 40% 5-year EFS.[3,6,7] Although patients often respond well initially, these early responses have not translated into cures. For example, Katzenstein, et al observed initial partial responses (PRs) to carboplatin alone in 55% of advanced-stage patients, but the 5-year EFS of Stage IV patients was still only 27%.[2] New agents for this high-risk group of children are urgently needed.

Irinotecan (IRIN) is a topoisomerase I inhibitor with significant anti-tumor activity against human tumor xenografts.[33-35] Irinotecan, with or without doxorubicin, is currently being administered to relapsed patients in a SIOPEL trial which has been accruing patients slowly and has yet to release results. Anecdotal data in the literature[36,37] and from members of the Liver Tumor committee exist for a total of more than 10 patients with recurrent or progressive hepatoblastoma who have been treated with irinotecan using different administration schedules (personal communication, Dr. O Beaty and Dr. H Katzenstein). Of these patients, 6 achieved a PR lasting 3 to 12 months. Two patients with lung metastases had complete disappearance of the lung nodules and normalization of AFP levels (6 and 11 months). Two other patients showed no response to therapy. Overall therapy was well tolerated with myelosuppression and diarrhea as the most common side effects. PRs in 6 of these very heavily pretreated patients suggest that irinotecan may be an active drug in this disease and justifies its evaluation in a group of patients who have a 70% chance of eventually succumbing to their disease with "standard therapy".

In the initial window therapy arm (Regimen W) of AHEP0731, vincristine was given with irinotecan. Outcome information remains blinded but sufficient responses were seen to evaluate a full cohort of 30 patients. This provides scientific rationale to attempt to build upon this potentially active novel combination. The regimen was well tolerated and suitable to be considered as a backbone for the addition of other agents.

2.3.4.1 Rationale for Addition of Temsirolimus to Irinotecan/Vincristine

The mammalian target of rapamycin, mTOR, is a serine/threonine kinase that is a component of the TORC1 complex that senses nutritional status of cells (e.g., amino acids, oxygen tension, glucose, and in mammalian cells, growth factor signaling), and regulates entry from G1 phase into S phase.[38,39] mTOR also regulates protein synthesis of HIF (hypoxia inducible factors) proteins[40-42] These proteins regulate tumor angiogenesis and survival pathways that permit tumor growth in the hypoxic conditions common in many solid tumors, suggesting that inhibition of mTOR would be detrimental to the survival of many solid tumors.

In fact, inhibition of mTOR with rapamycin results in decreased proliferation of human neuroblastoma cells in vitro,[43,44] and synergistically enhances chemotherapy-induced cytotoxicity to a number of standard chemotherapy agents including: paclitaxel, carboplatin, vinorelbine, cisplatin, as well as camptothecin in human breast cancer cells[45] and medulloblastoma cells.[46] In animal studies with subcutaneously implanted rhabdomyosarcoma, and neuroblastoma xenografts, tumor bearing mice received intravenous irinotecan (1.25 mg/kg) daily for 5 days on 2 consecutive weeks. Cycles of therapy were repeated at 21 days for a total of 3 cycles [designated [(dx5)2]3]. Rapamycin (5 mg/kg) was administered by intraperitoneal injection daily for 5 days for up to 12 consecutive weeks. There was superior activity for the combination against both rhabdomyosarcoma and neuroblastoma xenografts. Irinotecan induced a maintained complete response as did the combination, with no evidence of drug antagonism and combination treatment appeared to be additive in effect. These results suggest that rapamycin does not abrogate the activity of irinotecan, but may in some models potentiate its antitumor activity (Peter Houghton, unpublished data). Recently, the use of rapamycin has been shown to induce apoptosis in HB cells in vitro and to decrease HB growth in mouse xenografts.[47]

2.3.4.2 Temsirolimus in Children with Cancer

Temsirolimus is an mTOR inhibitor approved by the FDA for the treatment of renal cell carcinoma. It is an ester of sirolimus (rapamycin) and a recommended Phase II dosage as a single agent has been determined in children, although no maximum tolerated dosage was determined. Nineteen patients were enrolled on study. Dose limiting toxicities at 150 mg/m$^2$ included Grade 4 thrombocytopenia and Grade 3 anorexia. Other Grade 3 or 4 toxicities included leukopenia (17%), anemia (11%), neutropenia (22%) and elevated ALT. A dose of 75 mg/m$^2$ weekly IV was recommended for study in the Phase II pediatric setting.[48] In this Phase I study in children with refractory solid tumors, no patients with hepatoblastoma were entered. However there was one CR in a heavily pretreated neuroblastoma patient and three other patients (one each with an ependymoma, germ cell tumor and adrenocortical carcinoma) had disease stabilization for more than 4 months.[48]

In a study of newly diagnosed children with high-risk neuroblastoma at St. Jude Children's Research Hospital, 3 children were treated with 50 mg/m$^2$ of temsirolimus weekly x 6 with irinotecan at 20 mg/m$^2$/day x 5 x 2 repeated every 21 days for 2 courses. Three patients received 5 courses without significant chemotherapy related side effects. Two of these patients went on to receive weekly temsirolimus x 2 with each additional induction chemotherapy combination without significant increased toxicity (W. Furman, unpublished data). Additionally, the Children's Oncology Group has a Phase I study (ADVL0918) of temsirolimus in combination with irinotecan and temozolomide which completed accrual and has determined temsirolimus at a dose of 35 mg/m$^2$/dose d 1 and 8 to be tolerable in combination with irinotecan (90 mg/m$^2$/dose) d 1-5, and temozolomide (100 mg/m$^2$/dose) d 1-5 in children with refractory solid tumors

Thus temsirolimus is safe as a single agent, in children at dosages up to 150 mg/m$^2$ weekly IV and has evidence of single agent efficacy in heavily pretreated children with a variety of solid tumors. Also, there are data in a number of preclinical cancer models suggesting that an mTOR inhibitor in combination with several commonly used chemotherapeutic agents, including irinotecan[49] is at least additive.[45,46] Finally, temsirolimus has minimal systemic toxicity in humans and these untoward effects do not significantly overlap with the adverse effects seen with irinotecan or vincristine. In addition, since mTOR inhibitors are used to prevent solid organ rejection, mTOR inhibitor use in children with high-risk hepatoblastoma, some of whom may need liver transplantation, is intriguing in that if it is proven to have antitumor efficacy it may then be preferentially used as part of post-graft prophylaxis to preventing graft rejection and treat minimal residual disease at the same time.

Temsirolimus was tolerated at 35 mg/m2 weekly x 2 with 90 mg/m2 of irinotecan daily x5 and temozolomide 100 mg/m$^2$/d 1-5 in ADVL0918 [50], therefore we are proposing to use that same dose of temsirolimus with 50 mg/m$^2$/d, qd x5 of irinotecan and 1.5 mg/m$^2$/ dose of vincristine. Because of the young

age of hepatoblastoma patients, the oral agent temozolomide (as used in ADVL0918) will not be used and IV temsirolimus will be given in combination with IV irinotecan and vincristine. As noted above toxicities of vincristine and temsirolimus are non-overlapping and should be well tolerated.

AHEP0731 will estimate the response rate associated with 2 cycles of vincristine, irinotecan and temsirolimus (VIT) when administered as "up-front" window therapy for the treatment of high-risk children with metastatic hepatoblastoma (Stage IV).

Patients who develop frank progression after the first course of VIT will proceed directly to therapy with C5VD. Responders will continue treatment with VIT and C5VD and will receive a total of 4 cycles of VIT (Cycles 1, 2, 7 and 10) and 6 cycles of C5VD. All patients, with the exception of patients enrolled in Japan (where dexrazoxane is currently unavailable), will receive dexrazoxane with the final 2 cycles of C5VD.

### 2.4 Prognostic Variables

The decline of AFP levels after 4 cycles of chemotherapy and prior to surgical resection of the tumor has been shown to have prognostic value.[51] However, no data have been reported to suggest that the initial rate of decline or the magnitude of decline of AFP after each cycle can be used to guide therapy. Data analyzed from INT-0098 and P9645 do not support AFP decline as a useful tool in low-risk patients (personal communication, Dr. M Malogolowkin). Initial AFP < 100 ng/mL has been described as being associated with an adverse outcome. While older reports of liver tumors with low AFP levels may include some misdiagnoses with other malignant liver disorders, recent reports continue to suggest that AFP < 100 ng/mL is associated with worse prognosis in hepatoblastoma. Data from SIOPEL evidenced 3-year EFS of 13% in patients with a low AFP regardless of stage.[21] As a result, patients in AHEP0731 with a low AFP at the time of initial diagnosis regardless of stage will be considered to be high-risk and treated accordingly (see Section 7.1).

Additional risk factors including histologic subtype, especially macrotrabecular and small cell undifferentiated,[52,53] PRETEXT group,[54] surgical margin,[55,56] surgical complications,[57,58] and diffuse multifocal tumors[59] have been reported to have potential prognostic value in hepatoblastoma and should be further investigated in a prospective, multigroup setting. Collaboration among international colleagues would be particularly advantageous for the collection of these potential prognostic variables, thereby enabling the data to be pooled into a cooperative database and allowing increased statistical power to make subtle, or rare, observations.

### 2.5 Surgical Considerations

When the proportion of Stage I patients in INT-0098 is compared with P9645, it appears that over the 1990's there was a trend away from upfront surgical resection. Stage I patients accounted for 28% (51/182) of the total in INT-0098 and 23% (40/175) of the total in P9645. However, as the data below suggest, this phenomenon occurred prior to the start of P9645 and is now static. Recent anecdotal trends in hepatoblastoma treatment within COG institutions have hinted at a possible decrease in the numbers of Stage I patients and an increase in the number of Stage III patients. This situation reflects a possible paradigm shift towards the SIOPEL strategy using pre-operative chemotherapy to shrink tumors, increase resectability, and decrease surgical morbidity associated with resection. However, one potential result of this practice is an overall increase in the amount of chemotherapy that patients receive. In the most recent COG study, P9645, patients who only had an initial biopsy performed received a total of 6 cycles of therapy which is 2 cycles more of chemotherapy than patients who underwent primary resection and received a total of 4 cycles of treatment. These additional cycles of chemotherapy result in increased short-term and long-term toxicity. In addition, "extra" cycles of chemotherapy are often administered by treating physicians and surgeons to make a tumor resectable. In spite of this, a review of data from INT-

0098 indicates that 4 extra cycles of therapy did not increase the likelihood of tumor resectability in patients who were not resected after the initial 4 cycles of chemotherapy.

The reported incidence of surgical morbidity and mortality on previously conducted COG studies has historically been extremely low. Yet, as a recent retrospective analysis of INT-0098 revealed (personal communication, Drs R Meyers and M Malogolowkin), this issue has not been rigorously investigated in prior studies. With the advanced surgical and radiological techniques currently available, it would be expected that surgical morbidity and mortality rates could be even lower. In an attempt to minimize surgical risk, specific surgical guidelines using PRETEXT criteria have been developed. It is expected that these guidelines will maximize the number of patients with localized PRETEXT 1 and 2 tumors that are most appropriately resected at diagnosis (Stage I), and minimize the number of patients with PRETEXT 3 and 4 tumors where attempts at resection at diagnosis would lead to increased surgical risk. It is interesting and important to note that the most recent publication of SIOPEL-2 reported 4 surgery-related deaths in patients treated preoperatively with chemotherapy.[3] This is more than reported in any previous COG study. A surgery-related death was reported in only 1 of the 182 patients with hepatoblastoma treated on INT-0098[6] In the HB-89 study, surgical complications occurred in 15% of patients who had a primary resection and 21% of patients who had a resection following chemotherapy, failing to validate the hypothesis that preoperative chemotherapy will diminish the incidence of surgical morbidity.[27] Although these numbers might suggest that upfront resection carries less risk of surgical morbidity, it is important to note that the PRETEXT classification of these tumors is not known. It is to be expected that much greater surgical morbidity would be observed in PRETEXT 3 and 4 tumors, the very tumors that are most likely to have been treated with neoadjuvant chemotherapy. The ultimate question is whether the risk of upfront surgical morbidity and mortality exceeds that of the additional chemotherapy administered to patients who have delayed resections. Various cooperative groups have established different criteria for diagnoses in part because of concerns with biopsy-related surgical morbidity. The SIOPEL group has treated patients on study without a diagnostic biopsy as was done in nearly 20% of patients on SIOPEL-1. Within COG, up to this point in time, a diagnostic sample has been required for all patients treated on study.

Specific guidelines for surgical approaches to hepatoblastoma are provided in AHEP0731 since surgery is the critical component necessary for obtaining a cure. Patients with PRETEXT 1 and 2 tumors that have a clear radiographic 1 cm margin on CT or MRI imaging at diagnosis should have a resection performed as soon as possible after the diagnosis of hepatoblastoma is confirmed. The surgical strategy for patients with more advanced PRETEXT-group disease is described in the surgical guidelines section of the protocol (see Section 13.0).

No patient with Stage IV disease will be offered a liver transplant unless all metastatic extra-hepatic disease has been radiographically documented to either have disappeared as a result of neoadjuvant chemotherapy or has been surgically removed.

The historical barrier of “unresectability” can be redefined with the concept of “total liver resection” and salvage OLT. Interestingly, although 1 of the first long-term survivors of liver transplantation was a child with hepatoblastoma, the role of liver transplantation in the treatment of pediatric hepatoblastoma has never been fully defined. Because liver transplant has not historically been offered to these children as part of a planned treatment algorithm, the optimal timing of transplantation and the potential role of post transplant adjuvant chemotherapy remain unclear. Largely due to negative experience with liver transplant in the treatment of adult hepatocellular carcinoma, liver transplant for the treatment of hepatic malignancy developed an early reputation as a dreaded, heroic last resort, and even potentially ethically-inappropriate intervention. But the biology of pediatric hepatoblastoma has proven to be very different from that of adult hepatocellular carcinoma, and experience with liver transplantation for hepatoblastoma has been far more favorable.

In study after study, complete surgical resection has been the most important predictor of survival.[6,51,60-62] Eleven studies reporting outcome after liver transplantation for unresectable hepatoblastoma have been published in the past decade.[63,64] All but 1 of these studies are single-institution studies, with small numbers of highly selected patients. Factors thought to contribute to improved survival rates include complete resection as soon as possible after completing planned Induction chemotherapy (usually 4 cycles), avoiding excessive cycles (> 4-6) of pre-transplant chemotherapy, and a favorable response to chemotherapy. In Birmingham, England, 5-year DFS was 100% when primary transplant was performed in patients with a good response to chemotherapy, 60% with primary transplantation in patients having a poor response to chemotherapy, only 50% in patients with transplant as a second option or "rescue transplantation", and 0% in patients not undergoing surgery.[65] In SIOPEL-1, overall survival at 10 years was 85% with a primary transplant, but only 40% for the children who underwent a rescue transplant.[66] In a collaborative report of the world experience of liver transplantation for hepatoblastoma,[64] overall survival rate at 6 years was 82% for 106 patients who received a "primary transplant", but only 30% for 41 patients who underwent a rescue transplant. These data stress the importance of facilitating primary transplant as it is far superior to rescue transplant in yielding long-term survival.

The current United Network of Organ Sharing (UNOS) policy for liver allograft allocation in children with pediatric hepatoblastoma gives the patient an automatic Pediatric End Stage Liver Disease (PELD) priority score of 30. The PELD system is used to determine allograft distribution priority in children. A similar scoring system called MELD is used for adults. A PELD/MELD score of 30 places the patient at the top of the list and takes priority over all other listed patients, except Status I. For non-cancer patients, Status I means the patient is dying from liver failure, in an intensive care unit (ICU), with a life expectancy < 7 days. Cancer patients are allowed to be listed as Status I, even though they are not in liver failure in an ICU, under the condition that they have not received a liver allograft within 30 days at the top of the PELD system. Average waiting time as a Status I patient is 3-7 days. The verbatim policy is quoted below:

> UNOS Policy 3.6.4.4.1, November 19, 2004. Pediatric Liver Transplant Candidates with Hepatoblastoma: A pediatric patient with non-metastatic hepatoblastoma who is otherwise a suitable candidate for liver transplantation may be assigned a PELD (less than 12 years old) or MELD (12-17 years old) score of 30. If the candidate does not receive a transplant within 30 days of being listed with a PELD/MELD of 30, then the candidate may be listed Status I.

Hepatoblastoma patients who are determined to be candidates for liver transplant and identified to UNOS, have a good chance of receiving a donor liver. This modality may present a viable method of obtaining complete extirpation of the tumor when conventional surgery is not possible. AHEP0731 will assess the feasibility of identifying appropriate hepatoblastoma patients in the context of the current healthcare system.

SIOPEL-1 introduced the PRETEXT system to the pediatric liver tumor community as an anatomic definition of the extent of liver involvement by the tumor, and the PRETEXT system depends upon accurate radiologic imaging and review.[67] The PRETEXT system aims to predict surgical resectability and prognosis. However, the PRETEXT system has not been fully validated. Results published on PRETEXT in the SIOPEL-1 study showed that preoperative PRETEXT grouping was accurate in only 51% of patients, and that 37% of patients were overstaged while 12% of patients were understaged using PRETEXT.[54] While this recent report claimed that PRETEXT was superior to the COG staging system, the validity of this conclusion is in question as the study excluded patients who failed neoadjuvant therapy and only included the select group of patients whose tumors were resectable. The number of surgically-staged metastatic patients in the study who survived was > 90%.[54] This result leads to questions about the reliability of this study as the survival of this cohort is so significantly superior and discordant from all other series in the

literature. The more recent SIOPEL-2 study did not fully validate PRETEXT either, as patients were categorized and treated as either high- or low-risk.[3] These high- and low-risk groups were each made up of several PRETEXT groups. No EFS data was provided for patients according to individual PRETEXT groups as is indicated in Tables 1 and 2 above. In addition, PRETEXT IV was not predictive of overall survival. So while the PRETEXT system has shown potential utility as a tool to compare treatment results between different multicenter trials, objectively quantify response to neoadjuvant chemotherapy, and predict surgical resectability, defining its precise role and validating its use is still required. Data to be collected for AHEP0731 will allow exploration of this issue.

In order to validate PRETEXT, central review of surgical and radiology CT scans must be performed to validate the PRETEXT grouping done at the local institutions. In AHEP0731, this review will be performed on an annual basis. CT scans will be repeated after the second cycle of chemotherapy in patients with Stage III and Stage IV tumors to determine potential surgical resectability. PRETEXT after the second cycle of chemotherapy will be denoted as POST-TEXT. The PRETEXT definition of potential need for a transplant is defined as:

- PRETEXT 3 extensive multifocal;
- PRETEXT 3 +V;
- PRETEXT 3 +P; or
- PRETEXT 4 extensive multifocal

Recent studies have shown long-term survival and cure in patients with known microscopic residual disease. For example, SIOPEL-1[66] evidenced that microscopic margins had no effect on the rate of survival.[57,66] The implications of microscopic margins are thus poorly understood and have never been evaluated prospectively in any hepatoblastoma trial. Microscopic positive margins have been repeatedly shown to increase the risk of local relapse, metastatic relapse, and death in patients with hepatocellular carcinoma. However, the implications of microscopically-positive margins on the recurrence and survival of patients with hepatoblastoma remains unclear. Data to be collected for AHEP0731 will allow exploration of this issue.

The most common site of metastasis for hepatoblastoma is the lung. The therapeutic approach and prognosis for patients with pulmonary metastases remains somewhat uncertain. A recent review of the INT-0098 data revealed that 18 patients who had previously achieved complete tumor clearance, experienced subsequent pulmonary relapse of their tumor (12 Stage I/II/III, 6 Stage IV). All 18 pulmonary relapse patients had salvage chemotherapy, 11 also had thoracotomy and pulmonary metastectomy (7) or thoracotomy and tumor biopsy (4). Only 2/11 were long-term survivors, both were Stage I relapse patients. For the 38 patients with metastatic disease at diagnosis, 9 underwent thoracotomy and pulmonary metastectomy either before (2), simultaneous with (5), or after (2) resection of their primary liver tumor. Six of these 9 patients with metastectomy were long-term survivors. These data demonstrate that there is much variation in the surgical approach to pulmonary metastasis in hepatoblastoma and that thoracotomy may have limited utility in the management of pulmonary relapse, but appears to be important in the management of metastases that persist following neoadjuvant chemotherapy. Other reports indicate that patients with metastatic disease, who are rendered free of gross disease by resection of the primary tumor, as well as resection of pulmonary metastases, may experience cure or long-term survival.[66,68] In SIOPEL-1, all 4 of the 22 patients with pulmonary metastases at diagnosis, in whom a metastectomy was performed, survived without residual disease.[66] Results were not as promising in SIOPEL-2 in which 8 out of 25 patients had surgery for lung metastases and only 3 of these patients survived.[3] The difference in outcomes for patients who achieve a clinical remission of pulmonary metastases as a result of surgical resection and for those who achieve clinical remission in response to chemotherapy remains unknown and needs to be defined. A better understanding of hepatoblastoma metastases isolated to the lung(s) would help guide therapy and predict prognosis more appropriately and reliably. Thus, adoption of a uniform strategy to pulmonary metastatic

lesions is critical. Data to be collected for AHEP0731 will allow exploration of the impact of surgical resection of metastatic pulmonary lesions on survival.

Because of the known potential side effects of impaired wound healing and thrombosis that could complicate primary tumor resection or orthotopic transplant, the protocol has been written to allow some latitude in the order of administration of chemotherapy cycles to optimally result in a 6 week temsirolimus free period prior to definitive resection. While theoretically possible, it is not expected that the order of therapy administration should affect outcome and that the total amount of delivered therapy for all window responders should be identical.

### 2.6 Significance

This study builds on the results of the last 20 years of hepatoblastoma clinical trials. AHEP0731 functionally divides patients into low-, intermediate-, and high-risk cohorts. It seeks to diminish toxicity in the approximately 30% of low-risk patients, increase survival in intermediate-risk patients and identify new agents(s) that may be used in high-risk and recurrent patients.

Since hepatoblastoma is a disease that is dependent upon surgical resection for curative potential, this study will ask several surgical questions that address key concepts in treatment and may be used to guide therapy in future trials. Survival rates are much better with primary transplant than after a rescue or salvage transplant. Unfortunately, too many children continue to be referred for transplant after having received additional undue chemotherapy and/or after a failed initial attempt at resection. Further concepts that remain unclear are: what is the optimal timing of transplantation and what, if any, is the role of post-transplant chemotherapy? The COG Liver Tumor Subcommittee would ultimately like to study these questions with a randomized protocol. However, unless appropriate patients will be referred to transplant centers in a timely fashion, embarking upon a randomized trial is likely doomed to failure. Thus, it must first be determined whether it is possible to capture at least 70% of eligible (potentially unresectable) patients and ensure that they can be referred in a timely fashion to a surgical center that offers surgical expertise in major pediatric liver resection and transplantation.

### 2.7 Race and Gender Statement

Previous studies completed and published by COG and others show no differences in outcome by race and/or gender when such parameters were analyzed.

### 2.8 COG and Japanese Study Group for Pediatric Liver Tumors (JPLT) Collaboration

The high-risk stratum on this protocol (Stratum 4) will be a collaborative effort between COG and JPLT. We believe that this collaboration is necessary for two reasons. First, institutions in Japan have extensive experience in the management of hepatoblastoma patients and have an excellent track record on clinical research. Given the rarity of the disease, a collaborative effort will facilitate good study accrual in a timely manner. Second, future studies of hepatoblastoma are intended to be performed as an international collaborative effort among COG, SIOPEL, GPOH, and JPLT. This is an opportunity to develop the working relationship with JPLT in anticipation of the successor(s) to this trial.

# 3.0 STUDY ENROLLMENT AND PATIENT ELIGIBILITY

## 3.1 Study Enrollment

### 3.1.1 Patient Registration

Prior to enrollment on this study, patients must be assigned a COG patient ID number. This number is obtained via the eRDE system once authorization for the release of protected health information (PHI) has been obtained. The COG patient ID number is used to identify the patient in all future interactions with COG. If you have problems with the registration, please refer to the online help.

In order for an institution to maintain COG membership requirements, every newly diagnosed patient needs to be offered participation in ACCRN07, *Protocol for the Enrollment on the Official COG Registry, The Childhood Cancer Research Network (CCRN)*. Participation in ACCRN07 is limited to patients who are residents of the United States, Canada or Mexico.

A Biopathology Center (BPC) number will be assigned as part of the registration process. Each patient will be assigned only 1 BPC number per COG Patient ID. For additional information about the labeling of specimens please refer to the Pathology and/or Biology Guidelines in this protocol.

Please see Appendix VI for detailed CTEP Registration Procedures for Investigators and Associates.

### 3.1.2 IRB Approval

Sites must obtain IRB/REB approval for this protocol and submit IRB/REB approval and supporting documentation to the Cancer Trials Support Unit (CTSU) Regulatory Office before they can be approved to enroll patients. Allow 3 business days for processing. The submission must include a fax coversheet (or optional CTSU IRB Transmittal Sheet) and the IRB approval document(s). The CTSU IRB Certification Form may be submitted in lieu of the signed IRB approval letter. All CTSU forms can be located on the CTSU web page (https://www.ctsu.org). Any other regulatory documents needed for access to the study enrollment screens will be listed for the study on the CTSU Member's Website under the RSS Tab.

IRB/REB approval documents may be faxed (1-215-569-0206), Emailed (CTSURegulatory@ctsu.coccg.org) or mailed to the CTSU Regulatory office.

When a site has a pending patient enrollment within the next 24 hours, this is considered a "Time of Need" registration. For Time of Need registrations, in addition to marking your submissions as 'URGENT' and faxing the regulatory documents, call the CTSU Regulatory Helpdesk at: 1-866-651-CTSU. For general (non-regulatory) questions, call the CTSU General Helpdesk at: 1-888-823-5923.

Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU members' web site by entering credentials at https://www.ctsu.org. For sites under the CIRB initiative, IRB data will automatically load to RSS.

### 3.1.3 Reservation Requirements for Stratum 4 Only

Reservations are required for patients enrolled on High Risk Stratum 4 only.
Investigators should refer to the COG website to determine if the study is currently open for accrual. If the study is listed as active, investigators should then access the Studies Requiring Reservations page to ensure that a reservation for the study is available. To access the Studies Requiring Reservations page:

1. Log in to https://members.childrensoncologygroup.org.
2. From the menu bar, click **eRDES**. *The eRDES sub-menu appears.*

3. Click **Reservation**. *The Studies requiring Reservations page appears.*

Prior to obtaining informed consent and enrolling a patient on Stratum 4, a reservation must be made following the steps above.

Reservations may be obtained 24-hours a day through the COG website. Please refer to the Reservation System eRDES User Guide that can be downloaded from:
https://members.childrensoncologygroup.org/_files/Help/eRDES_ReservationSystem_UserGuide.pdf

3.1.4 Study Enrollment

Patients may be enrolled on the study once all eligibility requirements for the study have been met. Study enrollment is accomplished by going to the Enrollment application in the RDE system. If you have problems with enrollment, refer to online help in the Applications area of the COG Website.

3.1.5 Timing

All patients must be enrolled on AHEP0731 before protocol treatment begins. The date protocol therapy is projected to start must be no later than 42 days (28 days preferred) from biopsy or definitive surgery, whichever occurs latest, except in the case AHEP0731 therapy is started in an emergent situation (see Section 3.2.2.b below). **Investigators are strongly encouraged to enroll patients immediately following histological diagnosis and begin protocol therapy within 28 days of the initial surgical procedure.**

**Patients with Stage I and II tumors (see Appendix III) require rapid central pathologic review** and enrollment of these patients on AHEP0731 must not occur until the results of rapid central pathologic review are known. Stage I and II tumor specimens are to be submitted immediately following histological diagnosis. Pathology specimens MUST be submitted no later than 14 calendar days (7 days preferred) from definitive surgery and be accompanied by a Rapid Review Transmittal Form found on the AHEP0731 protocol page of the COG website. If Stage I and II diagnostic specimens are not submitted within 14 days of initial surgery, the patient will **not** be eligible for this study. **Enrollment of Stage I and II patients onto this study must not occur until the results of rapid central pathologic review are known and these results must be provided by the institutional investigator on the AHEP0731 Eligibility CRF.**

Retrospective central pathologic review is also required for all other biopsied/resected specimens (liver and/or lung). Specimens must be submitted within 4 weeks from all biopsies/resections other than Stage I and II diagnostic procedures. These specimens will be submitted using the generic COG Specimen Transmittal form. See Section 14.1.1 for details.

**All clinical and laboratory studies to determine eligibility must be performed within 14 days prior to enrollment unless otherwise indicated in the eligibility section below.**

3.1.6 Bilingual Services

To allow non-English speaking patients to participate in the study, bilingual health care services will be provided in the appropriate language.

## 3.2 Patient Eligibility Criteria

**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.**

3.2.1 Age
Patients must be ≤ 21 years of age at the time of diagnosis.

3.2.2.a Diagnosis
Patients must be newly diagnosed with histologically-proven hepatoblastoma, except as noted in Section 3.2.2.b below.

3.2.2.b Emergent Treatment
In emergency situations when a patient meets all other eligibility criteria and has had baseline required observations as outlined in Section 7.4 or 7.5, but is too ill to undergo a biopsy safely, the patient may be enrolled on AHEP0731 without a biopsy.

Clinical situations in which such emergent treatment may be indicated include, but are not limited to, the following circumstances:
a. Anatomic or mechanical compromise of critical organ function by tumor (eg, respiratory distress/failure, abdominal compartment syndrome, urinary obstruction, etc)
b. Uncorrectable coagulopathy

**For a patient to maintain eligibility for AHEP0731 when emergent treatment is given, the following must occur**:

- The patient must have a clinical diagnosis of hepatoblastoma, including an elevated alphafetoprotein, and must meet all AHEP0731 eligibility criteria at the time of emergent treatment.
- Patient must be enrolled on AHEP0731 prior to initiating protocol therapy. Per protocol Section 3.2.9, a patient will be ineligible if any chemotherapy is administered prior to AHEP0731 enrollment.

- If the patient receives AHEP0731 chemotherapy 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.

PATIENTS WILL BE STAGED FOR RISK CLASSIFICATION AND TREATMENT **AT DIAGNOSIS USING COG STAGING GUIDELINES,** as listed in Appendix III.

At the time of study enrollment, the patient's treatment regimen must be identified. If the patient's primary tumor was resected prior to the day of enrollment and a blood specimen for the determination of serum alphafetoprotein was not obtained prior to that surgery, the patient will be considered to have alphafetoprotein of greater than 100 ng/mL for the purpose of treatment assignment. If tumor samples obtained prior to the date of enrollment were not sufficient to determine whether small cell undifferentiated (SCU) histology was present, treatment assignment will be made assuming SCU is not present in the tumor.

For patients with Stage I or II disease, specimens for rapid central review have been submitted and the rapid central review diagnosis and staging must be available to be provided on the AHEP0731 Eligibility CRF.

3.2.3 Performance Level
(See https://members.childrensoncologygroup.org/prot/reference_materials.asp under Standard Material for Protocols.)
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.

3.2.4 Prior Therapy

Patients may have had surgical resection of some or all sites of hepatoblastoma prior to enrollment.

3.2.5 Organ Function Requirements

Organ function requirements are not required for enrolled patients who are Stage I, PFH and will not be receiving chemotherapy.

3.2.5.1

Adequate renal function defined as:

- Creatinine clearance or radioisotope GFR ≥ 70 mL/min/1.73 $m^2$ 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 |
| ≥ 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.

3.2.5.2

For patients who will be assigned to protocol chemotherapy, adequate liver function defined as:

- Total bilirubin < 1.5 x upper limit of normal (ULN) for age, and
- SGOT (AST) or SGPT (ALT) < 10 x ULN for age.

3.2.5.3

For patients who will be assigned to protocol chemotherapy, adequate bone marrow function defined as:

- Absolute neutrophil count (ANC) > 750/µL
- Platelet count > 75,000/µL

3.2.5.4

For intermediate- and high-risk patients who will be assigned to protocol chemotherapy, adequate cardiac function defined as:

- Shortening fraction ≥ 27% by echocardiogram, or
- Ejection fraction ≥ 47% by radionuclide angiogram (MUGA).

Note: the echocardiogram (or MUGA) may be done within 28 days prior to enrollment.

3.2.6 Additional Eligibility Criteria for High-Risk Patients

3.2.6.1
Serum triglyceride level ≤ 300 mg/dL (≤ 3.42 mmol/L) and serum cholesterol level ≤ 300 mg/dL (7.75 mmol/L)

3.2.6.2
Random or fasting blood glucose within the upper normal limits for age. If the initial blood glucose is a random sample that is outside of the normal limits, then a follow-up fasting blood glucose can be obtained and must be within the upper normal limits for age.

3.2.6.3 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).

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

3.2.6.4 Adequate Neurologic Function Defined as:

- Patients with seizure disorder may be enrolled if on non-enzyme inducing anticonvulsants and if seizures are well controlled. (See Appendix IV for a list of recommended non-enzyme inducing anticonvulsants).

3.2.6.5 Adequate Clotting Function Defined as:

- Prothrombin Time (PT) < 1.2 x ULN

3.2.7 Exclusion Criteria for All Patients

3.2.7.1
Patients with Stage I or II disease who do not have specimens submitted for rapid central pathology review by Day 14 after initial surgical resection.

3.2.7.2
Patients that have been previously treated with chemotherapy for hepatoblastoma or other hepatoblastoma-directed therapy (eg, radiation therapy, biologic agents, local therapy [embolization, radiofrequency ablation, laser]) are not eligible.

3.2.7.3
Patients who have received any prior chemotherapy are not eligible.

3.2.7.4 Investigational drugs
Patients who are currently receiving another investigational drug are not eligible.

3.2.7.5 Anti-Cancer Agents
Patients who are currently receiving other anticancer agents are not eligible.

3.2.7.6 Transplant
Patients who have previously received a solid organ transplant are not eligible.

3.2.7.7 Infection

Patients who have an uncontrolled infection are not eligible.

3.2.7.8 Pregnancy and breast feeding

3.2.7.8.1

Females who are pregnant or breast feeding are not eligible for this study since fetal toxicities and teratogenic effects have been noted for several of the study drugs.

3.2.7.8.2

Female patients of childbearing potential are not eligible unless a negative pregnancy text result has been obtained.

3.2.7.8.3

Males and females of reproductive potential are not eligible unless they have agreed to use an effective contraceptive method.

3.2.8 Additional Exclusion Criteria for High-Risk Patients

3.2.8.1 Corticosteroids

Patients receiving corticosteroids are not eligible. Patients must have been off corticosteroids for 7 days prior to start of chemotherapy.

3.2.8.2 Enzyme-Inducing Anticonvulsants:

Patients who are currently receiving enzyme inducing anticonvulsants are not eligible. (See Appendix IV for a list of unacceptable enzyme inducing anticonvulsants.)

3.2.8.3 CYP3A4 Active Agents

Patients must not be receiving any of the following potent CYP3A4 inducers or inhibitors: erythromycin, clarithromycin, azithromycin, ketoconazole, itraconazole, voriconazole, posaconazole, grapefruit juice or St. John's wort. A list of other known CYP3A4 inducers and inhibitors that should be avoided during study therapy is included in Appendix V.

3.2.8.4 Anticoagulants

Patients who are currently receiving therapeutic anticoagulants (including aspirin, low molecular weight heparin, warfarin and others) are not eligible.

3.2.8.5 Angiotensin-Converting Enzyme (ACE) Inhibitors

Patients who are currently receiving ACE inhibitors are not eligible due to the development of angioneurotic edema-type reactions in some subjects who received concurrent treatment with temsirolimus + ACE inhibitors.

3.2.8.6 Surgery

Patients must not have had major surgery within 6 weeks prior to enrollment on the high risk stratum. Patients with history of recent minor surgical procedures (vascular catheter placement, bone marrow evaluation, laparoscopic surgery, liver tumor biopsy) will be eligible.

3.2.9 Regulatory

3.2.9.1

All patients and/or their parents or legal guardians must sign a written informed consent.

3.2.9.2
All institutional, FDA, and NCI requirements for human studies must be met.

## 4.0 TREATMENT PLAN

Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. Minor unavoidable departures (up to 72 hours) from protocol directed therapy and/or disease evaluations (and up to 1 week for surgery) for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable per COG Administrative Policy 5.14 (except where explicitly prohibited within the protocol).

### 4.1 Overview of Treatment Plan

AHEP0731 builds on the results of the last 20 years of hepatoblastoma clinical trials and seeks to diminish toxicity in the approximately 30% of low-risk patients, increase survival in intermediate-risk patients and identify new agents(s) that may be used in high-risk and recurrent patients.

All patients with Stage I PFH hepatoblastoma will be classified as very low-risk (Stratum 1) and will be treated with surgery only. Patients with Stage I non-PFH, non-SCU hepatoblastoma or with Stage II non-SCU hepatoblastoma will be classified as low-risk (stratum 2)and will be treated on Regimen T with 2 adjuvant cycles of cisplatin, 5-flouorouracil, and vincristine (C5V), a reduction from the standard 4 cycles of chemotherapy given on previous COG trials. Patients with Stage I SCU, Stage II SCU, or any Stage III hepatoblastoma will be classified as intermediate-risk (stratum 3) and will be treated with Regimen F (intermediate risk, stratum 3, has been closed to accrual as of 03/12/12). This treatment regimen is based on previous COG trials that administered 6 cycles of C5V therapy plus surgical resection of the tumor. However, to improve resection and survival rates, doxorubicin, an agent with proven efficacy will be added to the C5V therapy (C5VD). All patients with any Stage IV hepatoblastoma as well as patients with any stage of hepatoblastoma and initial AFP < 100 ng/mL will be classified as high-risk (stratum 4).

Initial Treatment Plan for High-Risk Patients (Stratum 4): Regimen W
Initially, high-risk (Stratum 4) patients were treated on Regimen W. This regimen included 2 cycles of "up-front" VI window therapy. Patients who respond to VI were considered as responders. Responder patients then received a total of 6 cycles of C5VD therapy with 1 cycle of VI in between each 2-cycle block of C5VD. Non-responder patients only received 6 cycles of C5VD following the "up-front" window therapy.

As of Amendment # 3B, Regimen W has been replaced by Regimen H
As of Amendment # 3B, patients in the high-risk group (Stratum 4) will be treated with experimental treatment consisting of vincristine, irinotecan and temsirolimus (VIT) in Regimen H in order to identify a new active combination. Patients assigned to Regimen H will receive 2 cycles of "up-front" VIT. Patients who respond to VIT will be considered responders. Responding patients will then receive a total of 6 cycles of C5VD (Cycles 3, 4, 5, 6, 8, 9) therapy with 4 total cycles of VIT (Cycles 1, 2, 7 and 10). Non-responding patients will only receive the 6 cycles of C5VD following the "up-front" window therapy. All patients, with the exception of those patients enrolled in Japan, will receive dexrazoxane with the final 2 cycles of C5VD. The table below illustrates the treatment plan overview.

| Stage | Histology | AFP | Risk Stratification | Regimen | VIT Response | Total Chemo Cycles |
|---|---|---|---|---|---|---|
| I | PFH | > 100 ng/mL | Very Low-Stratum 1 | Surgery Only | - | 0 |
| I | Non-PFH Non-SCU | > 100 ng/mL | Low-Stratum 2 | T | - | 2 (C5V) |
| I | SCU | > 100 ng/mL | Intermediate-Stratum 3 | F | - | 6 (C5VD) |
| II | Non-SCU | > 100 ng/mL | Low-Stratum 2 | T | - | 2 (C5V) |
| II | SCU | > 100 ng/mL | Intermediate-Stratum 3 | F | - | 6 (C5VD) |
| III | Any | > 100 ng/mL | Intermediate-Stratum 3 | F | - | 6 (C5VD) |
| IV | Any | Any | High-Stratum 4 | H | Yes | 4 (VIT) + 6 (C5VD) |
| IV | Any | Any | High-Stratum 4 | H | No | 2 (VIT) + 6 (C5VD) |
| Any | Any | < 100 ng/mL | High-Stratum 4 | H | Yes | 4 (VIT) + 6 (C5VD) |
| Any | Any | < 100 ng/mL | High-Stratum 4 | H | No | 2 (VIT) + 6 (C5VD) |

Response to the initial 2 cycles of VIT treatment will be assessed by central review to determine if these patients will be considered as responders and treated accordingly, see Section 4.6. The assessment of response is based on central review of imaging, the alphafetoprotein values and sampling dates. The results of the central review will be returned to the institutional investigator within 3 weeks of submission of the imaging and AFP material. If there is a discrepancy between the assessment by central review and by institutional assessment, the study PI will discuss with the treating physician to resolve the discrepancy. If the investigator selects a post-induction regimen that is *not* indicated by the central review of response, the patient will be considered off protocol therapy as of the start date of consolidation therapy.

## 4.2 General Therapy Guidelines

### 4.2.1 Staging

PATIENTS WILL BE STAGED FOR RISK CLASSIFICATION AND TREATMENT **AT DIAGNOSIS USING COG STAGING GUIDELINES** as listed in Appendix III. PRETEXT grouping of the patient's disease prior to any surgical intervention will also be performed as detailed in Section 10.2 and Appendix I. PRETEXT grouping will not be used for risk classification but it will be used to guide the surgical approach and specifically which patients should be considered unresectable at diagnosis. PRETEXT grouping will be done at diagnosis and also at any time subsequent abdominal scans are performed preoperatively (called POST-TEXT if assigned after chemotherapy).

Based on staging and risk classification at diagnosis, patients will receive therapy as outlined in Section 4.1. Throughout the protocol, staging refers to COG staging (Appendix III) and grouping refers to PRETEXT/POST-TEXT grouping (Section 10.2).

### 4.2.2 Chemotherapy

#### 4.2.2.1

Each cycle of chemotherapy should only be initiated if the absolute neutrophil count is ≥750/µL and the platelet count is ≥ 75,000/µL.

4.2.2.2
**Patients < 10 kg will have dosing in mg/kg for all agents.**

4.2.2.3
Filgrastim (G-CSF) should not be given initially and should only be administered prophylactically if there is either a 1 week delay in the administration of chemotherapy because of neutropenia or if the patient requires hospitalization for fever and neutropenia or for sepsis.

4.2.3 Concomitant Medications Restrictions

4.2.3.1 Cytochrome P450 interactions
Clinically significant drug interactions have been reported when using irinotecan or vincristine with strong CYP450 3A4 inhibitors and inducers. Selected strong inhibitors of cytochrome P450 3A4 (such as the azole antifungals, fluconazole, voriconazole, itraconazole, ketoconazole and posaconazole) and strong inducers of cytochrome P450 3A4 (e.g. rifampin, phenytoin, phenobarbital, carbamazepine, and St. John's wort) should be avoided while the patient is receiving vincristine, irinotecan or temsirolimus. Aprepitant also interacts with CYP3A4 and should be used with caution with vincristine, irinotecan or temsirolimus. For a list of CYP3A4 inhibitors and inducers see Appendix V.

Fluorouracil may increase the level and effect or CYP2C9 substrates like phenytoin and warfarin. Phenytoin levels and international normalized ratio (INR) should be closely monitored.

The clinical outcome and significance of CYP450 interactions with doxorubicin is less clear. CYP450 3A4 stimulators or inhibitors should be avoided or used with great caution. Additional inducers or inhibitors of CYP450 enzymes can be found at http://medicine.iupui.edu/clinpharm/ddis.

4.2.3.2 Anticonvulsant levels (phenytoin, valproic acid and carbamazepine) should be monitored during concurrent use with doxorubicin and cisplatin and phenytoin levels should be monitored in patients receiving cisplatin alone. Patients who are currently receiving enzyme inducing anticonvulsants are not eligible for Stratum 4 (see Section 3.2.8.2). See Appendix IV for a list of unacceptable enzyme inducing anticonvulsants.

4.2.4 Supportive Care
For general Supportive Care Guidelines see:
https://members.childrensoncologygroup.org/prot/reference_materials.asp under Standard Sections for Protocols.

4.2.5 Radiation Therapy
Since the role of radiation therapy in the treatment of hepatoblastoma is not clearly defined and not typically part of standard care, radiation therapy is **not** permitted on this study.

4.2.6 Treatment Initiation

4.2.6.1
**Please note**: It is recommended that patients who have had > 75% of their liver resected wait at least 2 weeks prior to beginning protocol therapy to allow liver regeneration.

4.2.6.2
**Also note**: Stage I or II patients cannot be enrolled on study or begin protocol treatment until rapid central pathology review is complete.

### 4.3 Treatment for Very Low-Risk Patients (Stratum 1 – No further treatment)

Patients who have had their tumor completely resected at diagnosis **must** have tumor specimens submitted for rapid central pathology review prior to enrollment onto this study (see Section 14.0 for details). Patients must sign consent giving permission to submit tumor specimens prior to shipment and cannot be enrolled on study until the results of rapid review are known. Patients classified as very low-risk will have their tumor completely resected at diagnosis and then be observed with no further therapy. See Section 7.6.1 for recommended follow-up.

### 4.4 Treatment for Low-Risk Patients (Stratum 2 - Regimen T)

Patients classified as low-risk **must** have tumor specimens submitted for rapid central pathology review prior to enrollment onto this study (see Section 14.0 for details). Patients must sign consent giving permission to submit tumor specimens prior to shipment and cannot be enrolled on study or start treatment until the results of rapid review are known. Low risk patients will have the tumor completely resected at diagnosis and then receive 2 cycles (each cycle is 21 days) of adjuvant C5V. Patients **must begin protocol therapy within 42 days of definitive surgery to allow for recovery from any surgical complications. However, it is strongly encouraged that patients begin protocol therapy within 28 days of the initial surgical procedure**. Begin each cycle of Regimen T only when the absolute neutrophil count is ≥ 750/µL and the platelet count is ≥ 75,000/µL. **Note: All patients < 10 kg will have dosing in mg/kg**.

#### 4.4.1 CISplatin: IV over 6 hours

100 mg/m$^2$/dose (3.3 mg/kg/dose for patients < 10 kg) on Day 1.

Recommended hydration and administration guidelines:
Urine specific gravity should be < 1.010 prior to starting CISplatin.
Hours -2 to 0: Prehydrate with 300 mL/m$^2$ $D_5$ ½ NS + $MgSO_4$ 8 mEq/L + KCL 20 mEq/L.
Hours 0-6: Infuse CISplatin + mannitol 8000 mg/m$^2$ in 750 mL/m$^2$ NS @ 125 mL/m$^2$/hr.
Hours 6-24: $D_5$½NS+ $MgSO_4$ 8 mEq/L + KCL 20 mEq/L to run at 125 mL/m$^2$/hr.

#### 4.4.2 5-Fluorouracil: Slow IV Push over 2-4 minutes

600 mg/m$^2$/dose (20 mg/kg/dose for patients < 10 kg) on Day 2.

#### 4.4.3 VinCRIStine: IV Push over 1 minute or infusion via minibag as per institutional policy

1.5 mg/m$^2$/dose (0.05 mg/kg/dose for patients < 10 kg) [Maximum dose: 2 mg] on Days 2, 9 and 16.

Special precautions: FOR INTRAVENOUS USE ONLY.
The container or the syringe containing vinCRIStine must be enclosed in an overwrap bearing the statement "Do not remove covering until moment of injection. For intravenous use only - Fatal if given by other routes."

Medication errors have occurred due to confusion between vinCRIStine and vinBLAStine. VinCRIStine is available in a liposomal formulation (vinCRIStine sulfate liposomal injection, VSLI, Marqibo®). Use conventional vincristine only; the conventional and liposomal formulations are NOT interchangeable.

**See Section 5.0 for Dose Modifications based on Toxicities.** The therapy delivery map (TDM) for Regimen T is on the next page (see Section 4.4.4).

| 4.4.4 **Regimen T – Low-Risk Patients (Stratum 2) Cycles 1 & 2**<br>Low-risk patients receive 2 adjuvant cycles of C5V. Tumor tissue is strongly encouraged for banking: see ABTR01B1 or other appropriate study for details. This therapy delivery map relates to 2 cycles of C5V therapy. Each cycle lasts 21 days. One cycle is described on this TDM. This TDM is on 1 page. Use a copy of this page once for each cycle (please note cycle number below). | _____ Patient name or initials _____ DOB |
|---|---|

Criteria to start each cycle: ANC ≥ 750/µL and the platelet count is ≥ 75,000/µL.

| DRUG | ROUTE | DOSAGE | DAYS | IMPORTANT NOTES | OBSERVATIONS |
|---|---|---|---|---|---|
| CISplatin (CDDP) | IV over 6 hours | 100 mg/m$^2$/dose OR (3.3 mg/kg/dose for < 10 kg) | 1 | Recommended administration guidelines: Urine S.G. should be < 1.010 prior to starting CDDP. See Section 4.4.1 for pre- and post- hydration & mannitol guidelines. | a. History, physical, ht/wt, BSA, VS **(Start of each cycle & end of therapy)**<br>b. CBC (diff/plt) **(Weekly & end of therapy)**<br>c. Electrolytes, $Ca^{++}$, $Mg^{++}$, $PO_4$, creatinine, ALT/AST, bilirubin, total protein/albumin, AFP **(Start of each cycle & end of therapy)**<br>d. Tumor disease evaluation **(End of therapy only)**, see Section 7.3.<br>e. Audiogram **(End of therapy only)**<br><br>**OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE** |
| 5-Fluorouroracil (FU) | Slow IV push over 2-4 minutes | 600 mg/m$^2$/dose OR (20 mg/kg/dose for < 10 kg) | 2 | | |
| VinCRIStine (VCR) | IV push over 1 minute** | 1.5 mg/m$^2$/dose OR (0.05 mg/kg/dose for < 10 kg) | 2, 9 & 16 | **Maximum dose: 2 mg**<br>** or infusion via minibag as per institutional policy | |

**Circle Cycle #: 1 (Weeks 1-3) 2 (Weeks 4-6) Ht_____cm Wt_____kg BSA_____m$^2$**

| Date Due | Date Given | Day | CDDP mg | FU mg | VCR mg | Studies | Comments (Include any held doses, or dose modifications) |
|---|---|---|---|---|---|---|---|
| | | | **Enter calculated dose above and actual dose administered below** | | | | |
| | | 1 | _____mg | | | a, b, c | |
| | | 2 | | _____mg | _____mg | | |
| | | 9 | | | _____mg | b | |
| | | 16 | | | _____mg | b | |
| | | 21 | Repeat cycle or (End therapy after Cycle 2) | | | (a, b ,c, d, e)* | * End of therapy |

**See Section 5.0 for Dose Modifications for Toxicities and for general Supportive Care Guidelines see https://members.childrensoncologygroup.org/prot/reference_materials.asp under Standard Sections for Protocols.**

### 4.5 Treatment for Intermediate-Risk Patients (Stratum 3 - Regimen F)

**Note: Stratum 3 has been closed to accrual as of 03/12/12.**

All patients with Stage I SCU, Stage II SCU, and Stage III disease will be treated with Regimen F (C5VD). Patients will receive 4 cycles of therapy repeated every 21 days, followed by surgical resection of the tumor or liver transplant (OLT). Patients whose tumors are removed surgically or by OLT after Cycle 4 will receive 2 post-operative cycles of chemotherapy. Patients may have their tumor removed if deemed feasible after 2 cycles of chemotherapy but will then receive 4 cycles of post-operative chemotherapy. **All intermediate-risk patients will receive a total of 6 cycles of chemotherapy**. Patients whose tumors remain unresectable after 4 cycles will be considered off protocol therapy, but will continue to be followed on the AHEP0731 off protocol therapy follow-up CRF. These patients can at the discretion of the primary physician. Additional pre-operative cycles of chemotherapy after Cycle 4 are **NOT** permitted in an attempt to make the tumor resectable or if a liver is not available for transplantation. Patients with progressive disease at any time are off-protocol therapy.

Tumors that are unresectable at diagnosis should be referred to a surgical center with expertise in pediatric liver transplant and "extreme" liver resection as soon as possible. Optimally for planning purposes, this liver transplant consultation should be obtained but at the latest it should be done following the first 2 cycles of neoadjuvant chemotherapy. The consent for the PLUTO registry should be obtained within one month of undergoing liver transplant and is usually obtained by the liver transplant team.

For the purposes of this study, consultation will be defined and may be accomplished in one of two ways:

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

Resection planning is to be completed before completion of the 4$^{th}$ cycle of chemotherapy. Transplant or "extreme" resection is intended to occur within 4 weeks of the completion of the 4$^{th}$ cycle of chemotherapy.

Chemotherapy should resume as soon as possible after surgical resection. In most circumstances this can typically be achieved within 3 weeks following surgery. Patients who do not resume post resection chemotherapy within 42 days of resection will be considered off protocol therapy. Further treatment will be at the discretion of the treating physician.

Patients classified as intermediate-risk will receive 6 cycles of C5VD. Surgical resection of tumor or liver transplant will occur following Cycle 2 (if feasible) or Cycle 4. All patients < 10 kg will have dosing in mg/kg.

#### 4.5.1 CISplatin: IV over 6 hours

100 mg/m$^2$/dose (3.3 mg/kg/dose for patients < 10 kg) on Day 1.

Recommended hydration and administration guidelines:
Urine specific gravity should be < 1.010 prior to starting cisplatin.
Hours -2 to 0: Prehydrate with 300 mL/m$^2$ $D_5$ ½ NS + $MgSO_4$ 8 mEq/L + KCL 20 mEq/L.
Hours 0-6: Infuse CISplatin + mannitol 8000 mg/m$^2$ in 750 mL/m$^2$ NS @ 125 mL/m$^2$/hr.
Hours 6- 24: $D_5$½NS+ $MgSO_4$ 8 mEq/L + KCL 20 mEq/L to run at 125 mL/m$^2$/hr.

4.5.2 5-Fluorouracil: Slow IV Push over 2-4 minutes
600 mg/m$^2$/dose (20 mg/kg/dose for patients < 10 kg) on Day 2.

4.5.3 VinCRIStine: IV Push over 1 minute or infusion via minibag as per institutional policy
1.5 mg/m$^2$/dose (0.05 mg/kg/dose for patients < 10 kg) [Maximum dose: 2 mg] on Days 2, 9 and 16.

4.5.4 DOXOrubicin: IV over 15 minutes
30 mg/m$^2$/dose (1 mg/kg/dose for patients < 10 kg) on Days 1 and 2.
It is suggested that DOXOrubicin be administered through the tubing of rapidly infusing solution of $D_5W$ or 0.9% NaCl and that it is infused into a large vein.

4.5.5 Dexrazoxane: Slow IV Push over 5-15 minutes immediately prior to DOXOrubicin dose
300 mg/m$^2$/dose (10 mg/kg/dose for patients < 10 kg) on Days 1 and 2 in **Cycles 5 and 6 ONLY.**
The elapsed time from the beginning of the dexrazoxane dose to the end of the DOXOrubicin infusion should be 30 minutes or less.

**See Section 5.0 for Dose Modifications based on Toxicities.**

### 4.6 Treatment for High-Risk Patients (Stratum 4) - Regimen H

All high-risk patients will receive 2 cycles of vinCRIStine, irinotecan and temsirolimus (VIT), using a 5 day irinotecan schedule, as "up-front" window therapy on Regimen H. Each cycle lasts 21 days and cycles will start on Weeks 1 and 4. Antibiotics will be given to patients receiving irinotecan who develop chemotherapy-related diarrhea. See "Diarrhea Secondary to Irinotecan" in the Supportive Care Guidelines at: **https://members.childrensoncologygroup.org/prot/reference_materials.asp** under Standard Sections for Protocols.

Following 2 cycles of VIT, patients will be evaluated for response (see Section 10.3). The assessment of response is based on central review of imaging, the alphafetoprotein values and sampling dates. The results of the central review will be returned to the institutional investigator within 3 weeks of submission of the imaging and AFP material. If there is a discrepancy between the assessment by central review and by institutional assessment, the study PI will discuss with the treating physician to resolve the discrepancy. If the investigator selects a post-induction regimen that is *not* indicated by the central review of response, the patient will be considered off protocol therapy as of the start date of consolidation therapy.

Patients who *respond* (demonstrate a complete or partial response) to VIT will then receive a total of 6 cycles of C5VD therapy and 2 more cycles of VIT. Following first 2 cycles of VIT, no further VIT should be given until after surgical resection/liver transplant to avoid potential surgical complications of thrombosis and wound dehiscence. Each cycle lasts 21 days. A total of 10 cycles of chemotherapy (6 cycles of C5VD and 4 cycles of VIT, including the "up-front" window therapy) will be given. VIT is intended to be given during Cycles 7 and 10. However, the order of chemotherapy cycles can be switched at the discretion of the treating oncologists and surgeons to optimize surgical outcomes and minimize complications.

Patients who *do not respond* to VIT will continue with 6 cycles of C5VD repeated every 21 days and receive no further VIT. A total of 8 cycles of chemotherapy (6 cycles of C5VD and 2 cycles of VIT, including the "up-front" window therapy) will be given.

Tumors that are unresectable at diagnosis, even if metastatic disease is present, should be referred to a surgical center with expertise in pediatric liver transplant and "extreme" liver resection should be done as soon as possible. Optimally for planning purposes, this liver transplant consultation should be obtained at diagnosis and no later than the FIRST DAY of the 3$^{rd}$ cycle of C5VD chemotherapy. The consent for the PLUTO registry should be obtained within one month of liver transplant and usually is obtained by the liver transplant team.

For the purposes of this study, consultation will be defined and may be accomplished in one of two ways:

- The FIRST TIME there is documented telephone or email/letter contact and a request for consultation between the treating oncologist and the liver specialty/transplant team.
- 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 liver specialty/transplant physician/team will communicate the result of this consultation back to the referring physician.

Resection planning is to be completed before completion of the 4$^{th}$ cycle of C5VD chemotherapy. See Surgical Guidelines in Section 13.0.

Patients will be evaluated after every 2 cycles of C5VD chemotherapy that occur prior to resection. Patients may have their primary tumor removed whenever it is feasible. It is the intent of the treatment that patients should have their tumors removed surgically or by OLT at the latest after Cycle 6 in both responders and

non-responders (ie, after the 4th cycle of C5VD) so that they can receive post-operative cycles of chemotherapy.

Chemotherapy should resume as soon as possible after surgical resection. In most circumstances this can typically be achieved within 3 weeks following surgery. **Patients who do not resume post resection chemotherapy within 42 days of resection will be considered off protocol therapy but not off study**. Further treatment will be at the discretion of the treating physician. Patients will continue to be followed on the AHEP0731 off protocol therapy follow-up CRF.

Regardless of the timing of surgery, patients should receive the total number of cycles as described above.

**Patients whose tumors remain unresectable at the completion of planned therapy will be considered to have experienced an adverse EFS event. No further protocol therapy is planned for such patients. These patients can be treated at the discretion of the primary physician.**

Patients with pulmonary metastases will receive the first 2 cycles of Regimen H chemotherapy described above. If metastases disappear with chemotherapy, no pulmonary surgical intervention will be performed. If metastases are persistent after 4 total cycles of C5VD chemotherapy and the patient is considered a candidate for liver transplant at that time, metastases are to be resected to render the patient free of extrahepatic disease prior to transplant. Transplant may then be undertaken. If the liver tumor can be primarily resected after either 2 or 4 cycles of C5VD chemotherapy without transplant, this should be performed and the final cycles of chemotherapy should be administered. If the metastases are still present, they should then be resected. Pulmonary metastectomy may be performed earlier in the course of therapy if it can be done without resulting in delays in the administration of scheduled chemotherapy.

**Regimen H for Responders**

| **Cycle** | **1** | **2** | **Eval** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Week | 1 | 4 | | 7 | 10 | 13 | 16 | 19 | 22 | 25 | 28 |
| Chemotherapy | VIT | VIT | | C5VD | C5VD | C5VD | C5VD | VIT | C5VD+ DXRZ* | C5VD+ DXRZ* | VIT |

Responders will receive a total of 8 cycles post VIT window.

**Regimen H for Non-Responders**

| **Cycle** | **1** | **2** | **Eval** | **3** | **4** | **5** | **6** | **7** | **8** |
|---|---|---|---|---|---|---|---|---|---|
| Week | 1 | 4 | | 7 | 10 | 13 | 16 | 19 | 22 |
| Chemotherapy | VIT | VIT | | C5VD | C5VD | C5VD | C5VD | C5VD+ DXRZ* | C5VD+ DXRZ* |

Non responders will receive 6 total cycles of C5VD post VIT window.

*Dexrazoxane administration is not required for patients enrolled in Japan.

**NOTE: For high-risk patients being assessed at the end of Cycle 2, the central review assessment will be returned to the institutional investigator and will indicate the post-induction treatment regimen.**

4.6.1 Criteria to Start Cycle 1 of Regimen H and Subsequent Cycles

4.6.1.1 Criteria to Start Cycle 1 of Regimen H for **All** High-Risk Patients
Begin Cycle 1 of Regimen H, when ANC ≥ 750/μL and the platelet count is ≥ 75,000/μL and all the eligibility criteria have been met.

4.6.1.2 Criteria to Start Cycle 2 of Regimen H for **All** High-Risk Patients and Cycles 3-10 of Regimen H for All High-Risk ***Responders***

- ANC ≥ 750/µL and the platelet count is ≥ 75,000/µL.
- Total Cholesterol ≤ 400 mg/dL OR ≤ 500 mg/dL and on lipid lowering medication, AND triglycerides ≤ 300 mg/dL OR ≤ 500 mg/dL and on lipid lowering medication. If cholesterol or triglyceride parameters are not met based on testing performed in a non-fasting patient, these tests should be repeated after fasting.

4.6.1.3 Criteria to Start Cycles 3-8 of Regimen H for All High-Risk ***Non-Responder*** Patients

- ANC ≥ 750/µL and the platelet count is ≥ 75,000/µL.

Note: Beyond Cycle 2, the cholesterol and triglyceride parameters to start a cycle of therapy are not applicable for non-responders, as they will not receive any further VIT therapy.

**Note**: All patients < 10 kg will have dosing in mg/kg

4.6.2 VinCRIStine: IV Push over 1 minute or infusion via minibag as per institutional policy
During 'Upfront' Window Therapy for **All** High-Risk Patients
1.5 mg/m$^2$/dose (0.05 mg/kg/dose for patients < 10 kg) [Maximum dose: 2 mg] on Days 1 and 8 of Cycles 1 and 2.

During Post 'Upfront' Window Therapy for All High-Risk ***Responder*** Patients
1.5 mg/m$^2$/dose (0.05 mg/kg/dose for patients < 10 kg) [Maximum dose: 2 mg] on Days 2, 9 and 16 of Cycles 3-6, 8-9 **and** Days 1 and 8 of Cycles 7 and 10.

During Post 'Upfront' Window Therapy for All High-Risk ***Non-responder*** Patients
1.5 mg/m$^2$/dose (0.05 mg/kg/dose for patients < 10 kg) [Maximum dose: 2 mg] on Days 2, 9 and 16 of Cycles 3-8.

Special precautions: FOR INTRAVENOUS USE ONLY.
The container or the syringe containing vinCRIStine must be enclosed in an overwrap bearing the statement "Do not remove covering until moment of injection. For intravenous use only - Fatal if given by other routes."

Medication errors have occurred due to confusion between vinCRIStine and vinBLAStine. VinCRIStine is available in a liposomal formulation (vinCRIStine sulfate liposomal injection, VSLI, Marqibo®). Use conventional vincristine only; the conventional and liposomal formulations are NOT interchangeable.

4.6.3 Irinotecan: IV over 90 minutes
During 'Upfront' Window Therapy for **All** High-Risk Patients
50 mg/m$^2$/dose (1.67 mg/kg/dose for patients < 10 kg) [Maximum dose: 100 mg] on Days 1-5 of Cycles 1 and 2.

During Post 'Upfront' Window Therapy for All High-Risk ***Responder*** Patients
50 mg/m$^2$/dose (1.67 mg/kg/dose for patients < 10 kg) [Maximum dose: 100 mg] on Days 1-5 of Cycles 7 and 10.

See: https://members.childrensoncologygroup.org/prot/reference_materials.asp

Under Standard Sections for Protocols – Supportive Care Guidelines for prophylactic antibiotics and treatment recommendation for diarrhea secondary to irinotecan.

4.6.4 Temsirolimus: IV over 30 minutes

During **'Upfront'** Window Therapy for **All** High-Risk Patients

35 mg/m$^2$/dose (1.2 mg/kg/dose for patients < 10 kg) on Days 1 and 8 of Cycles 1 and 2.

On Day 1

Administer diphenhydramine (1 mg/kg, max 50 mg) immediately upon completion of irinotecan infusion. Begin temsirolimus infusion 30 minutes after administration of diphenhydramine.

On Day 8

Administer diphenhydramine (1 mg/kg, max 50 mg) immediately upon completion of vinCRIStine. Begin temsirolimus infusion 30 minutes after administration of diphenhydramine.

During **Post 'Upfront'** Window Therapy for All High-Risk ***Responder*** Patients

35 mg/m$^2$/dose (1.2 mg/kg/dose for patients < 10 kg) on Days 1 and 8 of Cycles 7 and 10.

On Day 1

Administer diphenhydramine (1 mg/kg, max 50 mg) immediately upon completion of irinotecan infusion. Begin temsirolimus infusion 30 minutes after administration of diphenhydramine.

On Day 8

Administer diphenhydramine (1 mg/kg, max 50 mg) immediately upon completion of vinCRIStine. Begin temsirolimus infusion 30 minutes after administration of diphenhydramine.

4.6.5 CISplatin: IV over 6 hours

Recommended hydration and administration guidelines:
Urine specific gravity should be < 1.010 prior to starting CISplatin.
Hours -2 to 0: Prehydrate with 300 mL/m$^2$ $D_5$ ½ NS + Magnesium sulfate 8 mEq/L + KCL 20 mEq/L.
Hours 0-6: Infuse CISplatin + mannitol 8000 mg/m$^2$ in 750 mL/m$^2$ NS @ 125 mL/m$^2$/hr.
Hours 6- 24: $D_5$½NS+ Magnesium sulfate 8 mEq/L + KCL 20 mEq/L to run at 125 mL/m$^2$/hr.

During Post 'Upfront' Window Therapy for All High-Risk ***Responder*** Patients

100 mg/m$^2$/dose (3.3 mg/kg/dose for patients < 10 kg) on Day 1 of Cycles 3-6 and 8-9.

During Post 'Upfront' Window Therapy for All High-Risk ***Non-responder*** Patients

100 mg/m$^2$/dose (3.3 mg/kg/dose for patients < 10 kg) on Day 1 of Cycles 3-8.

4.6.6 5-Fluorouracil: Slow IV Push over 2-4 minutes

During Post 'Upfront' Window Therapy for All High-Risk ***Responder*** Patients

600 mg/m$^2$/dose (20 mg/kg/dose for patients < 10 kg) on Day 2 of Cycles 3-6 and 8-9. .

During Post 'Upfront' Window Therapy For All High-Risk ***Non-responder*** Patients

600 mg/m$^2$/dose (20 mg/kg/dose for patients < 10 kg) on Day 2 of Cycles 3-8.

4.6.7 Dexrazoxane: Slow IV Push over 5-15 minutes immediately prior to doxorubicin dose
The elapsed time from the beginning of the dexrazoxane dose to the end of the DOXOrubicin infusion should be 30 minutes or less.
Note: Dexrazoxane administration is not required for patients enrolled in Japan.

During Post 'Upfront' Window Therapy for All High-Risk ***Responder*** Patients
300 mg/m$^2$/dose (10 mg/kg/dose for patients < 10 kg) on Days 1 and 2 beginning 15 minutes prior to DOXOrubicin dose in **Cycles 8-9 ONLY**.

During Post 'Upfront' Window Therapy For All High-Risk ***Non-responder*** Patients
300 mg/m$^2$/dose (10 mg/kg/dose for patients < 10 kg) on Days 1 and 2 beginning 15 minutes prior to DOXOrubicin dose of **Cycles 7-8 ONLY**

4.6.8 DOXOrubicin: IV over 15 minutes
During Post 'Upfront' Window Therapy for All High-Risk ***Responde***r Patients
30 mg/m$^2$/dose (1 mg/kg/dose for patients < 10 kg) on Days 1 and 2 of Cycles 3- 6 and 8-9.

During Post 'Upfront' Window Therapy For all High-Risk **Non-responder** Patients
30 mg/m$^2$/dose (1 mg/kg/dose for patients < 10 kg) on Days 1 and 2 of Cycles 3-8.

Medication errors have occurred due to confusion between DAUNOrubicin and DOXOrubicin. DOXOrubicin is available in a liposomal formulation. Use conventional DOXOrubicin only; the conventional and liposomal formulations are NOT interchangeable.

**See Section 5.0 for Dose Modifications based on Toxicities.**
The therapy delivery maps (TDMs) for Regimen H are on the next 8 pages (see Sections 4.6.9-4.6.11.b)

### 4.6.9 Regimen H – All High-Risk Patients (Stratum 4) ('Upfront' Window Therapy) Cycles 1 & 2

All High-Risk patients receive 2 cycles of "upfront" VIT window therapy, with subsequent treatment dependent upon response to "upfront" cycles. This therapy delivery map relates to the first 2 cycles of VIT therapy (Cycles 1& 2). Each cycle lasts 21 days. One cycle is described on this TDM. This TDM is on 1 page. Tumor tissue is strongly encouraged for banking: see ABTR01B1 or other appropriate study for details. Use a copy of this page once for each cycle (please note cycle number below).

_____
Patient name or initials

_____
DOB

Criteria to start Cycle 1 see Section 4.6.1.1. Criteria to start Cycle 2 see Section 4.6.1.2

| DRUG | ROUTE | DOSAGE | DAYS | IMPORTANT NOTES | OBSERVATIONS |
|---|---|---|---|---|---|
| VinCRIStine (VCR) | IV push over 1 minute** | 1.5 mg/m$^2$/dose OR (0.05 mg/kg/dose for < 10 kg) | 1 and 8 | **Maximum dose: 2 mg** **or infusion via minibag as per institutional policy | a. History, physical, ht/wt, BSA, VS<br>b. CBC (diff/plt) **(Weekly)**<br>c. Electrolytes, $Ca^{++}$, $Mg^{++}$, $PO_4$, creatinine, ALT/AST, bilirubin, total protein/albumin, AFP^, triglycerides & cholesterol^<br>d. Bilirubin<br>e. Urine glucose^<br>f. Tumor disease evaluation **(End of Cycle 2 only)**^<br>g. Liver transplant consult should be obtained ASAP post diagnosis but no later than end of Cycle #4.<br>h. POST-TEXT grouping (**End of Cycle 2 only)**^<br>^ See Section 7.5 for details<br>**OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE** |
| Irinotecan (IRIN) | IV over 90 minutes | 50 mg/m$^2$/dose OR (1.67 mg/kg/dose for < 10 kg) | 1-5 | **Maximum dose: 100 mg** | |
| Temsirolimus (TORI) | IV over 30 minutes | 35 mg/m$^2$/dose OR (1.2 mg/kg/dose for < 10 kg ) | 1 and 8 | See Section 4.6.4 for diphenhydramine premedication administration details | |

**Circle Cycle #: 1 (Weeks 1-3) 2 (Weeks 4-6) Ht_____cm Wt_____kg BSA_____m$^2$**

| Date Due | Date Given | Day | VCR mg | IRIN mg | TORI mg | Studies | Comments (Include any held doses, or dose modifications) |
|---|---|---|---|---|---|---|---|
| | | | **Enter calculated dose above and actual dose administered below** | | | | |
| | | 1 | _____mg | _____mg | _____mg | a, b, c*, d, e | |
| | | 2 | | _____mg | | | |
| | | 3 | | _____mg | | | |
| | | 4 | | _____mg | | | |
| | | 5 | | _____mg | | | |
| | | 8 | mg | | mg | b, d, e | |
| | | 15 | | | | b, e | |
| | | 21 | Start post window therapy at the end of Cycle 2. Responders will receive 6 cycles of C5VD with 2 cycles of VIT (see Sections 4.6.10.a–4.6.10.d). Non-responders will receive 6 cycles of C5VD and no further VIT (see Section 4.6.11.a and 4.6.11.b). | | | f, g, h | |

* The AFP obtained post Cycle 2/prior to Cycle 3 must be submitted for central review assessment of response in Reporting Period 1. For details see Section 10.3.

**See Section 5.0 for Dose Modifications for Toxicities and for general Supportive Care Guidelines see https://members.childrensoncologygroup.org/prot/reference_materials.asp under Standard Sections for Protocols**

4.6.10.a **Regimen H – Continuation for High-Risk Patients(Stratum 4): Window Therapy for Responders Cycles 3, 4, 5 and 6 (C5VD)**

Responders to "upfront" VIT window therapy will next receive C5VD and VIT chemotherapy: a total of 6 cycles of C5VD and 2 more cycles of VIT. This therapy delivery map relates to 4 cycles of C5VD therapy (Cycles 3-6). Each cycle lasts 21 days. One cycle is described on this TDM. This TDM is on 1 page. Use a copy of this page once for each cycle (please note cycle number below).
Tumor resection or liver transplant should occur whenever feasible BUT ideally by the end of Cycle 6 (4th C5VD cycle) and prior to any further VIT. Patients should resume chemotherapy as soon as possible following surgical resection and within 42 days of surgery or will be off protocol therapy.

_____
Patient name or initials

_____
DOB

Criteria to start each cycle: see Section 4.6.1.2

| DRUG | ROUTE | DOSAGE | DAYS | IMPORTANT NOTES | OBSERVATIONS |
|---|---|---|---|---|---|
| CISplatin (CDDP) | IV over 6 hours | 100 mg/m$^2$/dose OR (3.3 mg/kg/dose for < 10 kg) | 1 | Recommended administration guidelines: Urine S.G. should be < 1.010 prior to starting CDDP. See Section 4.6.5 for pre- and post-hydration & mannitol guidelines. | a. History, physical, ht/wt, BSA, VS<br>b. CBC (diff/plt) **(Weekly)**<br>c. Electrolytes, $Ca^{++}$, $Mg^{++}$, $PO_4$, creatinine, ALT/AST, bilirubin, total protein/albumin, AFP^, triglycerides & cholesterol^, urine glucose^<br>d. Tumor disease evaluation **(End of Cycles 4 and 6 only)**^<br>e. Liver transplant consult should be performed ASAP post diagnosis but no later than FIRST day of Cycle 5.<br>f. Consent for PLUTO registry should be obtained within one month of liver transplant, see (See Section 13.4)<br>g. See Section 14.0 for details regarding pathology slides/tumor tissue.<br>h. POST-TEXT grouping (when scans are performed - **End of Cycles 4 and 6 if appropriate)**^<br>i. Audiogram **(End of Cycle 6 only)**<br>j. Echocardiogram or MUGA **(End of Cycle 6 only)**<br>^ See Section 7.5 for details<br>**OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE** |
| 5-Fluorouroracil (FU) | Slow IV push over 2-4 minutes | 600 mg/m$^2$/dose OR (20 mg/kg/dose for < 10 kg) | 2 | | |
| VinCRIStine (VCR) | IV push over 1 minute** | 1.5 mg/m$^2$/dose OR (0.05 mg/kg/dose for < 10 kg) | 2, 9 and 16 | **Maximum dose: 2 mg**<br>**or infusion via minibag as per institutional policy | |
| DOXOrubicin (DOXO) | IV over 15 minutes | 30 mg/m$^2$/dose OR (1 mg/kg/dose for < 10 kg) | 1 & 2 | | |

**Circle Cycle #: 3 (Wks 7-9) 4 (Wks 10-12) 5 (Wks 13-15) 6 (Wks 16-18) Ht_____cm Wt_____kg BSA_____m$^2$**

| Date Due | Date Given | Day | CDDP _____ mg | FU _____ mg | VCR _____ mg | DOXO _____ mg | Studies | Comments (Include any held doses, or dose modifications) |
|---|---|---|---|---|---|---|---|---|
| | | | **Enter calculated dose above and actual dose administered below** | | | | | |
| | | 1 | mg | | | mg | a, b, c*, e | |
| | | 2 | | mg | mg | mg | | |
| | | 9 | | | mg | | b | |
| | | 16 | | | mg | | b | |
| | | 21 | If feasible, proceed to tumor resection or transplant at the end of Cycle 6. See Section 4.6.10.b. to start Cycle 7. | | | | d, f, g, h, i, j | |

* The AFP obtained post Cycle 2/prior to Cycle 3 must be submitted for central review assessment of response in Reporting Period 1. For details see Section 10.3.
Note: If an AFP was obtained post Cycle 2, do not repeat prior to Cycle 3.
**See Section 5.0 for Dose Modifications for Toxicities and for general Supportive Care Guidelines see https://members.childrensoncologygroup.org/prot/reference_materials.asp under Standard Sections for Protocols**

4.6.10.b **Regimen H – Continuation for High-Risk Patients (Stratum 4): Window Therapy Responders Cycle 7 (VIT)**

This therapy delivery map relates to 1 cycle of VIT therapy and will last 21 days. One cycle is described on this TDM. This TDM is on 1 page. Tumor resection or liver transplant should have occurred prior to any additional post Cycle 2 VIT therapy. Patients should resume chemotherapy as soon as possible following surgical resection and within 42 days of surgery or will be off protocol therapy. The order of chemotherapy cycles can be switched at the discretion of the treating oncologists and surgeons to optimize surgical outcomes and minimize complications (see Section 4.6 for details).

_____
Patient name or initials

_____
DOB

Criteria to start each cycle: See Section 4.6.1.2

| DRUG | ROUTE | DOSAGE | DAYS | IMPORTANT NOTES | OBSERVATIONS |
|---|---|---|---|---|---|
| VinCRIStine (VCR) | IV push over 1 minute** | 1.5 mg/m$^2$/dose OR (0.05 mg/kg/dose for < 10 kg) | 1 & 8 | **Maximum dose: 2 mg** **or infusion via minibag as per institutional policy | a. History, physical, ht/wt, BSA, VS<br>b. CBC (diff/plt) **(Weekly)**<br>c. Electrolytes, $Ca^{++}$, $Mg^{++}$, $PO_4$, creatinine, ALT/AST, bilirubin, total protein/albumin, AFP , triglycerides & cholesterol^, urine glucose^<br>d. Bilirubin<br><br>^ See Section 7.5 for details<br>**OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE** |
| Irinotecan (IRIN) | IV over 90 minutes. | 50 mg/m$^2$/dose OR (1.67 mg/kg/dose for < 10 kg) | 1-5 | **Maximum dose: 100 mg** | |
| Temsirolimus (TORI) | IV over 30 minutes | 35 mg/m$^2$/dose OR (1.2 mg/kg for < 10 kg) | 1& 8 | See Section 4.6.4 for diphenhydramine premedication administration details | |

**Enter Cycle #: _____ Ht_____cm Wt_____kg BSA_____m$^2$**

| Date Due | Date Given | Day | VCR _____mg | IRIN _____mg | TORI _____mg | Studies | Comments (Include any held doses, or dose modifications) |
|---|---|---|---|---|---|---|---|
| | | | **Enter calculated dose above and actual dose administered below** | | | | |
| | | 1 | _____mg | _____mg | _____mg | a, b, c, d | |
| | | 2 | | mg | | | |
| | | 3 | | _____mg | | | |
| | | 4 | | _____mg | | | |
| | | 5 | | mg | | | |
| | | 8 | _____mg | | _____mg | b, d | |
| | | 15 | | | | b | |
| | | 21 | See Section 4.6.10.c to start Cycle 8. | | | | |

**See Section 5.0 for Dose Modifications for Toxicities and for general Supportive Care Guidelines see https://members.childrensoncologygroup.org/prot/reference_materials.asp under Standard Sections for Protocols.**

4.6.10.c **Regimen H – Continuation for High-Risk Patients (Stratum 4): Window Therapy Responders Cycles 8 and 9 (C5VD + DXRZ)**

This therapy delivery map relates to 2 Cycles of C5VD + DXRZ therapy (Cycles 8 and 9). Each Cycle lasts 21 days. One cycle is described on this TDM. This TDM is on 1 page. Patients should resume chemotherapy as soon as possible following surgical resection and within 42 days of surgery or will be off protocol therapy. The order of chemotherapy cycles can be switched at the discretion of the treating oncologists and surgeons to optimize surgical outcomes and minimize complications (see Section 4.6 for details). Use a copy of this page once for each cycle (please note cycle number below).

_____
Patient name or initials

_____
DOB

Criteria to start each cycle: See Section 4.6.1.2

| DRUG | ROUTE | DOSAGE | DAYS | IMPORTANT NOTES | OBSERVATIONS |
|---|---|---|---|---|---|
| CISplatin (CDDP) | IV over 6 hours | 100 mg/m$^2$/dose OR (3.3 mg/kg/dose for < 10 kg) | 1 | Recommended administration guidelines: Urine S.G. should be <1.010 prior to starting CDDP. See Section 4.6.5 for pre- and post-hydration & mannitol guidelines. | a. History, physical, ht/wt, BSA, VS<br>b. CBC (diff/plt)<br>c. Electrolytes, Ca++, Mg++, $PO_4$ creatinine, ALT/AST, bilirubin, total protein/albumin, AFP, triglycerides & cholesterol^, urine glucose^<br><br>^ See Section 7.5 for details<br>**OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE** |
| 5-Fluorouroracil (FU) | Slow IV push over 2-4 minutes | 600 mg/m$^2$/dose OR (20 mg/kg/dose for < 10 kg) | 2 | | |
| VinCRIStine (VCR) | IV push over 1 minute** | 1.5 mg/m$^2$/dose OR (0.05 mg/kg/dose for < 10 kg) | 2, 9 and 16 | **Maximum dose: 2 mg**<br>**or infusion via minibag as per institutional policy | |
| Dexrazoxane[$] (DXRZ) | Slow IV push over 5-15 minutes[##] | 300 mg/m$^2$/dose OR (10 mg/kg/dose for < 10 kg) | 1 & 2 | **Give immediately prior to DOXO . The elapsed time from the beginning of the DXRZ to the end of the DOXO infusion should be 30 minutes or less.** | |
| DOXOrubicin (DOXO) | IV over 15 minutes | 30 mg/m$^2$/dose OR (1 mg/kg/dose for < 10 kg) | 1 & 2 | | |

**Enter Cycle #:** _____ **Ht**_____**cm** **Wt**_____**kg** **BSA**_____**m$^2$**

| Date Due | Date Given | Day | CDDP _____ mg | FU _____ mg | VCR _____ mg | DXRZ[$] _____ mg | DOXO _____ mg | Studies | Comments (Include any held doses, or dose modifications) |
|---|---|---|---|---|---|---|---|---|---|
| | | | **Enter calculated dose above and actual dose administered below** | | | | | | |
| | | 1 | _____ mg | | | _____ mg | _____ mg | a, b, c | |
| | | 2 | | _____ mg | _____ mg | _____ mg | _____ mg | | |
| | | 9 | | | _____ mg | | | b | |
| | | 16 | | | _____ mg | | | b | |
| | | 21 | See Section 4.6.10.d to start Cycle 10. | | | | | | |

[$]Dexrazoxane administration is not required for patients enrolled in Japan.

**See Section 5.0 for Dose Modifications for Toxicities and for general Supportive Care Guidelines see https://members.childrensoncologygroup.org/prot/reference_materials.asp under Standard Sections for Protocols**

4.6.10.d **Regimen H – Continuation for High-Risk Patients (Stratum 4): Window Therapy Responders Cycle 10 (VIT)**

This therapy delivery map relates to 1 Cycle of VIT therapy and will last 21 days. One cycle is described on this TDM. This TDM is on 1 page. Tumor resection or liver transplant should have occurred prior to any additional post Cycle 2 VIT therapy. Patients should resume chemotherapy as soon as possible following surgical resection and within 42 days of surgery or will be off protocol therapy. The order of chemotherapy cycles can be switched at the discretion of the treating oncologists and surgeons to optimize surgical outcomes and minimize complications (see Section 4.6 for details).

_____
Patient name or initials

_____
DOB

Criteria to start each cycle: See Section 4.6.1.2

| DRUG | ROUTE | DOSAGE | DAYS | IMPORTANT NOTES | OBSERVATIONS |
|---|---|---|---|---|---|
| VinCRIStine (VCR) | IV push over 1 minute** | 1.5 mg/m$^2$/dose OR (0.05 mg/kg/dose for < 10 kg) | 1 & 8 | **Maximum dose: 2 mg** **or infusion via minibag as per institutional policy | a. History, physical, ht/wt, BSA, VS<br>b. CBC (diff/plt) **(Weekly)**<br>c. Electrolytes, $Ca^{++}$, $Mg^{++}$, $PO_4$, creatinine, ALT/AST, total protein/albumin, AFP , triglycerides & cholesterol^, urine glucose^<br>d. Bilirubin<br>e. Tumor disease evaluations<br>f. Echocardiogram or MUGA<br>g. Audiogram<br>^ See Section 7.5 for details<br>**OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE** |
| Irinotecan (IRIN) | IV over 90 minutes. | 50 mg/m$^2$/dose OR (1.67 mg/kg/dose for < 10 kg) | 1-5 | **Maximum dose: 100 mg** | |
| Temsirolimus (TORI) | IV over 30 minutes | 35 mg/m$^2$/dose OR (1.2 mg/kg for < 10 kg) | 1& 8 | See Section 4.6.4 for diphenhydramine premedication administration details | |

**Cycle #: 10 (Wks 28-30)** **Ht_____cm** **Wt_____kg** **BSA_____m$^2$**

| Date Due | Date Given | Day | VCR mg | IRIN mg | TORI mg | Studies | Comments (Include any held doses, or dose modifications) |
|---|---|---|---|---|---|---|---|
| | | **Enter calculated dose above and actual dose administered below** | | | | | |
| | | 1 | _____mg | _____mg | _____mg | a, b, c, d | |
| | | 2 | | _____mg | | | |
| | | 3 | | _____mg | | | |
| | | 4 | | _____mg | | | |
| | | 5 | | _____mg | | | |
| | | 8 | mg | | mg | b, d | |
| | | 15 | | | | b | |
| | | 21 | Completion of Cycle 10 is the end of therapy for High-Risk (Stratum 4) Responders | | | a, b, c, e, f, g | |

**See Section 5.0 for Dose Modifications for Toxicities and for general Supportive Care Guidelines see https://members.childrensoncologygroup.org/prot/reference_materials.asp under Standard Sections for Protocols.**

4.6.11.a **Regimen H – High-Risk Patients (Stratum 4): Window Therapy Non-responders Cycles 3-6 (C5VD)**

This therapy delivery map relates to 4 Cycles of C5VD therapy (Cycles 3-6). Each Cycle lasts 21 days. One cycle is described on this TDM. This TDM is on 1 page. Use a copy of this page once for each cycle (please note cycle number below.)
Tumor resection or liver transplant should occur whenever feasible BUT ideally by the end of Cycle 6 (4th C5VD cycle). Patients should resume chemotherapy as soon as possible and within 42 days of surgery or will be off protocol therapy.

_____
Patient name or initials

_____
DOB

Criteria to start each cycle: ANC ≥ 750/µL and the platelet count is ≥ 75,000/µL.

| DRUG | ROUTE | DOSAGE | DAYS | IMPORTANT NOTES | OBSERVATIONS |
|---|---|---|---|---|---|
| CISplatin (CDDP) | IV over 6 hours | 100 mg/m$^2$/dose OR (3.3 mg/kg/dose for < 10 kg) | 1 | Recommended administration guidelines: Urine S.G. should be < 1.010 prior to starting CDDP. See Section 4.6.5 for pre- and post- hydration & mannitol guidelines. | a. History, physical, ht/wt, BSA, VS<br>b. CBC (diff/plt) **(Weekly)**<br>c. Electrolytes, $Ca^{++}$, $Mg^{++}$, $PO_4$, creatinine, ALT/AST, bilirubin, total protein/albumin, AFP^, triglycerides & cholesterol^, urine glucose^<br>d. Tumor disease evaluation **(End of Cycles 4 & 6,Only)**^<br>e. Audiogram **(End of Cycle 6 only)**<br>f. Echocardiogram or MUGA **(End of Cycle 6 only)**<br>g. Liver transplant consult should be performed ASAP post diagnosis but no later than FIRST day of Cycle 5.<br>h. Consent for PLUTO registry should be obtained within one month of liver transplant, see Section 13.4<br>i. POST-TEXT grouping (when scans are performed - **End of Cycle 4 & 6 if appropriate)**^<br>j. See Section 14.0 for details regarding pathology slides/tumor tissue.<br>^ See Section 7.5 for details<br>**OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE** |
| 5-Fluorouroracil (FU) | Slow IV push over 2-4 minutes | 600 mg/m$^2$/dose OR (20 mg/kg/dose for < 10 kg) | 2 | | |
| VinCRIStine (VCR) | IV push over 1 minute** | 1.5 mg/m$^2$/dose OR (0.05 mg/kg/dose for < 10 kg) | 2, 9 and 16 | **Maximum dose: 2 mg**<br>**or infusion via minibag as per institutional policy | |
| DOXOrubicin (DOXO) | IV over 15 minutes | 30 mg/m$^2$/dose OR (1 mg/kg/dose for < 10 kg) | 1 & 2 | | |

**Circle Cycle #: 3 (Wks 7-9) 4 (Wks 10-12) 5 (Wks 13-15) 6 (Wks 16-18) Ht_____cm Wt_____kg BSA_____m$^2$**

| Date Due | Date Given | Day | CDDP _____mg | FU _____mg | VCR _____mg | DOXO _____mg | Studies | Comments (Include any held doses, or dose modifications) |
|---|---|---|---|---|---|---|---|---|
| | | | **Enter calculated dose above and actual dose administered below** | | | | | |
| | | 1 | _____mg | | | _____mg | a, b, c*, h | |
| | | 2 | | _____mg | _____mg | _____mg | | |
| | | 9 | | | _____mg | | b | |
| | | 16 | | | _____mg | | b | |
| | | 21 | If feasible, proceed to tumor resection or transplant at the end of Cycle 6. See Section 4.6.10.b. to start Cycle 7. | | | | d, e, h, i , j | |

* The AFP obtained post Cycle 2/prior to Cycle 3 must be submitted for central review assessment of response in Reporting Period 1. For details see Section 10.3.
Note: If an AFP was obtained post Cycle 2, do not repeat prior to Cycle 3.

**See Section 5.0 for Dose Modifications for Toxicities and for general Supportive Care Guidelines see https://members.childrensoncologygroup.org/prot/reference_materials.asp under Standard Sections for Protocols.**

4.6.11.b **Regimen H – High-Risk Patients (Stratum 4) (Window Therapy Non- responders) Cycles 7 and 8 (C5VD + DXRZ)**

This therapy delivery map relates to 2 Cycles of C5VD + DXRZ therapy (Cycles 7 and 8). Each Cycle lasts 21 days. One cycle is described on this TDM. This TDM is on 1 page. Patients should resume chemotherapy as soon as possible and within 42 days of surgery or will be off protocol therapy. Use a copy of this page once for each cycle (please note cycle number below).

_____
Patient name or initials

_____
DOB

Criteria to start each cycle: ANC ≥ 750/µL and the platelet count is ≥ 75,000/µL.

| DRUG | ROUTE | DOSAGE | DAYS | IMPORTANT NOTES | OBSERVATIONS |
|---|---|---|---|---|---|
| CISplatin (CDDP) | IV over 6 hours | 100 mg/m$^2$/dose OR (3.3 mg/kg/dose for < 10 kg) | 1 | Recommended administration guidelines: Urine S.G. should be < 1.010 prior to starting CDDP. See Section 4.6.5 for pre- and post-hydration & mannitol guidelines | a. History, physical, ht/wt, BSA, VS, performance status<br>b. CBC (diff/plt) **(Weekly)**<br>c. Electrolytes, $Ca^{++}$, $Mg^{++}$, $PO_4$, creatinine, ALT/AST, bilirubin, total protein/albumin, AFP, triglycerides & cholesterol^, urine glucose^<br>d. Tumor/ disease evaluations^ **(End of therapy only)**,<br>e. Audiogram **(End of therapy only)**<br>f. Echocardiogram or MUGA **(End of therapy only)**<br>^ See Section 7.5 for details<br>**OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE** |
| 5-Fluorouroracil (FU) | Slow IV push over 2-4 minutes | 600 mg/m$^2$/dose OR (20 mg/kg/dose for < 10 kg) | 2 | | |
| VinCRIStine (VCR) | IV push over 1 minute** | 1.5 mg/m$^2$/dose OR (0.05 mg/kg/dose for < 10 kg) | 2, 9 & 16 | **Maximum dose: 2 mg**<br>**or infusion via minibag as per institutional policy | |
| Dexrazoxane[$] (DXRZ) | Slow IV push over 5-15 minutes[##] | 300 mg/m$^2$/dose OR (10 mg/kg/dose for < 10 kg) | 1 & 2 | **Give immediately prior to DOXO. The elapsed time from the beginning of the DXRZ to the end of the DOXO infusion should be 30 minutes or less.** | |
| DOXOrubicin (DOXO) | IV over 15 minutes | 30 mg/m$^2$/dose OR (1 mg/kg/dose for < 10 kg) | 1 & 2 | | |

**Circle Cycle #: 7 (Wks 19-21) 8 (Wks 22-24)** **Ht_____cm** **Wt_____kg** **BSA_____m$^2$**

| Date Due | Date Given | Day | CDDP mg | FU mg | VCR mg | DXRZ[$] mg | DOXO mg | Studies | Comments (Include any held doses, or dose modifications) |
|---|---|---|---|---|---|---|---|---|---|
| | | | **Enter calculated dose above and actual dose administered below** | | | | | | |
| | | 1 | _____mg | | | _____mg | _____mg | a, b, c | |
| | | 2 | | mg | mg | mg | mg | | |
| | | 9 | | | _____mg | | | b | |
| | | 16 | | | _____mg | | | b | |
| | | 21 | Completion of Cycle 8 is the end of therapy for High-Risk (Stratum 4) Non-responders. | | | | | (a, b ,c, d, e, f)* | * End of therapy only |

[$]Dexrazoxane administration is not required for patients enrolled in Japan.

**See Section 5.0 for Dose Modifications for Toxicities and for general Supportive Care Guidelines see https://members.childrensoncologygroup.org/prot/reference_materials.asp under Standard Sections for Protocols**

## 5.0 DOSE MODIFICATIONS FOR TOXICITIES

### 5.1 Myelosuppression

#### 5.1.1 Myeloid Growth Factor Support

If the patient is due to begin a cycle of chemotherapy and the ANC < 750/µL and/or platelet count is < 75,000/µL on Day 1, delay the next cycle until recovery occurs. If the patient recovers to ANC > 750/µL and platelets > 75,000/µL within 7 days proceed to next cycle. Consider holding Bactrim. If the delay of therapy is more than 7 days due to neutropenia or if the patient requires hospitalization for fever and neutropenia or sepsis, then the patient should receive myeloid growth factors prophylactically starting 24 hours post chemotherapy in subsequent cycles. Cytokine support need not be limited to filgrastim; pegfilgrastim is also permitted according to institutional standard guidelines. Note: The use of erythropoietin is discouraged.

If filgrastim is used, continue it for at least 7 days and until ANC ≥ 5,000/µL after nadir. Filgrastim should be discontinued at least 24 hours before the start of the next chemotherapy cycle but may be given on days when vincristine is administered. Filgrastim **should be given subcutaneously if possible**, as it is less effective when given intravenously. If pegfilgrastim is used, the next chemotherapy cycle should start at least 14 days after pegfilgrastim administration.

### 5.2 Doxorubicin

#### 5.2.1 Mucositis

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 by 25% to 22.5 mg/m$^2$/dose (0.75 mg/kg/dose). 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 receives the 25% reduced dose and again has Grade 3 or 4 mucositis that is NOT attributable to infectious etiology 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 15 mg/m$^2$/dose (0.5 mg/kg/dose). If subsequent chemotherapy is tolerated without the recurrence of Grade 3 or 4 toxicity, then escalate to 22.5 mg/m$^2$/dose (0.75 mg/kg/dose). 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 experiences Grade 3 or 4 toxicity with the 50% dose reduction, the doxorubicin should be omitted from subsequent cycles.

#### 5.2.2 Change In Ejection/Shortening Fraction

If the cardiac ejection fraction falls below 47% or shortening fraction below 27% and the patient is asymptomatic following a cycle of doxorubicin, repeat the study in 1 week. If the ejection fraction or shortening fraction remains abnormal 1 week later, omit doxorubicin.

If doxorubicin is held from a cycle of therapy, repeat the study prior to the next cycle. If the cardiac ejection fraction returns to normal and is ≥ 47% and shortening fraction is ≥ 27%, resume doxorubicin at full dose.

#### 5.2.3 Symptomatic Congestive Heart Failure (CHF)

If at any time, the patient develops Grade 3 CHF or other cardiac disorders or any Grade 4 cardiac toxicity not related to underlying infection or metabolic abnormality, omit doxorubicin from all subsequent cycles.

5.2.4 Hepatotoxicity

If direct bilirubin is > 3 mg/dL prior to chemotherapy, omit doxorubicin. If direct bilirubin is > 1.5 mg/dL but ≤ 3 mg/dL (Grade 2 toxicity) prior to chemotherapy, reduce doxorubicin dose by 50% [15 mg/m$^2$/dose (0.5 mg/kg/dose)]. If doxorubicin is dose reduced because of direct hyperbilirubinemia, subsequent doses should be based on above criteria, ie, if direct bilirubin returns to < Grade 2 toxicity, the full dose of doxorubicin is to be given.

## 5.3 Cisplatin

5.3.1 Hearing Loss

Do not modify cisplatin dose based upon audiologic reports/loss of hearing.

5.3.2 Change in Renal Function

If the serum creatinine increases to greater than the maximum serum creatinine for age (see Section 3.2.5.1 for threshold creatinine values table), check a creatinine clearance or GFR.

No dose reductions in cisplatin will be made for a decrease in the baseline GFR or creatinine clearance as long as the value remains > 60 mL/min/1.73 m². Omit cisplatin therapy from a cycle of therapy if GFR or creatinine clearance is < 60 mL/min/1.73 m². If cisplatin is held for a cycle of therapy, repeat the study prior to next cycle. Resume therapy at full dose if GFR or creatinine clearance > 60 mL/min/1.73 m².

## 5.4 Vincristine

5.4.1 Peripheral Neuropathy

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$^2$/dose (0.025 mg/kg/dose)] and escalate to 75% of full dose [1.125 mg/m$^2$/dose (0.0375 mg/kg/dose)], 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.

5.4.2 Hepatotoxicity

If direct bilirubin is > 3 mg/dL prior to a cycle of chemotherapy, omit vincristine. If direct bilirubin is > 1.5 mg/dL but ≤ 3 mg/dL (Grade 2 toxicity) 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, ie, if direct bilirubin returns to < Grade 2 toxicity, the full dose of vincristine is to be given.

## 5.5 Irinotecan

5.5.1 Diarrhea

See Supportive Care Guidelines posted in 'Standard Sections for Protocols' on the COG Website https://members.childrensoncologygroup.org/prot/reference_materials.asp for recommendations concerning early and late diarrhea secondary to irinotecan.

If Grade 3 or 4 irinotecan-associated diarrhea is experienced by a patient despite maximal use of anti-diarrheal medications and cefixime/cefpodoxime, the dose of irinotecan should be reduced by 25% to 37.5 mg/m$^2$/dose (1.25 mg/kg/dose) for subsequent cycles. If Grade 3 or 4 diarrhea occurs despite maximal use of anti-diarrheals, cefixime/cefpodoxime and the 25% dose reduction in irinotecan, no further irinotecan should be administered. If irinotecan is discontinued, proceed with subsequent cycles of chemotherapy (C5VD) omitting the VI cycles.

## 5.6 Temsirolimus

Note: If temsirolimus therapy needs to be discontinued as detailed below, the patient can remain on study and continue with planned therapy while omitting all subsequent doses of temsirolimus.

### 5.6.1 Hyperglycemia

Therapy modifications for patients who develop hyperglycemia (based on random, non-fasting glucose levels) should be:

- Grade 1-2: Continue temsirolimus

- Grade 3
    - Initiate insulin therapy or oral diabetic agent* as indicated. Hold temsirolimus until resolves to ≤ Grade 2. Resume temsirolimus at same dose IF patient is asymptomatic, AND serum glucose is consistently < 250 mg/dL (≤ Grade 2) without glycosuria. The patient may continue to receive concomitant insulin or an oral diabetic agent for the management of hyperglycemia while receiving temsirolimus.

    - If Grade 3 hyperglycemia recurs despite a stable dose of insulin an oral diabetic agent should be used, as the effect of temsirolimus on glucose transport into cells may make patients refractory to insulin. Oral diabetic agents should be tried before declaring a patient's hyperglycemia refractory to therapy. If hyperglycemia recurs despite the use of an oral diabetic agent, temsirolimus therapy should be discontinued.

    - If a patient experiences Grade 3 hyperglycemia despite insulin, and an oral diabetic agent, patient should be taken off temsirolimus therapy.

- Grade 4
    - Initiate insulin therapy or an oral diabetic agent* as indicated. Hold temsirolimus until resolves to ≤ Grade 2. Resume temsirolimus at same dose IF patient is asymptomatic AND serum glucose is consistently < 250 mg/dL (≤ Grade 2) without glycosuria. The patient may continue to receive concomitant insulin or an oral diabetic agent for the management of hyperglycemia while receiving temsirolimus.

    - If Grade 4 hyperglycemia recurs despite a stable dose of insulin, or an oral diabetic agent, the patient should be taken off temsirolimus therapy.

***Recommended guidelines for use of oral diabetic agents:**
**Initiation of treatment for hyperglycemia should occur under the guidance of a pediatric endocrinologist at the local institution.** Metformin or other oral antihyperglycemia agent may be used per local endocrinologist's recommendations. Insulin therapy should be directed by specialists in pediatric diabetes, with the goal of normal fasting blood sugars < 126 mg/dL and HgbA1C < 8%.

### 5.6.2 Dose Modification for Infusional Reactions to Temsirolimus

Therapy modifications for patients who develop infusional reactions to temsirolimus are:

- Grade 1-2: Only dose interruption/discontinuation, but not dose reduction is required for allergic/infusional reactions.
    - If a patient develops a hypersensitivity reaction despite diphenhydramine pretreatment, stop the infusion and wait 30 to 60 minutes (depending upon the reaction severity). At the

physician's discretion, it may be possible to resume treatment by administering an H2 blocker approximately 30 minutes before restarting the infusion. The manufacturer recommends famotidine 0.5 mg/kg IV maximum dose 20 mg, rather than cimetidine, because it lacks reported drug interactions. If famotidine is unavailable, administer ranitidine 1-2 mg/kg IV maximum dose 50 mg. Re-attempt infusion at a slower rate, possibly over 60 minutes.

- If Grade 1-2 infusion reactions recur with subsequent dose, add dexamethasone 0.2 mg/kg (max 10mg) IV or equivalent to premedications above.

- Grade 3: Stop infusion immediately and remove the infusion tube. Administer diphenhydramine hydrochloride 1 mg/kg IV (max 50 mg), dexamethasone 0.2 mg/kg (max 10 mg) IV (or equivalent), bronchodilators for bronchospasms, and other medications as medically indicated. Hospital admission should be considered. Discontinue temsirolimus treatment.

- Grade 4: Stop infusion immediately and remove the infusion tube. Administer diphenhydramine hydrochloride 1 mg/kg (max 50 mg) IV, dexamethasone 0.2 mg/kg (max 10mg) IV (or equivalent), and other anaphylaxis medications as indicated. Epinephrine or bronchodilators should be administered as indicated. Hospital admission for observation may be indicated. Discontinue temsirolimus treatment.

5.6.3 Dose Modifications for Pneumonitis

For patients who develop pneumonitis (cough, dyspnea, fever), temsirolimus should be held pending investigation. If events are considered at least possibly due to treatment, discontinue temsirolimus therapy. If the treating clinician determines that respiratory symptoms are not related to drug therapy, the patient should be retreated with the same doses of temsirolimus, irinotecan, and vincristine.

5.6.4 Dose Modifications for Mucositis or Rash

The following guidelines should be used for patients who develop mucositis, or rash. **In addition, stomatitis, mucositis, and/or mouth ulcers** due to temsirolimus (inflammation or ulcers in the mouth) should be treated using local supportive care.

- Grade 1-2: Continue temsirolimus

- Grade 3-4
  - Hold temsirolimus until recovery to ≤ Grade 1. If recovery takes ≤ 7 days, resume treatment with the same dose of temsirolimus. Upon retreatment, if Grade 3 or 4 toxicity recurs and persists >7 days, discontinue temsirolimus.
  - If recovery takes > 14 days, discontinue temsirolimus therapy.

5.6.5 Dose Modifications for Elevated Fasting Cholesterol

The following guidelines should be used for patients who develop elevated fasting cholesterol.

- Grade 2
  Continue temsirolimus; consider treatment with an HMG-CoA reductase inhibitor depending upon recommendations of institutional hyperlipidemia consultants

- Grade 3

An HMG-CoA reductase inhibitor should be started, and dosages adjusted based upon recommendations of institutional hyperlipidemia consultants. It is expected that optimal effects of the lipid lowering medication will be observed 2-4 weeks after its initiation. Treatment with temsirolimus can continue during this time provided that hypercholesterolemia remains ≤ Grade 3.

- Grade 4
  Hold temsirolimus. An HMG-CoA reductase inhibitor should be started, and dosages should be adjusted based upon recommendations from institutional hyperlipidemia consultants. It is expected that optimal effect of the lipid lowering medication will be observed 2-4 weeks after initiation. Temsirolimus is to be restarted at the same dose level when recovery to ≤ Grade 3 cholesterol is observed. Upon retreatment with temsirolimus concurrent with an HMGCoA reductase inhibitor, if Grade 4 elevations recurs, temsirolimus should be discontinued.

Note: There is a potential drug interaction between mTOR inhibitors and cholesterol lowering agents, particularly atovastatin. This should be considered when prescribing a cholesterol lowering agent.

5.6.6 Dose Modifications for Elevated Fasting Triglycerides

The following guidelines should be used for patients who develop elevated fasting triglycerides.

- Grade 2
  Continue temsirolimus; if triglycerides are between 301 and 400 mg/dL consider treatment with an HMG-CoA reductase inhibitor depending upon recommendations of institutional hyperlipidemia consultants. HMG-CoA reductase inhibitor is recommended if triglycerides are between 401 and 500.

- Grade 3-4
  Hold temsirolimus until recovery to ≤ Grade 2. An HMG-CoA reductase inhibitor should be started, and dosages should be adjusted based upon recommendations from institutional hyperlipidemia consultants. Upon retreatment at the same dose level, if Grade 3 or 4 toxicity recurs, lipid lowering medication should be adjusted in consultation with institutional hyperlipidemia consultants. Temsirolimus should be held until recovery to ≤ Grade 2. Upon retreatment with temsirolimus concurrent with an HMGCoA reductase inhibitor, if Grade 3 or 4 elevations recur, temsirolimus should be discontinued.

Note: There is a potential drug interaction between mTOR inhibitors and cholesterol lowering agents, particularly atovastatin. This should be considered when prescribing a cholesterol lowering agent.

5.6.7 Dose Modifications for Hyperbilirubinemia

- If bilirubin is ≥ Grade 2 toxicity (> 1.5×ULN) prior to chemotherapy, omit temsirolimus dose. If temsirolimus dose is omitted because of hyperbilirubinemia, subsequent doses should be based on above criteria, ie. if bilirubin returns to < Grade 2 toxicity, the full dose of temsirolimus is to be given.
  If the temsirolimus dose has to be omitted twice due to hyperbilirubinemia, temsirolimus should be discontinued permanently.

## 6.0 DRUG INFORMATION

### 6.1 TEMSIROLIMUS

(Torisel®, CCI-779, rapamycin analog, WAY-130779) NSC# 683864

(10/24/18)

**Source and Pharmacology:** Temsirolimus is an ester of the immunosuppressive compound sirolimus (rapamicin, Rapamune®). Its chemical name is rapamycin 42-[2,2-bis(hydroxymethyl)propionate]. Temsirolimus is a specific inhibitor of the mammalian target of rapamycin (mTOR), an enzyme that regulates cell growth and proliferation. Temsirolimus binds to an intracellular protein FK506 binding protein (FKBP) 12 and the protein-drug complex inhibits the activity of mTOR and controls cell division. Inhibition of mTOR prevents progression from $G_1$ to S phase of the cell cycle. *In vitro* studies show that inhibition of the activity of mTOR resulted in reduced levels of the hypoxia-inducible factors HIF-1 and HIF-2 alpha and the vascular endothelial growth factor.

Pharmacokinetic studies of a single intravenous (IV) dose of temsirolimus in adults showed that over a dose range of 1 mg to 25 mg, the drug exposure increased with increasing doses in a less than proportional fashion. After a single 25 mg IV dose, the volume of distribution was large (172 L) with preferential partitioning into blood, the mean clearance was 16.2 L/h, and the terminal half-life was 17.3 hours.

The pharmacokinetics of temsirolimus was assessed in 19 pediatric subjects with relapsed or refractory advanced solid tumors. The typical subject was an 11-year-old male child, with a body weight of 44.4 kg and a body surface area of 1.38 $m^2$. Subjects received doses of 10, 25, 75, and 150 mg/$m^2$ once weekly. Comparisons of exposure with adult subjects show that temsirolimus $C_{max}$ and $AUC_{sum}$ (sum of temsirolimus and sirolimus area under the concentration vs time curve) in the pediatric subjects was comparable to adult subjects, while temsirolimus AUC was higher in the pediatric subjects. This greater exposure to parent drug in the pediatric population was balanced by the shorter half-lives of sirolimus metabolite and corresponding lower AUCs.

The safety and pharmacokinetics of temsirolimus were evaluated in a dose escalation phase 1 study in 110 patients with normal or varying degrees of hepatic impairment. Patients with baseline bilirubin > 1.5× the upper limit of normal (ULN) experienced greater toxicity than patients with baseline bilirubin ≤ 1.5×ULN when treated with temsirolimus. The overall frequency of ≥ Grade 3 adverse reactions and deaths, including deaths due to progressive disease, were greater in patients with baseline bilirubin > 1.5×ULN due to increased risk of death. Caution should be used when treating patients with hepatic impairment. Concentrations of temsirolimus and its metabolite sirolimus were increased in patients with elevated AST or bilirubin levels. Temsirolimus is contraindicated in patients with bilirubin > 1.5 X ULN.

Temsirolimus is metabolized extensively in the liver mainly by the isoenzyme cytochrome (CYP) P450 3A4. The main active metabolite is sirolimus and the other four metabolites account for less than 10% of the parent drug. The activity of temsirolimus is dictated both by the parent drug and by the equipotent metabolite sirolimus. Sirolimus half life is longer (54.6 hours) and after a single 25 mg IV dose its AUC is 2.7-fold that of temsirolimus AUC due to mainly the longer half-life of sirolimus. Temsirolimus elimination occurs primarily in the liver with only minor amounts of drug-related products eliminated in the urine. Multiple doses of 25 mg administered once weekly exhibited little or no substantial accumulation.

Since the primary oxidative metabolism of temsirolimus is via CYP3A4, inhibitors and inducers of the CYP3A4 enzyme system may alter the metabolism of temsirolimus; however, temsirolimus does not induce CYP3A4. Temsirolimus may inhibit the metabolic clearance of substrates of CYP3A4/5 or CYP2D6, but not CYP2C9 or CYP2C8. Caution should be used when administering strong CYP3A4 inhibitors or strong

CYP3A4/5 inducers with temsirolimus IV. In Phase I drug interaction studies, coadministration of IV temsirolimus with ketoconazole, a potent CYP3A4 inhibitor, had no significant effect on temsirolimus, but increased the major metabolite sirolimus exposure. Coadministration of temsirolimus with rifampin, a potent CYP3A4 inducer, had no significant effect on temsirolimus, but decreased sirolimus exposure.

*In vitro* studies showed that temsirolimus is subject to P-gp-mediated efflux; additionally temsirolimus inhibited the transport of digoxin, a P-gp substrate. These results indicate that temsirolimus has the potential to alter the transport of agents that are P-gp substrates as well as to be altered by P-gp inhibitors. Clinical implications related to concomitant administration of P-gp substrates are unknown and dose modifications for co-administration with P-gp substrates or inhibitors are not provided in the drug package insert.

The combination of temsirolimus and angiotensin converting enzyme (ACE) inhibitors resulted in angioedema-type reactions (including delayed reactions occurring up to 2 months after initiation of therapy). Coadministration of sunitinib and temsirolimus resulted in increase toxicity. During temsirolimus treatment, the coadministration of sunitinib or ACE inhibitors should be avoided. Prothrombin time and INR should be monitored if warfarin is added or discontinued.

**Toxicity:**

**Comprehensive Adverse Events and Potential Risks list (CAEPR)**
**for**
**Temsirolimus (CCI-779, NSC 683864)**

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 1927 patients.* Below is the CAEPR for temsirolimus (CCI-779).

**NOTE**: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

**Version 2.6, August 19, 2018**[1]

| **Adverse Events with Possible Relationship to Temsirolimus (CCI-779) (CTCAE 5.0 Term) [n= 1927]** | | | **Specific Protocol Exceptions to Expedited Reporting (SPEER)** |
|---|---|---|---|
| **Likely (>20%)** | **Less Likely (<=20%)** | **Rare but Serious (<3%)** | |
| BLOOD AND LYMPHATIC SYSTEM DISORDERS | | | |
| Anemia | | | ***Anemia (Gr 3)*** |
| | Febrile neutropenia | | ***Febrile neutropenia (Gr 3)*** |
| ENDOCRINE DISORDERS | | | |
| | Testosterone deficiency | | ***Testosterone deficiency (Gr 2)*** |
| GASTROINTESTINAL DISORDERS | | | |
| | Abdominal distension | | ***Abdominal distension (Gr 2)*** |
| | Abdominal pain | | ***Abdominal pain (Gr 3)*** |

| Adverse Events with Possible Relationship to Temsirolimus (CCI-779) (CTCAE 5.0 Term) [n= 1927] | | | Specific Protocol Exceptions to Expedited Reporting (SPEER) |
|---|---|---|---|
| **Likely (>20%)** | **Less Likely (<=20%)** | **Rare but Serious (<3%)** | |
| | Anal mucositis[2] | | ***Anal mucositis[2] (Gr 2)*** |
| | Constipation | | ***Constipation (Gr 3)*** |
| Diarrhea | | | ***Diarrhea (Gr 3)*** |
| | | Gastrointestinal fistula[3] | |
| | | Gastrointestinal perforation[4] | ***Gastrointestinal perforation[4] (Gr 4)*** |
| Mucositis oral[2] | | | ***Mucositis oral[2] (Gr 3)*** |
| Nausea | | | ***Nausea (Gr 3)*** |
| | Rectal mucositis[2] | | ***Rectal mucositis[2] (Gr 2)*** |
| | Small intestinal mucositis[2] | | ***Small intestinal mucositis[2] (Gr 2)*** |
| | Vomiting | | ***Vomiting (Gr 3)*** |
| GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS | | | |
| | Chills | | ***Chills (Gr 2)*** |
| | Edema face | | ***Edema face (Gr 2)*** |
| | Edema limbs | | ***Edema limbs (Gr 3)*** |
| Fatigue | | | ***Fatigue (Gr 3)*** |
| | Fever | | ***Fever (Gr 2)*** |
| | Flu like symptoms | | ***Flu like symptoms (Gr 2)*** |
| | Non-cardiac chest pain | | ***Non-cardiac chest pain (Gr 2)*** |
| | Pain | | |
| IMMUNE SYSTEM DISORDERS | | | |
| | Allergic reaction[5] | | ***Allergic reaction[5] (Gr 2)*** |
| INFECTIONS AND INFESTATIONS[6] | | | |
| | Infection[7] | | ***Infection[7] (Gr 3)*** |
| INJURY, POISONING AND PROCEDURAL COMPLICATIONS | | | |
| | Wound dehiscence[8] | | ***Wound dehiscence[8] (Gr 2)*** |
| INVESTIGATIONS | | | |
| | Alanine aminotransferase increased | | ***Alanine aminotransferase increased (Gr 3)*** |
| | Alkaline phosphatase increased | | ***Alkaline phosphatase increased (Gr 3)*** |
| | Aspartate aminotransferase increased | | ***Aspartate aminotransferase increased (Gr 3)*** |
| Cholesterol high[9] | | | ***Cholesterol high[9] (Gr 4)*** |
| | Creatinine increased | | ***Creatinine increased (Gr 3)*** |
| | Fibrinogen decreased | | ***Fibrinogen decreased (Gr 2)*** |
| | GGT increased | | ***GGT increased (Gr 2)*** |
| | Lymphocyte count decreased | | ***Lymphocyte count decreased (Gr 4)*** |
| | Neutrophil count decreased | | ***Neutrophil count decreased (Gr 4)*** |
| Platelet count decreased[10] | | | ***Platelet count decreased[10] (Gr 4)*** |
| | Weight loss | | ***Weight loss (Gr 3)*** |
| | White blood cell decreased | | ***White blood cell decreased (Gr 4)*** |
| METABOLISM AND NUTRITION DISORDERS | | | |

| Adverse Events with Possible Relationship to Temsirolimus (CCI-779) (CTCAE 5.0 Term) [n= 1927] | | | Specific Protocol Exceptions to Expedited Reporting (SPEER) |
|---|---|---|---|
| **Likely (>20%)** | **Less Likely (<=20%)** | **Rare but Serious (<3%)** | |
| | Acidosis | | ***Acidosis (Gr 2)*** |
| Anorexia | | | ***Anorexia (Gr 3)*** |
| | Glucose intolerance[11] | | ***Glucose intolerance[11] (Gr 2)*** |
| | Hyperglycemia[11] | | ***Hyperglycemia[11] (Gr 3)*** |
| | Hyperlipidemia[9] | | ***Hyperlipidemia[9] (Gr 4)*** |
| | Hypertriglyceridemia[9] | | ***Hypertriglyceridemia[9] (Gr 4)*** |
| | Hypocalcemia | | ***Hypocalcemia (Gr 3)*** |
| | Hypokalemia | | ***Hypokalemia (Gr 4)*** |
| | Hypophosphatemia | | ***Hypophosphatemia (Gr 4)*** |
| MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS | | | |
| | Arthralgia | | ***Arthralgia (Gr 2)*** |
| | Back pain | | ***Back pain (Gr 2)*** |
| | Myalgia | | ***Myalgia (Gr 2)*** |
| NERVOUS SYSTEM DISORDERS | | | |
| | Depressed level of consciousness | | ***Depressed level of consciousness (Gr 2)*** |
| | Dysgeusia | | ***Dysgeusia (Gr 2)*** |
| | Headache | | ***Headache (Gr 3)*** |
| | | Intracranial hemorrhage | |
| PSYCHIATRIC DISORDERS | | | |
| | Depression | | ***Depression (Gr 2)*** |
| | Insomnia | | ***Insomnia (Gr 2)*** |
| | Libido decreased | | ***Libido decreased (Gr 2)*** |
| RENAL AND URINARY DISORDERS | | | |
| | | Acute kidney injury[12] | |
| | | Nephrotic syndrome | |
| | | Proteinuria | |
| REPRODUCTIVE SYSTEM AND BREAST DISORDERS | | | |
| | Erectile dysfunction | | ***Erectile dysfunction (Gr 2)*** |
| RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS | | | |
| | Cough | | ***Cough (Gr 3)*** |
| | Dyspnea | | ***Dyspnea (Gr 3)*** |
| | Epistaxis | | ***Epistaxis (Gr 2)*** |
| | Laryngeal mucositis[2] | | ***Laryngeal mucositis[2] (Gr 2)*** |
| | Pharyngeal mucositis[2] | | ***Pharyngeal mucositis[2] (Gr 2)*** |
| | Pleural effusion | | ***Pleural effusion (Gr 3)*** |
| | Pneumonitis[13] | | ***Pneumonitis[13] (Gr 3)*** |
| | Sinus disorder | | ***Sinus disorder (Gr 2)*** |
| | Tracheal mucositis[2] | | ***Tracheal mucositis[2] (Gr 2)*** |
| SKIN AND SUBCUTANEOUS TISSUE DISORDERS | | | |
| | Dry skin | | ***Dry skin (Gr 2)*** |
| | Nail changes[14] | | ***Nail changes[14] (Gr 1)*** |
| | Pruritus | | ***Pruritus (Gr 2)*** |
| | Rash acneiform | | ***Rash acneiform Gr 2)*** |

| Adverse Events with Possible Relationship to Temsirolimus (CCI-779) (CTCAE 5.0 Term) [n= 1927] | | | Specific Protocol Exceptions to Expedited Reporting (SPEER) |
|---|---|---|---|
| **Likely (>20%)** | **Less Likely (<=20%)** | **Rare but Serious (<3%)** | |
| Rash maculo-papular | | | ***Rash maculo-papular (Gr 3)*** |
| | Urticaria | | ***Urticaria (Gr 2)*** |
| VASCULAR DISORDERS | | | |
| | Hypertension | | ***Hypertension (Gr 3)*** |
| | Hypotension | | ***Hypotension (Gr 3)*** |
| | | Thromboembolic event | ***Thromboembolic event (Gr 4)*** |

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Mucositis/stomatitis: Gingivitis, mucositis/stomatitis, ulcers in mouth and throat, pharyngitis, and dysphagia have been reported in subjects receiving temsirolimus.

[3]Gastrointestinal fistula includes Anal fistula, Colonic fistula, Duodenal fistula, Esophageal fistula, Enterovesical fistula, Gastric fistula, Gastrointestinal fistula, Ileal fistula, Jejunal fistula, Oral cavity fistula, Pancreatic fistula, Rectal fistula, and Salivary gland fistula under the GASTROINTESTINAL DISORDERS SOC.

[4]Gastrointestinal perforation includes Colonic perforation, Duodenal perforation, Esophageal perforation, Gastric perforation, Ileal perforation, Jejunal perforation, Rectal perforation, and Small intestinal perforation under the GASTROINTESTINAL DISORDERS SOC. GI perforation (including fatal outcome) has been observed in subjects who received temsirolimus.

[5]Hypersensitivity /infusion reactions (including some life threatening and rare fatal reactions), including and not limited to flushing, chest pain, dyspnea, hypotension, apnea, loss of consciousness, hypersensitivity, and anaphylaxis, have been associated with the administration of temsirolimus. These reactions can occur very early in the first infusion but may also occur with subsequent infusions. Patients should be monitored early during infusion and appropriate supportive care should be available. Temsirolimus infusion should be interrupted in all patients with severe infusion reactions and appropriate medical care administered. A risk-benefit assessment should be done prior to the continuation of temsirolimus therapy in patients with severe life-threatening reactions.

[6]Infections: Bacterial and viral infections including opportunistic infections have been reported in subjects. Infections may originate in a variety of organ systems/body regions and may be associated with normal or grade 3-4 neutropenia. Bacterial and viral infections have included cellulitis, herpes zoster, herpes simplex, bronchitis, abscess, pharyngitis, urinary tract infection (including dysuria hematuria, cystitis, and urinary frequency), rhinitis folliculitis, pneumonia, and upper respiratory tract infection.

[7]Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

[8]Wound Dehiscence: The use of temsirolimus has been associated with abnormal wound healing. Therefore, caution should be exercised with the use of temsirolimus in the perisurgical period.

[9]Cholesterol High: The use of temsirolimus in subjects has been associated with increases in serum levels of triglycerides and cholesterol. This may require initiation of or increase in the dose of lipid-lowering agents.

[10]Thrombocytopenia and Neutropenia: Grades 3 and 4 thrombocytopenia and/or neutropenia have been observed at higher frequency in subjects with mantle cell lymphoma (MCL).

[11]Hyperglycemia/Glucose Intolerance: The use of temsirolimus in subjects was associated with increases in serum glucose level. This may result in the need for an increase in the dose of, or initiation of, insulin and/or oral hypoglycemic agent therapy.

[12]Acute Kidney Injury: Renal failure (including fatal outcome) has been observed in subjects receiving temsirolimus for advanced RCC and/or with pre-existing renal insufficiency.

[13]Interstitial Lung Disease: There have been cases of nonspecific interstitial pneumonitis, including rare fatal reports. Some subjects were asymptomatic with pneumonitis detected on computed tomography scan or chest radiograph. Others presented with symptoms such as dyspnea, cough, and fever. Some subjects required discontinuation of temsirolimus or treatment with corticosteroids and/or antibiotics, while some subjects continued treatment without additional intervention.

[14]Nail Changes includes Nail discoloration, Nail loss, and Nail ridging under the SKIN AND SUBCUTANEOUS TISSUE DISORDERS SOC.

[15]Gastrointestinal hemorrhage includes Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage, Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper gastrointestinal hemorrhage under the GASTROINTESTINAL DISORDERS SOC.

**Adverse events reported on temsirolimus (CCI-779) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that temsirolimus (CCI-779) caused the adverse event:**

**BLOOD AND LYMPHATIC SYSTEM DISORDERS** - Blood and lymphatic system disorders - Other (coagulopathy); Hemolysis; Leukocytosis
**CARDIAC DISORDERS** - Atrial fibrillation; Atrial flutter; Cardiac arrest; Chest pain - cardiac; Heart failure; Left ventricular systolic dysfunction; Myocardial infarction; Pericardial effusion; Right ventricular dysfunction; Sinus tachycardia; Supraventricular tachycardia; Ventricular fibrillation; Ventricular tachycardia
**EAR AND LABYRINTH DISORDERS** - Vertigo
**ENDOCRINE DISORDERS** - Endocrine disorders - Other (Cushing's syndrome); Endocrine disorders - Other (diabetes mellitus)
**EYE DISORDERS** - Blurred vision; Cataract; Dry eye; Eye disorders - Other (diplopia); Eye pain; Flashing lights; Photophobia; Retinopathy
**GASTROINTESTINAL DISORDERS** - Anal fissure; Anal pain; Anal ulcer; Ascites; Bloating; Colitis; Colonic obstruction; Colonic ulcer; Dry mouth; Duodenal ulcer; Dyspepsia; Dysphagia; Enterocolitis; Esophageal pain; Esophageal ulcer; Esophagitis; Flatulence; Gastritis; Gastrointestinal disorders - Other (gastroenteritis); Gastrointestinal hemorrhage[15]; Hemorrhoids; Ileus; Oral pain; Pancreatitis; Periodontal disease; Proctitis; Rectal pain; Small intestinal obstruction; Stomach pain; Typhlitis; Visceral arterial ischemia
**GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS** - Edema trunk; Facial pain; Gait disturbance; Injection site reaction; Localized edema; Malaise; Multi-organ failure; Sudden death NOS
**HEPATOBILIARY DISORDERS** - Hepatic failure
**IMMUNE SYSTEM DISORDERS** - Anaphylaxis
**INJURY, POISONING AND PROCEDURAL COMPLICATIONS** - Bruising; Fracture; Postoperative hemorrhage; Vascular access complication; Wound complication

**INVESTIGATIONS** - Activated partial thromboplastin time prolonged; Blood bilirubin increased; Blood lactate dehydrogenase increased; CD4 lymphocytes decreased; INR increased (potential interaction with Coumadin); Investigations - Other (BUN increased); Lipase increased; Lymphocyte count increased; Serum amylase increased; Weight gain
**METABOLISM AND NUTRITION DISORDERS** - Dehydration; Hypercalcemia; Hyperkalemia; Hypermagnesemia; Hypernatremia; Hyperuricemia; Hypoalbuminemia; Hypoglycemia; Hypomagnesemia; Hyponatremia; Metabolism and nutrition disorders - Other (albuminuria); Metabolism and nutrition disorders - Other (blood urea increased); Metabolism and nutrition disorders - Other (hypoproteinemia)
**MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS** - Arthritis; Avascular necrosis; Bone pain; Chest wall pain; Generalized muscle weakness; Joint effusion; Muscle cramp; Muscle weakness lower limb; Neck pain; Pain in extremity
**NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)** - Leukemia secondary to oncology chemotherapy; Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (carcinoma of the lung); Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (lymphoma); Treatment related secondary malignancy
**NERVOUS SYSTEM DISORDERS** - Ataxia; Cognitive disturbance; Dizziness; Dysesthesia; Hydrocephalus; Lethargy; Neuralgia; Paresthesia; Peripheral motor neuropathy; Peripheral sensory neuropathy; Reversible posterior leukoencephalopathy syndrome; Seizure; Somnolence; Spasticity; Stroke; Syncope
**PSYCHIATRIC DISORDERS -** Agitation; Anxiety; Confusion; Mania; Psychiatric disorders - Other (bipolar disorder); Psychosis
**RENAL AND URINARY DISORDERS** - Bladder spasm; Cystitis noninfective; Hematuria; Hemoglobinuria; Renal hemorrhage; Urinary frequency; Urinary retention; Urinary tract pain; Urinary urgency
**REPRODUCTIVE SYSTEM AND BREAST DISORDERS** - Hematosalpinx; Irregular menstruation; Menorrhagia; Ovarian hemorrhage; Prostatic hemorrhage; Reproductive system and breast disorders - Other (female genital tract fistula); Spermatic cord hemorrhage; Testicular disorder; Testicular hemorrhage; Testicular pain; Uterine hemorrhage; Vaginal discharge; Vaginal dryness; Vaginal fistula; Vaginal hemorrhage; Vaginal inflammation
**RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS** - Adult respiratory distress syndrome; Allergic rhinitis; Bronchopulmonary hemorrhage; Bronchospasm; Hiccups; Hypoxia; Nasal congestion; Pharyngolaryngeal pain; Pleuritic pain; Productive cough; Pulmonary edema; Pulmonary fibrosis; Pulmonary hypertension; Respiratory failure; Voice alteration
**SKIN AND SUBCUTANEOUS TISSUE DISORDERS** - Alopecia; Erythema multiforme; Hyperhidrosis; Pain of skin; Palmar-plantar erythrodysesthesia syndrome; Photosensitivity; Skin and subcutaneous tissue disorders - Other (angioneurotic edema); Skin ulceration; Stevens-Johnson syndrome
**VASCULAR DISORDERS** - Flushing; Phlebitis; Superficial thrombophlebitis

**Note:** Intracerebral Bleeding: Subjects with central nervous system (CNS) tumors (primary CNS tumors or metastases) and/or receiving anticoagulation therapy may be at an increased risk of intracerebral bleeding (including fatal outcomes) while receiving therapy with temsirolimus (CCI-779).

**Note**: Temsirolimus (CCI-779) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

**Effect in pregnancy:**
**Temsirolimus is Pregnancy Category D.** It can cause fetal harm. Female of childbearing potential should be advised to avoid becoming pregnant throughout treatment and for three months after temsirolimus therapy has stopped. Male with partners of childbearing potential should use reliable contraception throughout treatment and are recommended to continue this for three months after the last dose of temsirolimus.

**Formulation and Stability:**
Temsirolimus (Torisel®) is supplied as the commercially labeled kit consisting of a concentration solution and a diluent. The kit components are:

- Temsirolimus injection (25 mg/mL), 1.2 mL
- DILUENT vial that includes a deliverable volume of 1.8 mL.

Temsirolimus injection 25 mg/mL is a clear, colorless to light yellow, non-aqueous, ethanolic, sterile solution. The inactive ingredients include dehydrated alcohol (39.5% w/v), *dl*-alpha-tocopherol, propylene glycol, and anhydrous citric acid. The diluent is a sterile, non-aqueous solution that includes polysorbate 80 (40.0% w/v), polyethylene glycol 400 (42.8% w/v) and dehydrated alcohol (19.9% w/v). After the temsirolimus injection vial has been diluted with the provided diluent, the solution contains 35.2% alcohol. The two-vial kit must be stored at 2°-8°C (36°-46°F) protected from light.

During handling and preparation of admixtures, temsirolimus should be protected from excessive room light and sunlight. In order to minimize the patient exposure to the plasticizer di-2-ethylhexyl phthalate (DEHP) which may be leached from polyvinyl chloride (PVC) infusion bags, the final temsirolimus dilution for infusion should be prepared in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin). The preparation of the solution for administration requires two-step dilution process in an aseptic manner. These mixing instructions apply to the commercial Torisel kit that is provided for this study.

**Step 1:**

- The temsirolimus injection vial contains 30 mg temsirolimus in 1.2 mL (25 mg/mL).
- Inject 1.8 mL of the provided diluent into the vial of temsirolimus injection (25 mg/mL). The resulting drug concentration is 10 mg/mL and the total volume is 3 mL.
- Mix well by inversion of the vial. DO NOT SHAKE. Allow sufficient time for air bubbles to subside. The solution is clear to slightly turbid, colorless to yellow, and free from visual particulates.
- The 10 mg/mL drug solution/diluent mixture is stable for up to 24 hours at controlled room temperature. This 10 mg/mL drug solution/diluent mixture must be further diluted as described in Step 2 below.

**Step 2:**

- Withdraw the amount of temsirolimus required for the dose from the 10 mg/mL drug solution/diluent mixture prepared in Step 1.
- For doses less than 10 mg, filter the concentrate/diluents mixture using a syringe filter unit before measuring required volume.
- Further dilute with 0.9% sodium chloride injection immediately in non-DEHP container (see above) to a final concentration between 0.04 mg/mL and 1 mg/mL.
- Mix by inversion of the bag or bottle. Avoid excessive shaking as this may cause foaming.
- The diluted solution for administration is stable at controlled room temperature for up to six hour from the time of the final dilution. Protect the bag/bottle from light.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

**Route of administration:** Intravenous with an appropriate in-line filter (i.e. 0.2 to 5 micron) for all temsirolimus doses equal to or greater than 10 mg. To avoid drug loss, prepare doses less than 10 mg by filtering the concentrate/diluent mixture as noted above in step 2 using a syringe filter unit.

**Guidelines for Administration:** See Treatment and Dose Modification sections of the protocol.

To prevent hypersensitivity reaction, an $H_1$ antihistamine (eg, diphenhydramine) should be administered before the start of the temsirolimus infusion.

For doses less than 10 mg, filter the concentrate/diluents mixture using a syringe filter unit before measuring required volume as noted above in step 2.

Avoid contact of the diluted product with polyvinyl chloride (PVC) equipment or devices that are plasticized with di- (2-ethylhexyl)pthalate (DEHP) to prevent DEHP leaching. Store diluted temsirolimus solutions in bottles (glass) or plastic bags (polyolefin or polypropylene). Infusion sets containing polyvinyl chloride should not be used to administer temsirolimus to avoid leaching of plasticizer.

The following are examples of in-line filters that are compatible with temsirolimus:

- IV 6200 Disposable I.V. Filter 0.2 micron by EPS®, Inc
- IV 6120 Disposable I.V. Filter 1.2 micron by EPS®, Inc
- LV 5000 Large Volume 5 micron Conical Filter by B. Braun
- Baxter Paclitaxel Set with 0.22 micron filter
- Codan 5 micron monofilter

Other polyethersulfone filters may be used.

**Supplier:** Supplied by Pfizer and distributed by the NCI DTCD. Do not use commercially available drug.

**Agent Ordering**

NCI supplied agent may be requested by the Principal Investigator (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained). The CTEP assigned protocol number must be used for ordering all CTEP supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA form 1572 (Statement of Investigator), Curriculum Vitae, Supplemental Investigator Data Form (IDF), and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees must submit agent requests through the PMB Online Agent Order Processing (OAOP) application < https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx >. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account < https://eapps-ctep.nci.nih.gov/iam/ > and the maintenance of an "active" account status and a "current" password. For questions about drug orders, transfers, returns, or accountability, call (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET) or email PMBAfterHours@mail.nih.gov anytime.

**Agent Accountability**

Agent Inventory Records – The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all agents received from DCTD using the NCI Drug Accountability Record Form (DARF). (See the CTEP home page at http://ctep.cancer.gov/protocolDevelopment/default.htm#agents_drugs for the Procedures for Drug

Accountability and Storage and http://ctep.cancer.gov/forms/default.htm to obtain a copy of the DARF and Clinical Drug Request form.)

**Agent Returns**
Investigators/Designees must return unused DCTD supplied investigational agent to the NCI clinical repository as soon as possible when: the agent is no longer required because the study is completed or discontinued and the agent cannot be transferred to another DCTD sponsored protocol; the agent is outdated or the agent is damaged or unfit for use. Regulations require that all agents received from the DCTD, NCI be returned to the DCTD, NCI for accountability and disposition. Return only unused vials/bottles. Do NOT return opened or partially used vials/bottles unless specifically requested otherwise in the protocol. See the CTEP web site for Policy and Guidelines for Investigational agent Returns at: http://ctep.cancer.gov/protocolDevelopment/default.htm#agents_drugs. The appropriate forms may be obtained at: http://ctep.cancer.gov/forms/docs/return_form.pdf.

## 6.2 Cisplatin

(Cis-diamminedichloroplatinum II, CDDP, cis-DDP, Platinol-AQ) NSC #119875 (05/06/11)

**Source and Pharmacology:** Cisplatin is an inorganic, water-soluble complex containing a central platinum atom, 2 chlorine atoms, and 2 ammonia molecules. In aqueous solution, the chloride ions are slowly displaced by water generating a positively charged aquated complex. This activated complex is then available to react with nucleophilic sites on DNA, RNA, or protein resulting in the formation of bi-functional covalent links, very similar to alkylating reactions. The intra-strand cross-links, in particular with guanine and cytosine, change DNA conformation and inhibit DNA synthesis leading to the cytotoxic and anti-tumor effects of cisplatin. Cisplatin has synergistic cytotoxicity with radiation and other chemotherapeutic agents. Cisplatin has a rapid distribution phase of 25-80 minutes with a slower secondary elimination half-life of 60-70 hours. The platinum from cisplatin, but not cisplatin itself, becomes bound to several plasma proteins including albumin, transferrin, and gamma globulin. Three hours after a bolus injection and two hours after the end of a three hour infusion, 90% of the plasma platinum is protein bound. The complexes between albumin and the platinum from cisplatin do not dissociate to a significant extent and are slowly eliminated with a minimum half-life of five days or more. Platinum is present in tissues for as long as 180 days after the last administration. Both cisplatin and platinum are excreted through the kidneys ranging from 10-50%. Fecal elimination is minimal. Cisplatin's penetration into the CNS is poor.

**Toxicity:**

| | **Common** Happens to 21-100 children out of every 100 | **Occasional** Happens to 5-20 children out of every 100 | **Rare** Happens to < 5 children out of every 100 |
|---|---|---|---|
| **Immediate:** Within 1-2 days of receiving drug | Nausea (L), vomiting (L) | Metallic taste (L) | Anaphylactic reaction (facial edema, wheezing, tachycardia, and hypotension), phlebitis, extravasation (rare) but if occurs = local ulceration (only in concentration > 0.5mg/mL) |
| **Prompt:** Within 2-3 weeks, prior to the next course | Anorexia (L), myelosuppression, hypomagnesemia (L), high frequency hearing loss (L), nephrotoxicity (↑ Cr, BUN, Uric Acid) (L) | Electrolyte disturbances (L) (hypocalcemia, natremia, kalemia, & phosphatemia) peripheral neuropathy, (paresthesias in a stocking-glove distribution) (L) | Vestibular dysfunction, tinnitus (L), rash, seizure (L), elevated liver function tests (L) |
| **Delayed:** Any time later during therapy | | Hearing loss in the normal hearing range | Areflexia, loss of proprioception and vibratory sensation, (very rarely loss of motor function) (L), optic neuritis, papilledema, cerebral blindness, blurred vision and altered color perception (improvement or total recovery usually occurs after discontinuing), chronic renal failure, deafness |
| **Late:** Any time after completion of treatment | | | Secondary malignancy |
| **Unknown Frequency and Timing**: | Fetal toxicities and teratogenic effects of cisplatin have been noted in animals and cisplatin can cause fetal harm in humans. Cisplatin is excreted into breast milk. | | |

*(L) Toxicity may also occur later.*

**Formulation and Stability:**
Available as an aqueous solution containing 1 mg/mL of cisplatin and 9 mg (1.54 mEq)/mL of sodium chloride in 50 mL, 100 mL, and 200 mL multi-dose non-preserved vials. Store at 15°-25°C (68º-77ºF). **Do not refrigerate**. Protect unopened container from light. The cisplatin remaining in the amber vial following initial entry is stable for 28 days protected from light or for 7 days under fluorescent room light. Cisplatin removed from its amber container should be protected from light if not used within 6 hours.

**Guidelines for Administration:** See the Treatment and Dose Modifications sections of this protocol.

Cisplatin may be further diluted in dextrose and saline solutions provided the solution contains >0.3% sodium chloride. The final infusion solution should contain ≥ 0.2% sodium chloride. Dextrose/saline/mannitol containing solutions, protected from light, are stable refrigerated or at room temperature for 24 to 72 hours, however, cisplatin solutions should not be stored in the refrigerator to avoid precipitation. Cisplatin is incompatible with sodium bicarbonate and alkaline solutions.

Needles or intravenous sets containing aluminum parts that may come in contact with cisplatin should not be used for preparation or administration. Aluminum reacts with cisplatin causing precipitate formation and a loss of potency.

Accidental extravasation with solutions that are > 0.5 mg/mL may result in significant tissue toxicity.

**Supplier:** Commercially available from various manufacturers. See package insert for more detailed information.

6.3 **Dexrazoxane** (ICRF-187, ADR-529, ZINECARD®, Totect®) NSC #169780 (10/28/11)

**Source and Pharmacology:**

Dexrazoxane is a synthetic chemical, a cyclic derivative of EDTA that readily penetrates cell membranes. Results of laboratory studies suggest that dexrazoxane is converted intracellularly to a ring opened chelating agent that interferes with iron mediated free radical generation thought to be responsible, in part, for anthracycline-induced cardiomyopathy. The disposition kinetics of dexrazoxane are dose-dependent with administered doses from 60 to 900 mg/m$^2$. The plasma half-life is 2 to 2.5 hours. Qualitative metabolism studies have confirmed the presence of unchanged drug, a diacid-diamide cleavage product, and two monoacid-monoamide ring products in the urine of animals and man. Metabolite levels were not measured in the pharmacokinetics studies. Urinary excretion plays an important role in the elimination of dexrazoxane: 42% of the drug (500 mg/m$^2$) was excreted in the urine. *In vitro* studies have shown that dexrazoxane is not bound to plasma proteins. The pharmacokinetics of dexrazoxane have not been evaluated in patients with hepatic or renal insufficiency. There was no significant effect of dexrazoxane on the pharmacokinetics of doxorubicin (50 mg/m$^2$) or its predominant metabolite, doxorubicinol, in a crossover study in cancer patients.

**Toxicity:**

| | **Common** Happens to 21-100 children out of every 100 | **Occasional** Happens to 5-20 children out of every 100 | **Rare** Happens to < 5 children out of every 100 |
|---|---|---|---|
| **Immediate:** Within 1-2 days of receiving drug | | Pain on injection, phlebitis, transient increases in triglycerides and amylase, increase in SGPT (ALT)/ SGOT (AST) and bilirubin, mild nausea, vomiting, diarrhea, increase in serum iron, decrease in serum zinc and calcium | Anorexia, malaise, extravasation (rare) but if occurs may = ulceration |
| **Prompt:** Within 2-3 weeks, prior to the next course | Myelosuppression | | Prolongation of PT/PTT |
| **Late:** Any time after completion of treatment | | | Secondary malignancies (have been reported with oral razoxane; the racemic mixture, of which dexrazoxane is the S(+)-enantiomer) |
| **Unknown Frequency and Timing**: | Fetal toxicities and teratogenic effects have been noted in animals. Dexrazoxane was maternotoxic, embryotoxic, and teratogenic when given to pregnant rats and rabbits during the period of organogenesis. It is not known whether dexrazoxane is excreted in human milk. | | |

**Formulation and Stability:**

Three products are available:

1. **Dexrazoxane for Injection (generic)**

a. Available as a sterile, pyrogen-free lyophilized powder in the following strengths: 250 mg single dose vial packaged with a 25 mL vial of 0.167 Molar (M/6) Sodium Lactate Injection, *USP,* and 500 mg single dose vial packaged with a 50 mL vial of 0.167 Molar (M/6) Sodium Lactate Injection, *USP*.
b. Store protected from light at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F).

2. **Dexrazoxane (Zinecard®, Pfizer brand)**
   a. Available in as a sterile, pyrogen-free lyophilized powder in 250 mg and 500 mg single use vials. Hydrochloric Acid, NF is added to the vials for pH adjustment.
   b. Intact vials should be stored at 25°C (77°F); excursions are permitted to 15° to 30°C (59° to 86°F).
3. **Totect® (dexrazoxane for anthracycline extravasation only)**
   a. Totect is packaged as an emergency treatment carton for single patient use. Each carton contains 10 vials of Totect (dexrazoxane for injection) 500 mg and 10 vials of 50 mL diluent, which provides a complete three day treatment.

**Reconstitution and dilution requirements and expiration dating vary based on the product used.** Refer to package insert for additional details.

1. **Dexrazoxane (generic)**
   a. Dexrazoxane (250 mg or 500 mg vials) must be reconstituted with a sufficient quantity of 0.167 Molar (M/6) Sodium Lactate Injection, *USP*, to a concentration of 10 mg dexrazoxane for each mL of sodium lactate.
   b. Further dilute solution in either $D_5W$ or NS to a final concentration of 1.3 to 5 mg/mL.
   c. The final solution is stable for up to 6 hours at room temperature, 15°C to 30°C (59°F to 86°F), or under refrigeration, 2°C to 8°C (36°F to 46°F).

2. **Dexrazoxane (Zinecard®, Pfizer brand)**
   a. Reconstitute with Sterile Water for Injection, USP as follows:
      - For 250 mg vials, reconstitute with 25 mL.
      - For 500 mg vials, reconstitute with 50 mL.
      - The resultant reconstituted solutions will have a concentration of 10 mg/mL.
   b. Following initial reconstitution, ZINECARD is stable for 30 minutes at room temperature or up to 3 hours when stored under refrigeration, 2° to 8°C (36° to 46°F).
   c. The pH of the resultant solution is 1.0 to 3.0. Further dilution with Lactated Ringer's Injection, USP is required to achieve a final concentration range of 1.3 to 3 mg/mL in intravenous infusion bags. The infusion solution has a pH of 3.5 to 5.5.
   d. The infusion solution is stable for one (1) hour at room temperature or if storage is necessary, up to 4 hours when stored under refrigeration, 2° to 8°C (36° to 46°F).

**Supplier:** Commercially available. See package insert for further information.

6.4 **Doxorubicin** (Adriamycin®) NSC #123127 (05/09/11)

**Source and Pharmacology**:
An anthracycline antibiotic isolated from cultures of *Streptomyces peucetius*. The cytotoxic effect of doxorubicin on malignant cells and its toxic effects on various organs are thought to be related to nucleotide base intercalation and cell membrane lipid binding activities of doxorubicin. Intercalation inhibits nucleotide replication and action of DNA and RNA polymerases. The interaction of doxorubicin with topoisomerase II to form DNA-cleavable complexes appears to be an important mechanism of doxorubicin

cytocidal activity. Doxorubicin cellular membrane binding may affect a variety of cellular functions. Enzymatic electron reduction of doxorubicin by a variety of oxidases, reductases, and dehydrogenases generate highly reactive species including the hydroxyl free radical (OH•). Free radical formation has been implicated in doxorubicin cardiotoxicity by means of Cu (II) and Fe (III) reduction at the cellular level. Cells treated with doxorubicin have been shown to manifest the characteristic morphologic changes associated with apoptosis or programmed cell death. Doxorubicin-induced apoptosis may be an integral component of the cellular mechanism of action relating to therapeutic effects, toxicities, or both.

Doxorubicin serum decay pattern is multiphasic. The initial distributive $t_{½}$ is approximately 5 minutes suggesting rapid tissue uptake of doxorubicin. The terminal $t_{½}$ of 20 to 48 hours reflects a slow elimination from tissues. Steady-state distribution volumes exceed 20 to 30 L/kg and are indicative of extensive drug uptake into tissues. Plasma clearance is in the range of 8 to 20 mL/min/kg and is predominately by metabolism and biliary excretion. The P450 cytochromes which appear to be involved with doxorubicin metabolism are CYP2D6 and CYP3A4. Approximately 40% of the dose appears in the bile in 5 days, while only 5 to 12% of the drug and its metabolites appear in the urine during the same time period. Binding of doxorubicin and its major metabolite, doxorubicinol, to plasma proteins is about 74 to 76% and is independent of plasma concentration of doxorubicin.

**Toxicity:**

| | **Common**<br>Happens to 21-100 children out of every 100 | **Occasional**<br>Happens to 5-20 children out of every 100 | **Rare**<br>Happens to < 5 children out of every 100 |
|---|---|---|---|
| **Immediate:**<br>Within 1-2 days of receiving drug | Nausea, vomiting, pink or red color to urine, sweat, tears, and saliva | Hyperuricemia, facial flushing, sclerosis of the vein | Diarrhea, anorexia, erythematous streaking of the vein (flare reaction), extravasation (rare) but if occurs = local ulceration, anaphylaxis, fever, chills, urticaria, acute arrhythmias |
| **Prompt:**<br>Within 2-3 weeks, prior to the next course | Myelosuppression (leukopenia, thrombocytopenia, anemia), alopecia | Mucositis (stomatitis and esophagitis), hepatotoxicity | Radiation recall reactions, conjunctivitis and lacrimation |
| **Delayed:**<br>Any time later during therapy | | Cardiomyopathy[1] (CHF occurs in 5-20% at cumulative doses ≥ 450 mg/m²) (L) | Cardiomyopathy[1] (CHF occurs in < 5% at cumulative doses ≤ 400 mg/m²) (L), ulceration and necrosis of colon, hyper-pigmentation of nail bed and dermal crease, onycholysis |
| **Late:**<br>Any time after completion of treatment | Subclinical cardiac dysfunction | CHF (on long term follow up in pediatric patients) | Secondary malignancy (in combination regimens) |
| **Unknown Frequency and Timing:** | Fetal and teratogenic toxicities. Carcinogenic and mutagenic effects of doxorubicin have been noted in animal models. Doxorubicin is excreted into breast milk in humans | | |

[1] *Risk increases with cardiac irradiation, exposure at a young or advanced age.*
*(L) Toxicity may also occur later.*

**Formulation and Stability:**
Doxorubicin is available as red-orange lyophilized powder for injection in 10 mg[1], 20 mg[1], 50 mg[1]vials and a preservative-free 2 mg/mL solution in 10 mg[1], 20 mg[1], 50 mg[1], 200 mg[2] vials.

[1]: *Contains lactose monohydrate, 0.9 NS, HCl to adjust pH to 3. The Adriamycin RDF® (rapid dissolution formula) also contains methylparaben, 1 mg per each 10 mg of doxorubicin, to enhance dissolution.*

[2] *Multiple dose vial contains lactose, 0.9% NS, HCl to adjust pH to 3.*

Aqueous Solution: Store refrigerated 2°-8°C, (36°-46°F). Protect from light. Retain in carton until contents are used.

Powder for Injection: Store unreconstituted vial at room temperature, 15°-30°C (59°-86°F). Retain in carton until contents are used. Reconstitute with preservative-free NS to a final concentration of 2 mg/mL. After adding the diluent, the vial should be shaken and the contents allowed to dissolve. The reconstituted solution is stable for 7 days at room temperature and 15 days under refrigeration, 2°-8°C (36°-46°F) when protected from light. Doxorubicin further diluted in 50 – 1000 mL of NS or D5W is stable for up to 48 hours at room temperature (25°C) when protected from light.

**Guidelines for Administration:** See Treatment and Dose Modification sections of the protocol.
Administer IV through the tubing of rapidly infusing solution of $D_5W$ or 0.9% NaCl preferably into a large vein. Protect the diluted solution from sunlight. To avoid extravasation, the use of a central line is suggested.

**Supplier:** Commercially available from various manufacturers. See package insert for further information.

6.5 **Fluorouracil** (5-Fluoruracil, 5-FU, 5-fluoro-2, 4 (1H, 3H)-pyrimidinedione, Adrucil®, Fluoro-Uracil®) NSC# 19893 (05/06/11)

**Source and Pharmacology:**
Fluorouracil, an analogue of the pyrimidine uracil, is an antimetabolite antineoplastic that requires intracellular activation to exert its cytotoxic effects. 5-FU is converted to FUdR by thymidine phosphorylase. Subsequent phosphorylation of FUdR by thymidine kinase results in formation of the active metabolite 5-fluoro-2 ' -deoxyuridine monophosphate (FdUMP). In the presence of the reduced folate cofactor 5,10-methylenetetrahydrofolate, FdUMP forms a stable covalent complex with thymidylate synthetase (TS). TS catalyzes the sole intracellular de novo formation of thymidine-5 ' -monophosphate from dUMP. Inhibition of TS leads to depletion of deoxythymidine triphosphate (dTTP), thus interfering with DNA biosynthesis and repair. 5-FU is also metabolized to fluorouridine monophosphate and further to fluorouridine diphosphate and then to the triphosphate form (FUTP), which is subsequently incorporated into RNA, thereby also interfering with RNA synthesis. Since DNA and RNA are essential for cell division and growth, the effect of fluorouracil may be to create a thymine deficiency which provokes unbalanced growth and death of the cell. The effects of DNA and RNA deprivation are most marked on those cells which grow more rapidly and which take up fluorouracil at a more rapid rate. Following intravenous injection, fluorouracil distributes into tumors, intestinal mucosa, bone marrow, liver and other tissues throughout the body. Seven to twenty percent of the parent drug is excreted unchanged in the urine in 6 hours; of this over 90% is excreted in the first hour. The remaining percentage of the administered dose is metabolized, primarily in the liver. The catabolic metabolism of fluorouracil results in degradation products (e.g., $CO_2$, urea and α-fluoro- β-alanine) which are inactive. The inactive metabolites are excreted in the urine over the next 3 to 4 hours. Following intravenous administration of fluorouracil, the mean half-life of elimination from plasma is approximately 16 minutes, with a range of 8 to 20 minutes, and is dose dependent. No intact drug can be detected in the plasma 3 hours after an intravenous injection. In spite of its limited lipid solubility, fluorouracil diffuses readily across the blood-brain barrier and distributes into cerebrospinal fluid and brain tissue.

**Toxicity*:**

| | **Common** Happens to 21-100 children out of every 100 | **Occasional** Happens to 5-20 children out of every 100 | **Rare** Happens to < 5 children out of every 100 |
|---|---|---|---|
| **Immediate:** Within 1-2 days of receiving drug | Nausea, vomiting, metallic taste, anorexia | | Hypotension, angina, ECG changes (rare cases of sudden death reported), anaphylaxis |
| **Prompt:** Within 2-3 weeks, prior to next course | Myelosuppression, alopecia | Diarrhea, stomatitis, esophagopharyngitis, photosensitivity, palmar-plantar erythrodysesthesia syndrome | Tearing, conjunctivitis and blurred vision, rashes, GI ulceration and inflammation, hypo/hyper calcemia |
| **Delayed:** Any time later during therapy, excluding the above conditions | | Hyperpigmentation of the skin including the vein through which the drug is given, dry skin | Nail changes (including: diffuse blue superficial pigment, onycholysis, dystrophy, pain and thickening of the nail bed, transverse striations), headache, visual disturbances, cerebellar ataxia, leukoencephalopathy (symptoms of which may include: ataxia, speech disturbances, memory loss, confusion, aphasia, seizures, coma), proctitis, elevated transaminases, hepatic necrosis (1 patient), MI (2 patients), ascites (4 patients with cancers metastatic to the liver) |
| **Unknown Frequency and Timing:** | **Fetal and teratogenic toxicities**: Fetal toxicities and teratogenic effects of 5-FU have been noted in animals. Malformations included cleft palates, skeletal defects and deformed appendages, paws and tails. The dosages which were teratogenic in animals are 1 to 3 times the maximum recommended human therapeutic dose. It is unknown whether the drug is excreted in breast milk. | | |

**Rarely, unexpected, severe toxicity (e.g., stomatitis, diarrhea, neutropenia and neurotoxicity) associated with 5-fluorouracil has been attributed to deficiency of dipyrimidine dehydrogenase activity. A few patients have been rechallenged with 5-fluorouracil and despite 5-fluorouracil dose lowering, toxicity recurred and progressed with worse morbidity. Absence of this catabolic enzyme appears to result in prolonged clearance of 5-fluorouracil.*

**Formulation and Stability:**
Fluorouracil injection is a sterile, nonpyrogenic injectable solution for intravenous administration. Fluorouracil 50 mg/mL is available in 10 mL, 50 mL and 100 mL vials; pH is adjusted to approximately 9.2 with sodium hydroxide. Store at room temperature 15°-30°C (59°-86°F). Protect from light. Retain in carton until time of use.

Although the fluorouracil solution may discolor slightly during storage, the potency and safety are not adversely affected. If a precipitate occurs due to exposure to low temperatures, resolubilize by gently heating to 60°C and shaking vigorously; allow to cool to body temperature before using.

**Guidelines for Administration:** See Treatment and Dose Modification sections of the protocol.

IV: For administration by IV push or by short infusion, no further dilution is required.

IV Continuous Infusion: For administration by continuous infusion, fluorouracil can be diluted in 50 – 1000 mL D5W or NS.

**Supplier:**
Commercially available from various manufacturers. See package insert for further information.

6.6 **Irinotecan** [CPT-11,Camptothecin-11,7-ethyl-10-(4-[1-piperidino]-1-piperidino)-carbonyloxy-camptothecin), Camptosar®], NSC #616348 (05/09/11)

**Source and Pharmacology:**
Irinotecan is a semisynthetic water-soluble analog of camptothecin (a plant alkaloid isolated from *Camptotheca acuminata)*. Irinotecan is a prodrug that requires conversion, by the carboxylesterase enzyme to the topoisomerase-I inhibitor, SN-38 in order to exert anti-tumor activity. SN-38 is approximately 1000 times more potent than irinotecan. Camptothecins interact specifically with the enzyme topoisomerase I which relieves torsional strain in DNA by inducing reversible single-strand breaks. Irinotecan and its active metabolite SN-38 bind to the topoisomerase I-DNA complex and prevent religation of these single-strand breaks. Current research suggests that the cytotoxicity of irinotecan is due to double-strand DNA damage produced during DNA synthesis when replication enzymes interact with the ternary complex formed by topoisomerase I, DNA, and either irinotecan or SN-38. Renal excretion is a minor route of elimination of irinotecan. The majority of the drug is metabolized in the liver. SN-38 is conjugated to glucuronic acid and this metabolite has no anti-tumor activity. The extent of conversion of SN-38 to its glucuronide has been inversely correlated with the risk of severe diarrhea, because the other major route of SN-38 excretion is biliary excretion by canalicular multispecific organic anion transporter (cMOAT) which presumably leads to mucosal injury. In addition, APC and NPC are oxidative metabolites of irinotecan dependent on the CYP3A4 isoenzyme. After intravenous infusion of irinotecan in humans, irinotecan plasma concentrations decline in a multiexponential manner, with a mean terminal elimination half-life of about 6 to 12 hours. The mean terminal elimination half-life of the active metabolite SN-38 is about 10 to 20 hours. Irinotecan is 30% to 68% bound to albumin and SN-38 is approximately 95% bound to albumin.

**Toxicity:**

| | **Common**<br>Happens to 21-100 children out of every 100 | **Occasional**<br>Happens to 5-20 children out of every 100 | **Rare**<br>Happens to < 5 children out of every 100 |
|---|---|---|---|
| **Immediate:**<br>Within 1-2 days of receiving drug | Nausea, vomiting, anorexia, fever, asthenia, cholinergic symptoms: (rhinitis, increased salivation, miosis, lacrimation, diaphoresis, flushing, and intestinal hyperperistalsis that can cause abdominal cramping and early diarrhea) | Constipation, headache, diarrhea (L) | Anaphylaxis, dehydration with dizziness & hypotension, bradycardia, dyspnea and cough, disorientation/confusion, somnolence, pain at infusion site |
| **Prompt:**<br>Within 2-3 weeks, prior to the next course | Neutropenia, alopecia, eosinophilia, elevations in transaminases, alkaline phosphatase, bilirubin, mucositis, infection | Anemia, rash, dyspepsia, thrombocytopenia | Colitis, renal failure (secondary to severe dehydration), thromboembolic events, ileus |
| **Delayed:**<br>Any time later during therapy | | | Pneumonitis |
| **Late:**<br>Any time after completion of treatment | | | |
| **Unknown Frequency and Timing**: | Fetal toxicities and teratogenic effects of irinotecan have been noted in animals at doses similar or less than those used in humans. Toxicities include: decreased skeletal ossification, multiple anomalies, low birth weight and increased fetal mortality. It is not known if irinotecan is excreted into breast milk but it is excreted into rat milk. | | |

*(L) Toxicity may also occur later.*

**Formulation & Stability:**
Each mL of irinotecan injection contains 20 mg irinotecan (on the basis of the trihydrate salt), 45 mg sorbitol, and 0.9 mg lactic acid. When necessary, pH has been adjusted to 3.5 (range, 3.0 to 3.8) with sodium hydroxide or hydrochloric acid. Irinotecan is available in single-dose amber glass vials in 40 mg (2 mL),100 mg (5 mL), 300 mg (15 mL), and 500 mg (25 mL). Store at controlled room temperature 15°-30°C (59°-86°F). Protect from light. It is recommended that the vial (and backing/plastic blister) should remain in the carton until the time of use.

**Guidelines for Administration:** See Treatment and Dose Modifications sections of the protocol.
Irinotecan must be diluted prior to infusion. Irinotecan should be diluted in D5W, (preferred) or NS to a final concentration range of 0.12-2.8 mg/mL. The solution is physically and chemically stable for up to 24 hours at room temperature (approximately 25°C) and in ambient fluorescent lighting. Solutions diluted in D5W and stored at refrigerated temperatures (approximately 2°-8°C), and protected from light are physically and chemically stable for 48 hours. Refrigeration of admixtures using NS is not recommended due to a low and sporadic incidence of visible particulates. Care should be taken to avoid extravasation; the use of a central line is suggested.

**Supplier:**
Commercially available from various manufacturers. See package insert for more detailed information.

6.7 **Vincristine Sulfate** (Oncovin®, VCR, LCR) NSC #67574 (08/16/12)

**Source and Pharmacology:**
Vincristine is an alkaloid isolated from Vinca rosea Linn (periwinkle). It binds to tubulin, disrupting microtubules and inducing metaphase arrest. Its serum decay pattern is triphasic. The initial, middle, and terminal half-lives are 5 minutes, 2.3 hours, and 85 hours respectively; however, the range of the terminal half-life in humans is from 19 to 155 hours. The liver is the major excretory organ in humans and animals; about 80% of an injected dose of vincristine sulfate appears in the feces and 10% to 20% can be found in the urine. The p450 cytochrome involved with vincristine metabolism is CYP3A4. Within 15 to 30 minutes after injection, over 90% of the drug is distributed from the blood into tissue, where it remains tightly, but not irreversibly bound. It is excreted in the bile and feces. There is poor CSF penetration.

**Toxicity:**

| | **Common**<br>Happens to 21-100 children out of every 100 | **Occasional**<br>Happens to 5-20 children out of every 100 | **Rare**<br>Happens to < 5 children out of every 100 |
|---|---|---|---|
| **Immediate:**<br>Within 1-2 days of receiving drug | | Jaw pain, headache | Extravasation (rare) but if occurs = local ulceration, shortness of breath, and bronchospasm |
| **Prompt:**<br>Within 2-3 weeks, prior to the next course | Alopecia, constipation | Weakness, abdominal pain, mild brief myelosuppression (leukopenia, thrombocytopenia, anemia) | Paralytic ileus, ptosis, diplopia, night blindness, hoarseness, vocal cord paralysis, SIADH, seizure, defective sweating |
| **Delayed:**<br>Any time later during therapy | Loss of deep tendon reflexes | Peripheral paresthesias including numbness, tingling and pain; clumsiness; wrist drop, foot drop, abnormal gait | Difficulty walking or inability to walk; sinusoidal obstruction syndrome (SOS, formerly VOD) (in combination); blindness, optic atrophy; urinary tract disorders (including bladder atony, dysuria, polyuria, nocturia, and urinary retention); autonomic neuropathy with postural hypotension; 8th cranial nerve damage with dizziness, nystagmus, vertigo and hearing loss |
| **Unknown Frequency and Timing:** | Fetal toxicities and teratogenic effects of vincristine (either alone or in combination with other antineoplastic agents) have been noted in humans. The toxicities include: chromosome abnormalities, malformation, pancytopenia, and low birth weight. It is unknown whether the drug is excreted in breast milk. | | |

**Formulation and Stability:**
Vincristine is supplied in 1 mL and 2 mL vials in which each mL contains vincristine sulfate 1 mg (1.08 µmol), mannitol 100 mg, SWFI; acetic acid and sodium acetate are added for pH control. The pH of vincristine sulfate injection, *USP* ranges from 3.5 to 5.5. This product is a sterile, preservative free solution. Store refrigerated at 2˚-8˚C or 36˚-46˚F. Protect from light and retain in carton until time of use.
Do not mix with any IV solutions other than those containing dextrose or saline.

**Guidelines for Administration:** See Treatment and Dose Modifications sections of protocol.

The World Health Organization, the Institute of Safe Medicine Practices (United States) and the Safety and Quality Council (Australia) all support the use of minibag rather than syringe for the infusion of vincristine. The delivery of vincristine via either IV slow push or minibag is acceptable for COG protocols. Vincristine should **NOT** be delivered to the patient at the same time with any medications intended for central nervous system administration. Vincristine is fatal if given intrathecally.

Injection of vincristine sulfate should be accomplished as per institutional policy. Vincristine sulfate must be administered via an intact, free-flowing intravenous needle or catheter. Care should be taken to ensure that the needle or catheter is securely within the vein to avoid extravasation during administration. The solution may be injected either directly into a vein or into the tubing of a running intravenous infusion.

**Special precautions:** FOR INTRAVENOUS USE ONLY.

The container or the syringe containing vinCRIStine must be enclosed in an overwrap bearing the statement: "Do not remove covering until moment of injection. For intravenous use only - Fatal if given by other routes."

Medication errors have occurred due to confusion between vinCRIStine and vinBLAStine. VinCRIStine is available in a liposomal formulation (vinCRIStine sulfate liposomal injection, VSLI, Marqibo®). Use conventional vincristine only; the conventional and liposomal formulations are NOT interchangeable.

## 7.0 EVALUATIONS/MATERIAL AND DATA TO BE ACCESSIONED

> Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. Minor unavoidable departures (up to 72 hours) from protocol directed therapy and/or disease evaluations (and up to 1 week for surgery) for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable per COG Administrative Policy 5.14 (except where explicitly prohibited within the protocol).

All baseline studies must be performed prior to starting protocol therapy unless otherwise indicated below.

### 7.1 Patients with low AFP levels

On rare occasions, laboratory assays have been described to be falsely low in patients whose true AFP levels are so high that they create a "hook" effect and overwhelm the methods of the assay. In patients with low AFP levels, discussion with the laboratory should be considered to determine if serial dilutions can be performed to verify whether an AFP level is truly low. As noted in the background, small cell undifferentiated phenotype is often associated with a truly low AFP level.[69]

### 7.2 Required Clinical, Laboratory and Disease Evaluations for Very Low Risk Patients-Stratum 1 (Stage I PFH)

See Section 7.6.1 for details.

### 7.3 Required Clinical, Laboratory and Disease Evaluations for Low-Risk Patients – Stratum 2

**All baseline studies must be performed prior to starting protocol therapy unless otherwise indicated below.**

**Obtain prior to start of each treatment cycle unless otherwise indicated.**

| STUDIES TO BE OBTAINED | Baseline | Each Cycle | End of Therapy |
|---|---|---|---|
| History | X | X | X |
| Physical exam (Ht, Wt, BSA, VS) | X | X | X |
| CBC, differential, platelets | X | Weekly | X |
| Urinalysis | X | | |
| Electrolytes including $Ca^{++}$, $PO_4$, $Mg^{++}$ | X | X | X |
| Creatinine, ALT/AST, bilirubin | X | X | X |
| Total protein/albumin | X | X | X |
| Primary tumor evaluation (CT and/or MRI)[4] | X[1] | | X |
| Metastatic tumor evaluation (CT chest)[4] | X[1] | | X |
| Abdominal ultrasound[4] | X[1] | | |
| PRETEXT Grouping[5] | X | | |
| Audiogram | X[1] | | X |
| AFP[6] | X | X | X |
| Pathology slides | X[2] | | |
| Tumor tissue | X [3] | | |
| Pregnancy test for females of childbearing potential | X | | |

1 Tumor evaluation, ultrasound and audiogram may be done within 28 days prior to enrollment.
2 Pathology slides required for rapid review of all Stage I and II patient's diagnostic specimens (see Section 14.0).
3 Tumor tissue is strongly encouraged to be submitted and can be submitted if consent has been obtained and patient is enrolled on ABTR01B1 or other appropriate study (see protocol for details).
4 See Section 15.0 for details.
5 PRETEXT grouping should be done by radiologist, surgeon and oncologist on diagnostic scans (see Section 10.2 and Appendix I).
6 Following resection, a repeat AFP should be obtained immediately prior to beginning chemotherapy (the same day).

**This table only includes evaluations necessary to answer the primary and secondary aims. Obtain other studies as required for good patient care.**

## 7.4 Required Clinical, Laboratory and Disease Evaluations for Intermediate-Risk Patients – Stratum 3

**Note: Stratum 3 has been closed to accrual as of 03/12/12**

**Obtain prior to start of each treatment cycle unless otherwise indicated.**

| STUDIES TO BE OBTAINED | Baseline | Each cycle | End of Cycle 2 | End of Cycle 4 | End of Therapy |
|---|---|---|---|---|---|
| History | X | X | | | X |
| Physical exam (Ht, Wt, BSA, VS) | X | X | | | X |
| CBC, differential, platelets | X | Weekly | | | X |
| Urinalysis | X | | | | |
| Electrolytes including $Ca^{++}$, $PO_4$, $Mg^{++}$ | X | X | | | X |
| Creatinine, ALT/AST, bilirubin | X | X | | | X |
| Total protein/albumin | X | X | | | X |
| Primary tumor evaluation (CT and/or MRI)[5] | X[1] | | X | X | X |
| Metastatic tumor evaluation (CT chest)[5] | X[1] | | | X | X |
| Abdominal ultrasound[5] | X[1] | | X | X | |
| PRETEXT/POST-TEXT Grouping[6] | X | | X | X | |
| Echocardiogram or MUGA[7] | X[1] | | | X | X |
| Audiogram | X[1] | | | X | X |
| AFP | X | X | | | X |
| Liver transplant consultation | X[2] | | X[2] | | |
| PLUTO registry consent | | | X[8] | | |
| Pathology slides | X[3] | | X[3] | X[3] | |
| Tumor tissue | X[4] | | X[4] | X[4] | |
| Pregnancy test for females of childbearing potential | X | | | | |

1 Tumor evaluation, ultrasound, echocardiogram (or MUGA) and audiogram may be done within 28 days prior to enrollment. It is highly recommended that patients have echocardiogram (or MUGA) and audiogram prior to treatment, but if patient is emergently treated (see Section 3.2.2) these may be deferred until clinically stable, but must be done before beginning Cycle 2.

2 A liver transplant consult should be performed as soon as possible after diagnosis but no later than after Cycle #2 (see Section 13.1.3).

3 Pathology slides required for rapid central review of all Stage I and II patient's diagnostic specimens. Pathology slides required for patients following all surgical (biopsy/resection) procedures (see Section 14.0).

4 Tumor tissue is strongly encouraged to be submitted and can be submitted if consent has been obtained and patient is enrolled on, ABTR01B1 or other appropriate study (see protocol for details).

5 See Section 15.0 for details. Ultrasound only needs repeating if initial U/S showed tumor thrombus & does not need to be performed once thrombus has resolved or surgery performed.

6 PRETEXT/POST-TEXT grouping should be done by radiologist, surgeon and oncologist on all scans performed at diagnosis and pre-operatively (see Section 10.2 and Appendix I).

7 The same modality is to be used each time for consistency.

8 Consent for PLUTO registry should be obtained within one month of liver transplant, see Section 13.4

**This table only includes evaluations necessary to answer the primary and secondary aims. Obtain other studies as required for good patient care.**

## 7.5 Required Clinical, Laboratory and Disease Evaluations for High-Risk Patients - Stratum 4

**All baseline studies must be performed prior to starting protocol therapy unless otherwise indicated below.**

**Obtain prior to start of each treatment cycle unless otherwise indicated.**

| STUDIES TO BE OBTAINED | Baseline | Each cycle | End of Cycle 2 | End of Cycle 4 | End of Cycle 6 (Responders and Non-responders) | End of Therapy |
|---|---|---|---|---|---|---|
| History | X | X | | | | X |
| Physical exam (Ht, Wt, BSA, VS) | X | X | | | | X |
| CBC, differential, platelets | X | Weekly | | | | X |
| Urinalysis | X | | | | | |
| Electrolytes including $Ca^{++}$, $PO_4$, $Mg^{++}$ | X | X | | | | X |
| Creatinine, ALT/AST, bilirubin | X | X | | | | X |
| Bilirubin | X | Day 1 of each cycle and Day 8 of VIT cycles | | | | |
| Total protein/albumin | X | X | | | | X |
| Urine glucose | X | X[1] | | | | |
| Triglycerides, Cholesterol (Total, HDL,LDL) | X[2] | X[2] | | | | |
| Primary tumor evaluation (CT and/or MRI)[8] | X[3] | | X | X[5] | X[5] | X |
| Metastatic tumor evaluation (CT chest)[8] | X[3] | | X | X[5] | X[5] | X |
| Abdominal ultrasound[8] | X[3] | | X | X | X | |
| PRETEXT/POST-TEXT Grouping[9] | X | | X | X | X | |
| Echocardiogram or MUGA[10] | X[3] | | | | X | X |
| Audiogram | X[3] | | | | X | X |
| AFP[12] | X | X[13] | X[13] | | | X |
| Liver transplant consult | X[4] | | X[4] | X[4] | | |
| PLUTO registry consent | | | | X[11] | | |
| Pathology slides | X[6] | | | X[6] | | |
| Tumor tissue | X[7] | | | X[7] | | |
| Pregnancy test for females of childbearing potential | X | | | | | |

1 If patients at baseline have ≥ Grade 2 hyperglycemia or polyuria or polydipsia, obtain urine glucose weekly during Cycle 1. Obtain at the start of each cycle and as clinically indicated **ONLY** in patients who develop ≥ Grade 2 hyperglycemia or polyuria or polydipsia on protocol therapy.

2 If Grade 3 or 4 hypercholesterolemia or Grade 3 or 4 hypertriglyceridemia is detected when routine (non-fasting) laboratory studies are performed, the tests should be repeated within 3 days in the fasting state to permit accurate grading

3 Tumor evaluation, ultrasound, echocardiogram (or MUGA), and audiogram may be done within 28 days prior to enrollment. It is highly recommended that patients have echocardiogram (or MUGA) and audiogram prior to treatment, but if patient is emergently treated (see Section 3.2.2) these may be deferred until clinically stable, but must be done before beginning Cycle 2.

4 A liver transplant consult should be performed as soon as possible after diagnosis but no later than first day of 3rd C5VD Cycle. (i.e. no later than first day of Cycle 5,) (See Section 13.1.5).

5 Tumor disease evaluation performed after VIT Cycle 2 for all patients and after Cycles 4, 6 & 8 for non-responders and after Cycles 4, 6 and 10 for responders until tumor removed. No scans required once all tumor has been removed or resolved until the end of therapy (see Section 15.3).

6 Pathology slides required for patients following all surgical (biopsy/resection) procedures (see Section 14.0).

7 Tumor tissue is strongly encouraged to be submitted and can be submitted if consent has been obtained and patient is enrolled on ABTR01B1 or other appropriate study (See protocol for details.)

8 See Section 15.0 for details. Ultrasound only needs repeating if initial U/S showed tumor thrombus & does not need to be performed once thrombus has resolved or surgery performed.

9 PRETEXT/POST-TEXT grouping should be done by radiologist, surgeon and oncologist on all scans performed at diagnosis and pre-operatively as appropriate. (See Section 10.2 and Appendix I).
10 The same modality is to be used each time for consistency.
11 Consent for PLUTO registry should be obtained within one month of liver transplant, see Section 13.4.
12 If a biopsy is performed to make diagnosis, a repeat AFP should be obtained immediately prior to beginning chemotherapy (the same day).
13 The AFP obtained at the end of Cycle 2/prior to Cycle 3 must be recorded on the Reporting Period 1 CRF and submitted for central review assessment of response. If an AFP was obtained post Cycle 2, do not repeat prior to Cycle 3. Note: The Reporting Period 1 CRF must be submitted without delay, see the Data Submission Schedule for details.

**This table only includes evaluations necessary to answer the primary and secondary aims. Obtain other studies as required for good patient care.**

## 7.6 Recommended Clinical, Laboratory and Disease Evaluations in Follow-up

### 7.6.1 Recommended Follow-up Evaluations for Patients with Stage I PFH Tumors (Very low-risk-Stratum 1)

History/Physical exam, AFP and other studies as required for good patient care

- Year 1 (Months 1, 2, 4, 6, 8, 10 and 12)
- Year 2 (Months 15, 18, 21 and 24)
- Year 3 (Months 28, 32 and 36)
- Year 4 (Months 42 and 48)

No specific imaging is required. CT (abdomen/chest), abdominal ultrasound and/or chest X-ray can be performed at the discretion of the treating physician.

### 7.6.2 Recommended Follow-up Evaluations for Patients Who Receive Chemotherapy

History/Physical exam, CBC, AFP, Electrolytes, creatinine (until normal)

- Year 1 off therapy (Months 1, 2, 4, 6, 8, 10 and 12)
- Year 2 (Months 15, 18, 21 and 24)
- Year 3 (Months 28, 32 and 36)
- Year 4 (Months 42 and 48)

Follow up in Year 5 and beyond is at the discretion of the treating physician. See COG Late Effects Guidelines for recommended post treatment follow-up at:
http://www.survivorshipguidelines.org

No specific imaging is required for patients who presented with elevated AFP (> 100 ng/mL) at diagnosis. CT (chest), CT or MRI (abdomen), abdominal ultrasound, and/or chest X-ray can be performed at the discretion of the treating physician.

For patients with a low AFP (< 100 ng/mL) at diagnosis, imaging studies (CT [chest], CT or MRI [abdomen] and/or chest X-ray) should be performed every 3 months during the first year off therapy, and then at the times of follow-up as listed above.

Audiograms should be performed when the patient is one year off therapy. Further audiograms can then be performed at the discretion of the treating physician. Patients who have evidence of hearing loss should be considered for yearly follow up audiograms.

Echocardiograms (or MUGAS) should be performed for patients who received doxorubicin yearly for the first 4 years off therapy, and can then be performed at the discretion of the treating physician.

If relapse is suspected, then CBC, AST, ALT, AFP, and CT (abdomen/chest) should be performed. A rise in AFP by itself will not be considered as progressive disease. If an AFP level is elevated compared to a previous level then weekly AFP measurements should be considered. Radiographic studies (CT chest and CT or MRI abdomen) should be considered in patients with an elevated AFP in an attempt to try and identify progressive disease.

## 8.0 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

### 8.1 Criteria for Removal from Protocol Therapy

a) Progressive disease.
b) Unresectability of tumors following 4 cycles of chemotherapy in intermediate-risk patients.
c) Unresectability of tumors following 10 cycles of chemotherapy in high-risk patients who responded (RECIST CR or PR) to "up-front" window therapy.
d) Unresectability of tumors following 8 cycles of chemotherapy in high-risk patients who did not respond to "up-front" window therapy.
e) Inability to have a liver transplant by the specified protocol timepoints for reasons unrelated to hepatoblastoma.
f) Failure to begin protocol therapy within 42 days of initial biopsy or definitive surgery whichever occurs last.
g) Failure to resume post resection chemotherapy within 42 days of resection in intermediate- or high-risk patients.
h) Refusal of further protocol therapy by patient/parent/guardian.
i) Completion of planned therapy.
j) Physician determines it is in patient's best interest.
k) Development of a second malignant neoplasm.
l) For high-risk patients, if the investigator selects a post-induction regimen that is not indicated by the central review of response.

Patients who are off protocol therapy are to be followed until they meet the criteria for Off Study (see below). Follow-up data will be required unless consent was withdrawn.

### 8.2 Off Study Criteria

a) Death.
b) Lost to follow-up.
c) Patient enrollment onto another COG study with tumor therapeutic intent (eg, at recurrence).
d) Withdrawal of consent for any further data submission.
e) Tenth anniversary of the date the patient was enrolled on this study.
f) Definitive surgery does not confirm the diagnosis of hepatoblastoma or reveals another pathological diagnosis in patient who was enrolled emergently without initial biopsy because too sick.

## 9.0 STATISTICAL CONSIDERATIONS

### 9.1 Patient Accrual and Expected Duration of Trial

Patients will be enrolled for five (5) years and analyses to address the primary study aims will be conducted with one more year of follow-up. The projected annual enrollment rates for each of the categories of patients are:

| Stratum | Patient Category | Estimated Annual Accrual |
|---|---|---|
| 1 | Stage I PFH with initial AFP ≥100 ng/mL or AFP not obtained prior to initial resection | 3 patients per year |
| 2 | Stage I, non-PFH, non-SCU, Stage II, non-SCU | 9.2 patients per year |
| 3 | Intermediate risk | 41.6 patients per year |
| 4 | Stage IV or patients with AFP <100 ng/mL at diagnosis | 16 patients per year |

### 9.2 Statistical Analysis Methods

Statistical Considerations

Patients will be enrolled to the study for Five years and followed for an additional year, by which time we expect most disease-related analytic events will have occurred. The design objectives will be different for the four subgroups: (1) Stage I PFH patients (stratum 1) with AFP ≥ 100 ng/mL or AFP not obtained prior to surgical resection of tumor; (2) low risk patients (stratum 2) defined as patients with Stage I non-PFH, non-SCU; Stage II non-SCU (3) intermediate risk patients (stratum 3); and (4) Stage IV patients or patients with AFP < 100 ng/mL at diagnosis (stratum 4). EFS will be the time from patient enrollment until last follow-up or an analytic event is observed, whichever comes first. Analytic events are: (1) progression of existing disease or occurrence of disease at new sites; (2) treatment failure defined as the presence of disease after four cycles of chemotherapy and post-induction surgery (if attempted) for patients enrolled with Stage III disease or presence of disease after planned chemotherapy (eight cycles for non-responders, ten cycles for responders) for patients enrolled with Stage IV disease (3) death from any cause prior to disease progression or diagnosis of a second malignant neoplasm; or (4) diagnosis of a second malignant neoplasm. Survival will be the time from enrollment until death from any cause or last follow-up, whichever comes first.

Section 3 requires that planned start of systemic therapy for patients whose protocol prescribed therapy includes chemotherapy must be within 42 days of enrollment. Experience from prior COG studies of hepatoblastoma demonstrates that this can be accomplished in most patients. All patients who die within 42 days of enrollment will be considered in the analytic plans below. All patients who survive more than 42 days after enrollment and whose protocol therapy prescribes chemotherapy but who do not have such systemic therapy started by the 43rd day after enrollment will be excluded from the analyses below.

A patient enrolled without histological confirmation (see Section 3.2.2.b) will be considered evaluable for all study analyses unless the tumor tissue obtained in a future surgical procedure is not consistent with hepatoblastoma or reveals another pathological diagnosis. If histological confirmation is not confirmed in the future for these patients by a biopsy or surgical resection, they will be considered off study.

The statistical analysis will include an assessment of the influence of the exclusion of cases for whom there is a discrepancy in diagnosis between institutional and central review, or for whom there is an atypical histological presentation. The influence will be assessed by comparing the EFS and survival, as estimated by the method of Kaplan and Meier[70] with and without such cases. This will provide an *ad hoc* assessment of the effect of such cases on outcome characterization. Formal statistical quantification of such effects will not be straightforward.

Surgical resection followed by observation was first tested on COG trial P9645 and has been demonstrated to be a successful approach for patients with stage I PFH. These patients will be enrolled on the trial, since

it will be necessary to submit all Stage I and II patients to mandatory central review to determine the appropriate analytic strategy. The results of this review will be returned for information to the relevant institutional investigator. Individuals considered Stage I PFH and treated with surgery only will be considered for the analysis described in the paragraph below. Individuals considered Stage I non-PFH, non-SCU, Stage II, non-SCU patients and treated with the chemotherapy for such patients will be considered in the analysis described in "Hypothesis 1.1" below.

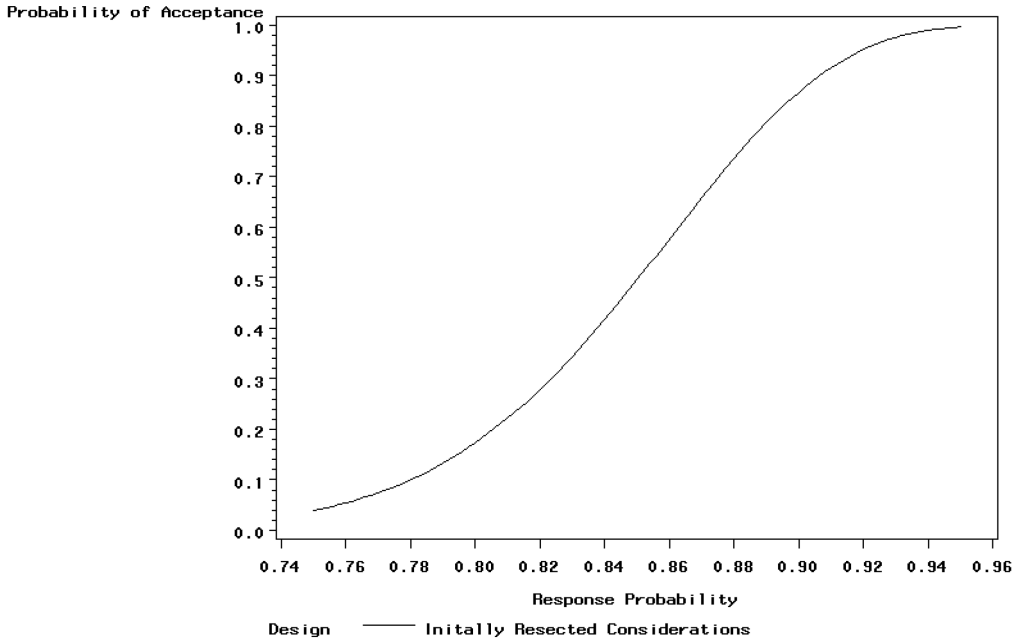
Nine (9) stage I PFH patients will be required for AHEP0731. We may enroll up to 12 patients to account for patients who are determined later to be ineligible. These patients will be followed closely for disease and life status. The outcome of these patients will be summarized through survival and EFS curves estimated by the method of Kaplan and Meier[70] If 2or more analytic events are observed, the strategy of surgery without any further therapy will identify enrollment to this strategy for possible termination because of insufficient disease control. If this strategy is associated with a long-term event-free survival of 65%, the probability of accepting it is 0.12. If this strategy is associated with a long-term event-free survival of 93%, the probability of accepting it is 0.89.

Toxicity will be reported using CTCAE criteria (version 4). All Grade 3 or 4 or greater non-hematological toxicities as well as any toxicity that requires submission of an CTEP-AERS report as outlined in protocol section 11.3, Table B, will be reported while the patient is on protocol therapy. The frequency of each toxicity type will be quantified as the percent of reporting periods on which the toxicity of the relevant grade is reported. All reporting periods where the patient receives at least one dose of each of the agents in the therapeutic plan for that individual will be included in the denominator for the rate calculation.

Follow-up data will be obtained on all patients considered eligible for the protocol. As part of the study design, slides sufficient to confirm the histological subtype of hepatoblastoma (PFH *v.* SCU *v*. neither PFH nor SCU) of all Stage I patients will be submitted to mandatory central review according to the time lines described above. Patients for whom the central review supports the therapeutic approach of the institutional investigator will constitute the analytic subgroup for each of the analyses planned for Stage I patients. The results of this review will be returned for information to the relevant institutional investigator as soon as the assessment becomes available in the COG data system.

Hypothesis 1.1: (Stage I, non-PFH, non- SCU, Stage II, non-SCU [Stratum 2]): Expected Annual Accrual: 9.2 patients per year. Total: 51 patients. We may enroll up to 60 patients to account for patients who are determined later to be ineligible.

If 7 or more analytic events are observed the strategy of surgery with reduced chemotherapy will identify enrollment to this strategy for possible termination because of insufficient disease control. If this strategy is associated with a long-term event-free survival of 78%, it will be rejected with probability 0.90. If this strategy is associated with a long-term event-free survival of 89%, it will be accepted with probability 0.81. The graph below describes the probability of accepting the strategy as a function of its long-term EFS:




Hypothesis 1.2 (Intermediate-risk patients [Stratum 3]): As of Amendment #3B enrollment to stratum 3 is terminated because sufficient patients have been enrolled to address the hypothesis. The total enrollment to stratum 3 was 105 patients.

*Feasibility of Delivery of C5VD:* The primary measure of feasibility will be rate of death as a first analytic event. All patients who receive at least one dose of the C5VD regimen will be considered evaluable for this endpoint. Any patient who dies on protocol therapy or within 30 days of the termination of protocol therapy of a cause considered possibly, probably or likely related to systemic chemotherapy will be considered to have experienced an on-protocol-therapy death. If five or fewer of the 99 patients experience on-protocol-therapy death, the regimen will be considered feasible for further development. If the regimen is associated with a death-event rate of 3%, that observed for patients who were assigned to chemotherapy on P9645, the regimen will be considered feasible with probability 0.92. If the regimen is associated with a death-event rate of 10%, the regimen will be considered not feasible with probability 0.94. If the sixth on-protocol-therapy death is reported, study enrollment will be suspended. In addition to this, at each report to the DSMC the estimated on-protocol-therapy death rate and its 95% confidence interval will be reported to the phase III DSMC as the cumulative incidence of on-treatment death and the 95% confidence intervals at four and six months.

Since the addition of doxorubicin to C5V may affect the delivery of all the agents in the combination, we will characterize the amount of each agent that can be delivered during the first four cycles of therapy and the actual amount of doxorubicin delivered on protocol therapy. During the first four cycles, the total dose of each agent administered will be collected, along with the patient's height and weight. The average amount of each drug, calculated as dose per meter squared will be calculated and a lower 95% confidence bound on the true average dose delivered will be calculated assuming a normal distribution of delivered dose. In addition the total doxorubicin dose, in milligrams per meter squared will be calculated for each patient as well as the average and the 95% confidence interval for this amount. This will be used in planning subsequent trials.

Hypothesis 1.3: (Stage IV [Stratum 4]): Expected Annual Accrual: 16 patients per year. Total: 43 patients (to account for patients who may be later determined to be ineligible.)

Prior to Amendment 3B, VI therapy was evaluated in stage IV patients. No patient assigned to VI experienced early progression. All patients evaluated for the VIT combination, therefore, will be evaluated only for response as defined in Section 10 of the protocol.

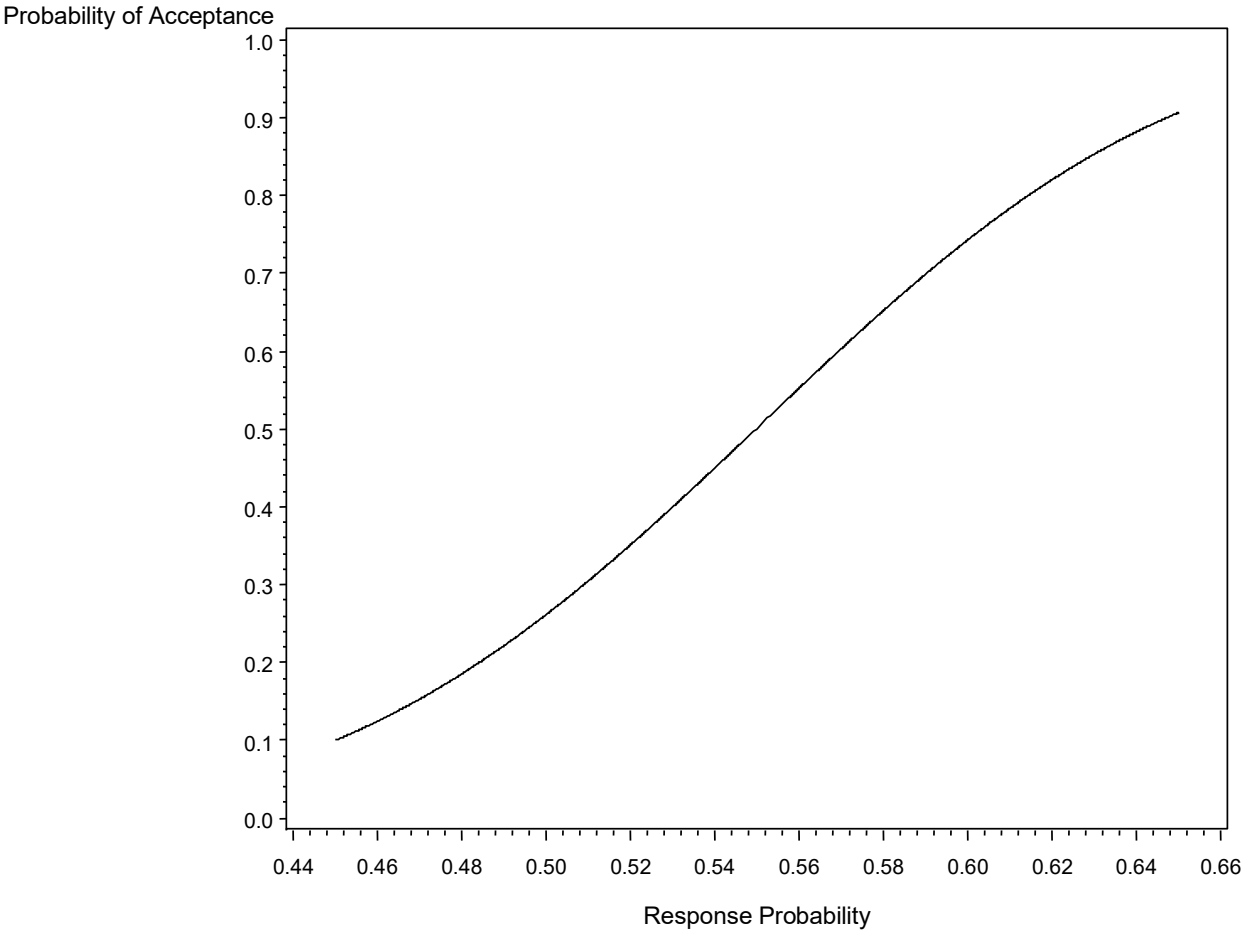
Disease status at the end of two cycles of therapy (or earlier in the case of early progressive disease) will be the endpoint for evaluable patients.

A patient will be considered evaluable if the individual is eligible, receives at least one dose of each agent in the combination being tested and is not removed from protocol therapy for reasons other than toxicity or disease progression. Any evaluable patient who has a CR or PR according the criteria prescribed Section 10 of the protocol will be considered a 'responder'. All other evaluable patients will be considered non-responders. Patients will be enrolled in two stages according to the design specified below:

| Number of Evaluable Patients Enrolled | Results | Decision |
|---|---|---|
| Stage I: 22 Evaluable Patients | 9 or fewer responders | Terminate the trial with the conclusion the regimen does not demonstrate sufficient disease control |
| | 10 or more responders | Continue to the next stage and enroll 19 more patients |
| Stage II: 19 Evaluable Patients (Total of 41) | Cumulatively 22 or fewer responders | Terminate the trial with the conclusion the regimen does not demonstrate sufficient disease control |
| | 23 or more responders | Terminate the trial with the conclusion the regimen demonstrates sufficient disease control for further investigation |

The statistical characteristic of this rule are presented in the figure below:

**Statistical Characteristics of the Two Stage Design**




If the regimen is associated with a true response rate of 45%, which is approximately the maximum likelihood estimate of the response rate associated with VI, the design will identify the regimen as not sufficiently effective for further development with probability 0.90. If the regimen is associated with a true response rate of 65%, the regimen will be considered of sufficient efficacy to warrant further development with probability 0.90. The probability enrollment will be terminated at the first stage of accrual if the true response rate is 45% is 0.435.

The response status used for the application of the statistical rule will be that obtained from the central review of RECIST response and the alphafetoprotein values and sampling dates provided by the institutional investigator. If there is a discrepancy between the assessment by central review and by institutional assessment, the study PI will discuss with the treating physician to resolve the discrepancy.
If the investigator selects a post-induction regimen that is *not* indicated by the central review of response, the patient will be considered off protocol therapy as of the start date of consolidation therapy.

Hypothesis 2.0: Referral Feasibility:
All patients enrolled on the planned COG phase III study of hepatoblastoma (AHEP0731) and who have Stage III or IV disease and whose tumor is PRETEXT classified as PRETEXT 3-4 extensive multifocal;

PRETEXT 3 +V; PRETEXT 3 +P; or PRETEXT 4 extensive multifocal will be evaluable for this portion of the study ('referable extent of disease'). A recent retrospective analysis of the data from INT-0098 looked at the PRETEXT grouping of tumors in patients with Stage III and Stage IV disease. In the years since INT-0098 the PRETEXT system has been increasingly employed by the European SIOPEL studies of pediatric hepatoblastoma in an attempt to define resectability.

INT-0098 was a POG/CCG cooperative trial enrolling 182 children with hepatoblastoma in the early 1990's. In our retrospective review, detailed surgical and pathology reports enabling accurate retrospective PRETEXT grouping were available for 155 of the initial 182 patients. By the proposed definition of resectability in this study, INT-0098 included 32 patients with potentially unresectable tumors who might have been referred early for potential transplantation. The precise breakdown from INT-0098 is as follows:

Stage III: PRETEXT 2 multifocal = 1
PRETEXT 3 multifocal or +V or +P = 8
PRETEXT 4 = 13
Stage IV: PRETEXT 2 multifocal = 0
PRETEXT 3 multifocal or +V or +P = 2
PRETEXT 4 = 8
Total = 32

INT-0098 was open for enrollment for 4 years. As a conservative estimate, using the 32 patients as the projected number of patients for whom referral is appropriate, we expect referral will be appropriate for approximately 25 patients enrolled to AHEP0731.

Patients enrolled on this study will be considered candidates for referral provided the patient has a referable stage of disease and receives two cycles of chemotherapy and is still considered on protocol therapy at the end of the second cycle. A patient will be considered a referral success if: (1) the patient is enrolled on regimen F or regimen H and referred for transplant prior to the start of the third cycle of chemotherapy; or (2) the patient is enrolled on regimen H or W and is referred for transplant by the start of the third cycle of C5VD. Otherwise the patient will be considered a referral failure. In particular, a patient who has a referable stage of disease, is treated on regimen H or W and has protocol therapy terminated after the completion of cycle 2 but before the completion of cycle 4 without being referred for transplant will be considered a referral failure.

The feasibility of referral will be evaluated for each of the expected 25 patients who would be amenable to OLT. A patient for whom referral is considered appropriate who receives a consultation after enrollment will be considered a success with respect to feasibility. If referral is accomplished for 16 or more patients, the strategy will be considered successful and identified for possible incorporation into a randomized study. The characteristics of this rule as a function of the true 'success' probability are:

| True Probability of Successful Referral | Chance Referral Will be Identified as Feasible |
|---|---|
| 0.50 | 11% |
| 0.55 | 24% |
| 0.60 | 42% |
| 0.65 | 63% |
| 0.70 | 81% |
| 0.75 | 93% |

If more than 25 patients are identified as candidates for referral, the number of patients for whom referral

is accomplished required to consider referral "feasible" will be increased in such a way as to yield "Chance Referral Will be Identified as Feasible" probabilities of greater than 80% for the scenarios identified by the last two lines in the table above.

All patients who are referred for OLT evaluation and considered candidates for such a surgery will contribute to the evaluation of secondary aim 1.3.2. If we conclude referral is feasible, we estimated conservatively 16 patients would be referred. We estimate that 2 such patients will not be candidates for OLT because of technical reasons. If 8 or more of the 14 patients considered candidates for OLT receive such a procedure, OLT will be considered a candidate for possible incorporation into a randomized trial. The characteristics of this rule as a function of the true 'success' probability is:

| Probability of OLT Performed on a Potential Candidate | Chance OLT will be Identified for Possible Incorporation Into a Randomized Trial |
|---|---|
| 0.50 | 0.40 |
| 0.55 | 0.55 |
| 0.60 | 0.69 |
| 0.65 | 0.82 |
| 0.70 | 0.90 |
| 0.75 | 0.96 |

If more than 14 patients are successfully referred for OLT the current cutoff of 8 noted in the paragraph above will be increased in a manner similar to that described for the analysis of feasibility of referral.

Any patient from this secondary endpoint analysis population that receives an OLT will be considered a success with respect to the secondary aim 1.3.3. All patients in this cohort will be further subdivided into one of four outcome-of-transplant attempt groups: (a) proven to be resectable with a conventional surgery; (b) remain unresectable, primary transplant performed after a good initial response to chemotherapy; (c) remain unresectable, no surgery performed due to persistent metastatic disease unresponsive to chemotherapy or surgical resection; or (d) do not proceed to surgery because of refusal or deteriorating patient condition.

Two years after the last patient is enrolled we will calculate the 95% confidence interval for the 2-year EFS. If OLT is considered for possible incorporation into a randomized trial, we estimate conservatively that 8 patients will have undergone an OLT. The expected width of the 95% confidence interval is:

Expected 95% Confidence Interval Widths as a Function of the True 2-Year EFS

| True 2-Year EFS | Expected 95% Confidence Interval for 2-Year EFS |
|---|---|
| 0.50 | 0.17-0.83 |
| 0.60 | 0.24-0.88 |
| 0.70 | 0.32-0.93 |
| 0.80 | 0.42-0.97 |
| 0.90 | 0.54-0.99 |

### 9.3 Gender and Minority Accrual Estimates

The gender and minority distribution of the study population is expected to be:

| Accrual Targets | | | |
|---|---|---|---|
| **Ethnic Category** | **Sex/Gender** | | |
| | **Females** | **Males** | **Total** |
| Hispanic or Latino | 24 | 37 | 61 |
| Not Hispanic or Latino | 89 | 103 | 192 |
| **Ethnic Category: Total of all subjects** | 113 | 140 | *253 |
| **Racial Category** | | | |
| American Indian or Alaskan Native | 3 | 0 | 3 |
| Asian | 2 | 10 | 12 |
| Black or African American | 8 | 8 | 16 |
| Native Hawaiian or other Pacific Islander | 0 | 0 | 0 |
| White | 100 | 122 | 222 |
| **Racial Category: Total of all subjects** | 113 | 140 | *253 |

* These totals must agree

This distribution was derived from P9645 and accounts for an aggregate ineligibility and inevlauability rate of 10%.

## 10.0 EVALUATION CRITERIA

### 10.1 Common Terminology Criteria for Adverse Events v4.0 (CTCAE)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting beginning July 1, 2011. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0 and a copy can be downloaded from the CTEP website (http://ctep.cancer.gov).

### 10.2 PRETEXT GROUPING (See **Appendix I**)

PRETEXT will be assessed at diagnosis and at the time of all subsequent abdominal scans performed. PRE-OPERATIVELY. The group assigned after the second cycle of chemotherapy and where applicable, after the 4th cycle of chemotherapy, will be referred to as POST-TEXT.

The number of affected liver sections determines the PRETEXT group as shown in Appendix I. The assignment of PRETEXT will be established by the consensus of the treating oncologist, radiologist, and surgeon at the local institution. Pre-operative abdominal scans will also be submitted for central radiologic and surgical review to assess concordance of local and central PRETEXT grouping.

The patient's liver tumor will be assigned PRETEXT (and/or POST-TEXT) according to the guidelines below. These guidelines are shown graphically in Appendix I.

| PRETEXT/POST-TEXT Group | Number of Affected Liver Sections |
|---|---|
| 1 | Tumor involves only 1 liver section; 3 adjoining sections are free of tumor. |
| 2 | Tumor involves 2 adjoining liver sections; 2 adjoining sections are free of tumor. |
| 3 | Tumor involves 3 adjoining sections or 2 nonadjoining sections; 1 section or 2 nonadjoining sections are free of tumor. |
| 4 | Tumor involves all 4 liver sections; there is no section free of tumor. |
| **Any PRETEXT/POST-TEXT Group can be annotated with the following:** | |
| +V | Tumor ingrowth of vena cava or ALL THREE hepatic veins |
| +P | Tumor ingrowth of main portal vein bifurcation or both right and left portal veins |
| +C | Tumor ingrowth of caudate lobe |
| +E | Extrahepatic contiguous tumor ingrowth of diaphragm, abdominal wall, bowel |
| +M | Distant metastatic disease |

### 10.3 Response Criteria for Patients with Solid Tumors

This study will evaluate response using the Response Evaluation Criteria in Solid Tumor (RECIST) from the NCI for the evaluation of radiographic response. Response will also be evaluated using the tumor marker alphafetoprotein for patients with initial serum elevation of that marker. Patients who did not have an alphafetoprotein level obtained prior to initial therapeutic intervention will not be able to use AFP as a response criteria.

For high-risk patients being assessed at the end of Cycle 2, the assessment of response is based on central review of imaging, the alphafetoprotein values and sampling dates. The results of the central review will be returned to the institutional investigator within 3 weeks of submission of the imaging and AFP material. If there is a discrepancy between the assessment by central review and by institutional assessment, the study PI will discuss with the treating physician to resolve the discrepancy. If the investigator selects a post-induction regimen that is *not* indicated by the central review of response, the patient will be considered off protocol therapy as of the start date of consolidation therapy.

#### 10.3.1 Measurable Disease

The presence of at least one lesion that can be accurately measured in at least one dimension with the longest diameter at least 20 mm. With spiral CT scan, lesions must be at least 10 mm. The investigator will identify up to 10 MEASURABLE lesions to be followed for response.

Serial measurements of lesions are to be done with CT or MRI. The same method of assessment should be used to characterize each identified and reported lesion at baseline and during follow-up.

Quantification of Disease Burden

The sum of the longest diameter (LD) for all target lesions will be calculated and reported as the disease measurement.

Complete Response (CR)

Disappearance of all target lesions. Serum alphafetoprotein is normal for age for patients with initially elevated markers and for patients for whom markers were not obtained prior to initial therapy.

Partial Response (PR)

**Either**

At least a 30% decrease in the disease measurement, taking as reference the disease measurement done to confirm measurable disease at study entry.

**OR**

Serum alphafetoprotein concentration decline of at least 90% of the highest AFP prior to the initiation of therapy ($\geq 1 \log_{10}$) for patients with initially elevated markers in the absence of disease progression.

$$\text{RECIST Measurement (\% decline)} = \frac{\text{Sum of longest diameter of each measurable lesion at diagnosis} - \text{Sum of longest diameter of each measurable lesion after chemotherapy}}{\text{Sum of longest diameter of each measurable lesion at diagnosis}} \times 100\%$$

To be included in RECIST calculation liver lesions must be > 20 mm and pulmonary lesions must be > 10 mm at the time of diagnosis.

$$\text{\% AFP decline} = \frac{(\text{Maximum AFP prior to beginning chemotherapy} - \text{Maximum AFP following chemotherapy})}{\text{Maximum AFP Prior to beginning chemotherapy}} \times 100\%$$

For evaluation of window response

Maximum AFP prior to beginning chemotherapy should be used. If a biopsy is performed to make diagnosis, a repeat AFP should be obtained immediately prior to beginning chemotherapy (the same day). AFP following window chemotherapy should be drawn at the end of Cycle 2 (Week 6/7) just prior to beginning Cycle 3.

Progressive Disease (PD)

At least a 20% increase in the disease measurement, taking as reference the smallest disease measurement recorded since the start of treatment, or the appearance of one or more new lesions.

Stable Disease (SD)

Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as reference the smallest disease measurement since the treatment started. Serum alpha fetoprotein concentration does not increase for patients with initially elevated markers.

Response Assessment

Each patient will be classified according to their "best response" for the purposes of analysis of treatment effect. Best response is determined from the sequence of the objective statuses described above.

### 10.3.2 Non-measurable Metastatic Disease

Non-target lesions: Includes all lesions that do not qualify as measurable disease at diagnosis. These lesions should be noted and recorded and response indicated as improved, no change or worse. These lesions should not be included as part of RECIST calculations.

10.3.3 Overall response assessment

The overall response assessment takes into account response in the measurable and non-measurable disease, and the appearance of new lesions, where applicable, and decline of alphafetoprotein according to the criteria described in the table below.

| Target Lesions | Non-target Lesions | New Lesions | Tumor Markers | Overall Response |
|---|---|---|---|---|
| CR | CR | No | Normalized[1] | CR[1] |
| CR | Incomplete response/SD | No | Decreased | PR |
| PR | Non-PD | No | Decreased | PR |
| NON-PD | Non-PD | No | ≥ 90% decrease from highest AFP prior to treatment (1 $\log_{10}$ decreased) | PR |
| SD | Non-PD | No | Stable | SD |
| PD | Any | Yes or No | Any | PD |
| Any | PD | Yes or No | Any | PD |
| Any | Any | Yes | Any | PD |

[1] An overall response of CR MUST include a normal AFP. Until the AFP has normalized, a patient can be considered PR at best.

It is not uncommon for a patient to complete therapy and have an AFP that remains minimally elevated. If there is no evidence of persistent clinical or radiographic disease, these patients can be followed as in Section 7.6

A rise in AFP by itself will not be considered as progressive disease. If an AFP level is elevated compared to a previous level then weekly AFP measurements should be considered. Radiographic studies (CT chest and CT or MRI abdomen) should be considered in patients with an elevated AFP in an attempt to try and identify progressive disease.

## 11.0 ADVERSE EVENT REPORTING REQUIREMENTS

### 11.1 Purpose

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Certain adverse events must be reported in an expedited manner to allow for timelier monitoring of patient safety and care. The following sections provide information about expedited reporting.

### 11.2 Determination of Reporting Requirements

Reporting requirements may include the following considerations: 1) whether the patient has received an investigational or commercial agent; 2) the characteristics of the adverse event including the *grade* (severity), the *relationship to the study therapy* (attribution), and the *prior experience* (expectedness) of the adverse event; 3) the Phase (1, 2, or 3) of the trial; and 4) whether or not hospitalization or prolongation of hospitalization was associated with the event.

An investigational agent is a protocol drug administered under an Investigational New Drug Application (IND). In some instances, the investigational agent may be available commercially, but is actually being tested for indications not included in the approved package label.

Commercial agents are those agents not provided under an IND but obtained instead from a commercial source. The NCI rather than a commercial distributor may on some occasions distribute commercial agents for a trial.

When a study includes both investigational and commercial agents, the following rules apply:

- *Concurrent administration*: When an investigational agent is used in combination with a commercial agent, the combination is considered to be investigational and expedited reporting of adverse events would follow the guidelines for investigational agents.
- *Sequential administration*: When a study includes an investigational agent and a commercial agent on the same study arm, but the commercial agent is given for a period of time prior to starting the investigational agent, expedited reporting of adverse events which occur prior to starting the investigational agent would follow the guidelines for commercial agents. Once therapy with the investigational agent is initiated, all expedited reporting of adverse events follow the investigational agent reporting guidelines.

### 11.3 Steps to Determine if an Adverse Event is to be Reported in an Expedited Manner

Step 1: *Identify the type of event using the NCI Common Terminology Criteria*

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Step 2: *Grade the event using the NCI CTCAE.*

Step 3: *Determine the attribution of adverse event in relation to the protocol therapy.* Attribution categories are: Unrelated, Unlikely, Possible, Probable, and Definite.

Step 4: Determine the prior experience *of the adverse event*

Expected events for a CTEP IND agent are defined as those listed in the SPEER (Specific Protocol Exceptions to Expedited Reporting), a subset of the CAEPR (Comprehensive Adverse Event and Potential Risks). For investigational agents that are not commercially available and are being studied under a company's IND, expected AEs are usually based on the Investigator's Brochure.

***Unexpected*** **events for a CTEP IND agent are defined as those NOT listed in the SPEER.**

Guidance on expectedness of the agent is provided in the Drug Information Section of this protocol.

Step 5: *Review Tables A and/or B in this section to determine if:*

- *there are any protocol-specific requirements for expedited reporting of specific adverse events that require special monitoring; and/or*
- *there are any protocol-specific exceptions to the reporting requirements.*

Step 6: *Determine if the protocol treatment given prior to the adverse event included an investigational agent, a commercial agent, or a combination of investigational and commercial agents.*

**Note:** If the patient received at least one dose of investigational agent, follow the guidelines in Table A. If no investigational agent was administered, follow the guidelines in Table B.

## 11.4 Reporting Methods

- Use the NCI's CTEP Adverse Event Reporting System (CTEP-AERS). The NCI's guidelines for CTEP-AERS can be found at:
  http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm

  An CTEP-AERS report must be submitted by the following method: https://eapps-ctep.nci.nih.gov/ctepaers

  Electronically submit the report via the CTEP-AERS Web-based application located at

- Fax supporting documentation **for AEs related to investigational agents** to:
  - The NCI for agents supplied under a CTEP IND **only** (fax # 301-230-0159).
  - and to COG for **all** studies (fax # 310-640-9193; email: COGAERS@childrensoncologygroup.org; Attention: COG CTEP-AERS Coordinator).

- **DO NOT send the supporting documentation for AEs related to commercial agents to the NCI.** Fax or email this material to COG (fax # 310-640-9193; email: COGAERS@childrensoncologygroup.org; Attention: COG AERS Coordinator).

**ALWAYS include the ticket number on all faxed documents.**

- **Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.**

## 11.5 When to Report An Event In An Expedited Manner

- Some adverse events require notification **within 24 hours** (refer to Table A) to NCI via the web based application **and/or by telephone call to the Study Chair.**

In the rare situation where Internet connectivity is disrupted, the 24-hour notification is to be made to the NCI for agents supplied under a CTEP IND by telephone call to 301-897-7497.

In addition, once Internet connectivity is restored, a 24-hour notification that was phoned in must be entered into the electronic CTEP-AERS system by the original submitter of the report at the site.

- Submit the report **within 5 calendar days** of learning of the event.

### 11.6 Other Recipients of Adverse Event Reports

COG will forward reports and supporting documentation to the Study Chair, to the FDA (when COG holds the IND) and to the pharmaceutical company (for industry sponsored trials).

Adverse events determined to be reportable must also be reported according to the local policy and procedures to the Institutional Review Board responsible for oversight of the patient.

### 11.7 Reporting of Adverse Events For Investigational Agents – CTEP-AERS 24-hour Notifications, and Complete Report Requirements.

Reporting requirements are provided in Table A. The investigational agent used in this study is Temsirolimus.

Table A

**Phase 2 and 3 Trials and COG Group-wide Pilot Studies utilizing an Agent under a CTEP IND or a Non-CTEP IND: CTEP-AERS Expedited Reporting Requirements for Adverse Events That Occur Within 30 Days[1] of the Last Dose of the Investigational Agent**

**FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)**
**NOTE:** Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death.
2) A life-threatening adverse event.
3) Any AE that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours. This does not include hospitalizations which are part of routine medical practice.
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6.)

**ALL SERIOUS** adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">7 Calendar Days</td><td rowspan="2">24-Hour Notification<br>5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not Required</td><td>7 Calendar Days</td></tr>
</table>

**NOTE:** Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR. Additional Special Situations as Exceptions to Expedited Reporting are listed below.

**Expedited AE reporting timelines are defined as:**
"24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour notification.
"7 Calendar Days" - A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE.

[1]SAEs that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
**Expedited 24-hour notification followed by complete report within 5 calendar days for:**

- All Grade 4, and Grade 5 AEs

**Expedited 7 calendar day reports for:**

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

Note: **All deaths on study require timely reporting to COG via RDE regardless of causality. Attribution to treatment or other cause must be provided.**

- **Expedited AE reporting timelines defined:**
  - "24 hours; 5 calendar days" – The investigator must initially report the AE (via CTEP-AERS for CTEP IND agents; via e-mail to COG AE Coordinator for agents in non-CTEP IND studies) within 24 hours of learning of the event followed by a complete CTEP-AERS report within 5 calendar days of the initial 24-hour report.
  - "5 calendar days" - A complete CTEP-AERS report on the AE must be submitted within 5 calendar days of the investigator learning of the event.

- Any medical event equivalent to CTCAE Grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.

- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via CTEP-AERS if the event occurs following treatment with an agent under a CTEP IND.

- Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

- Protocol specific reporting of AEs, in addition to the CTEP-AERS requirements, are to be entered in the COG remote data entry system.

**Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing an Agent under a CTEP IND or Non-CTEP IND:**

- **Any death that occurs more than 30 days after the last dose of treatment with an investigational agent which can be attributed (possibly, probably, or definitely) to the agent and is not due to cancer recurrence/progression must be reported via CTEP-AERS for an agent under a CTEP IND [and via CTEP-AERS for non-CTEP IND agent] per the timelines outlined in the table above.**

**Grades 1- 4 myelosuppression do not require expedited reporting unless unexpected.**

- As of August 25, 2010 all secondary malignancies should be reported via CTEP-AERS.

### 11.8 Reporting of Adverse Events for commercial agents – CTEP-AERS abbreviated pathway

The following are expedited reporting requirements for adverse events experienced by patients on study who have not received any doses of an investigational agent on this study.
Commercial reporting requirements are provided in Table B.

COG requires the CTEP-AERS report to be submitted **within 5 calendar days** of learning of the event.

**Table B**
**Reporting requirements for adverse events experienced by patients on study who have NOT received any doses of an investigational agent on this study.**

**CTEP-AERS Reporting Requirements for Adverse Events That Occur During Therapy With a Commercial Agent or Within 30 Days[1]**

| Attribution | Grade 4 | | Grade 5 |
|---|---|---|---|
| | Unexpected | Expected | |
| Unrelated or Unlikely | | | CTEP-AERS |
| Possible, Probable, Definite | CTEP-AERS | | CTEP-AERS |

[1]This includes all deaths within 30 days of the last dose of treatment with a commercial agent, regardless of attribution. Any death that occurs more than 30 days after the last dose of treatment with a commercial agent which can be attributed (possibly, probably, or definitely) to the agent and is not due to cancer recurrence must be reported via CTEP-AERS.

As of August 25, 2010 all secondary malignancies should be reported via CTEP-AERS.

### 11.9 Routine Adverse Event Reporting

**Note:** The guidelines below are for routine reporting of study specific adverse events on the COG case report forms and do not affect the requirements for CTEP-AERS reporting.

The NCI defines both routine and expedited AE reporting. Routine reporting is accomplished via the Adverse Event (AE) Case Report Form (CRF) within the study database. For this study, routine reporting will include non-hematological adverse events of Grade 3 or higher (any attribution), as well as any toxicity that required submission of an CTEP-AERS report as outlined above in Sections 11.7, Table A and 11.8, Table B.

## 12.0 RECORDS AND REPORTING

### 12.1 Categories of Research Records

Research records for this study can be divided into 3 categories:
Non-computerized information: Pathology Narrative Reports and Surgical Reports. These forms are submitted through the Document Imaging System in eRDES.

1. Reference Labs' required reports and IROC RI (QARC) data. These data accompany submissions to these centers which forward their review data electronically to the COG Statistics and Data Center.
2. Computerized Information Electronically Submitted: All other computerized data will be entered in the COG Remote Data Entry System with the aid of schedules and Case Report Forms (paper copies of the RDE screens) provided in the data form packet. The packet is posted on the COG Website with each protocol under "*Data Collection/Specimens*".

### 12.2 CDUS

This study will be monitored by the Clinical Data Update System (CDUS). Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31. This is not a responsibility of institutions participating in this trial.

## 13.0 SURGICAL GUIDELINES

Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. Minor unavoidable departures (up to 72 hours) from protocol directed therapy and/or disease evaluations (and

up to 1 week for surgery) for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable per COG Administrative Policy 5.14 (except where explicitly prohibited within the protocol).

### 13.1 Surgical Resection Guidelines

Surgical resection guidelines will be determined according to the PRETEXT grouping system, which was designed specifically for patients with liver tumors. See Section 10.2 and Appendix I for PRETEXT guidelines. Terminology for PRETEXT grouping at diagnosis is "PRETEXT". PRETEXT assignment AFTER chemotherapy is referred to as "POST-TEXT". Please refer to Appendix I for diagram of resection guidelines.

13.1.1a Tumors Considered Resectable at Diagnosis
Non-Extreme Resection

- PRETEXT 1.
- PRETEXT 2 with >1 cm radiographic margin on the middle hepatic vein, the retrohepatic IVC and the portal bifurcation.

13.1.1b Tumor Biopsy Only at Diagnosis (Stage III)

- PRETEXT 2 with ***less than*** 1 cm radiographic margin on the middle hepatic vein, the retrohepatic IVC, and the portal bifurcation.
- PRETEXT 3.
- PRETEXT 4.
- Biopsy technique at the discretion of the treating institution may be a percutaneous tru-cut, laparoscopic tru-cut or wedge, or open biopsy. Minimum biopsy size is 3 tru-cut cores of tissue. Larger biopsies, however, are strongly recommended where feasible to evaluate for the possibility of heterogenous foci of small-cell undifferentiated (SCU) tumor. (See Section 14.0 for Pathology specimen requirements.)

13.1.2 Tumors Considered Resectable After First 2 Cycles of C5VD Neoadjuvant Chemotherapy
Non-Extreme Resection
See Section 14.0 for Pathology specimen requirements.

- Tumors with POST-TEXT 1.
- Tumor with POST-TEXT 2 with > 1 cm radiographic margin on the middle hepatic vein, the retrohepatic IVC, or the portal bifurcation.

13.1.3 Tumors With Potential Need for Liver Transplant or Extreme Resection

- Definition of potential candidate for liver transplant or extreme resection based upon radiographic imaging obtained at diagnosis (PRETEXT) and after the SECOND cycle of C5VD chemotherapy (POST-TEXT):
  - Major Venous Invasion: Unifocal PRETEXT/POST-TEXT 3 with tumor ingrowth of all 3 hepatic veins or the retrohepatic vena cava (+V), or portal vein or both right and left (+P). The distinction between major venous "ingrowth" by tumor vs major venous "displacement" or "extrinsic compression" by tumor can be radiographically very difficult. Clinicians are encouraged to err on the side of "possible invasion" and refer patient for transplant evaluation if this distinction is very difficult to make.

- Unifocal PRETEXT/POST-TEXT 4

- Multifocal PRETEXT/POST-TEXT 3 and 4

- **Refer to surgical center with expertise in pediatric liver transplant and "extreme" liver resection at diagnosis if possible and no later than the first day of the 3rd cycle of C5VD neoadjuvant chemotherapy.** Resection planning is to be completed before completion of the 4th cycle of chemotherapy. Transplant or "extreme" resection is to occur within 4 weeks of completing the 4th cycle of chemotherapy.

13.1.4 Tumors Considered Resectable Within 4 weeks of Completing 4th Cycle of Chemotherapy Non-Extreme Resection

See Section 14.0 for Pathology specimen requirements.

- Tumors with POST-TEXT 3 and no major venous invasion. The surgeon must anticipate the ability to achieve a negative surgical margin on the right/left hepatic vein, retrohepatic IVC, or portal bifurcation. Margin may be less than 1 cm if the surgeon feels a complete resection will be feasible without transplant and patient has completed 4 cycles of C5VD chemotherapy.

13.1.5 Tumors Presenting with Metastatic Disease (Stage IV)

See Section 14.0 for Pathology specimen requirements.

- Complete 2 cycles of upfront experimental window chemotherapy.
- Repeat radiographic imaging after completing upfront window therapy
  - Resect (non-extreme) tumors POST-TEXT 1 or 2 with > 1 cm radiographic margin on the middle hepatic vein, retrohepatic IVC, and portal bifurcation
  - For all others, proceed with 2 cycles of C5VD
- Repeat radiographic imaging after completing first 2 cycles of C5VD
  - Resect (non-extreme) tumors downstaged to POST-TEXT Group 1, 2, or 3 tumors with > 1 cm radiographic margin on right/left hepatic vein, retrohepatic IVC, and portal bifurcation.
  - For patients potentially needing liver transplant/extreme resection (see definition in Section 13.1.3), refer to surgical center with expertise in pediatric liver transplant and "extreme" liver resection at diagnosis if possible and no later than the FIRST DAY of the 3rd cycle of C5VD chemotherapy. Resection planning is to be completed before completion of Cycle 7 in high risk responders and before completion of Cycle 6 in high risk non-responders. Transplant or "extreme" resection is to occur within 4 weeks of completing the 7th cycle of chemotherapy in high risk responders and the 6th cycle of chemotherapy in high-risk non-responders.
  - Repeat chest CT scan must demonstrate complete clearance of pulmonary metastatic disease within 1 week prior to liver transplant.
  - Those patients with persistent extrahepatic disease, may be resected (not transplanted) at the discretion of the surgical center with expertise in pediatric liver transplant and "extreme" liver resection.
  - Those patients with persistent extrahepatic disease who are not anatomically resectable without transplantation will continue chemotherapy.

13.1.6 Optional Central Assistance to Aid in Determination of Tumor Resectability

If the treating physicians/surgeons desire assistance with their clinical decision making this will be available from one of the study surgeons on the Surgical Review Committee with expertise in the treatment of pediatric liver tumors. Clinical consultation is NOT REQUIRED. However, at least one of these surgeons will be available AT ALL TIMES for emergent consultation. The local treating institution is ultimately responsible for making the treatment decision regarding resectability with the full backup of the OPTIONAL consultation. The consulting surgeon on call can be reached by contacting the surgical study chair or the study chair.

### 13.2 Central Surgical Review

For purposes of evaluating clinical predictive value and reproducibility of the PRETEXT system, central review will be completed for all scans obtained at diagnosis (PRETEXT) and after neoadjuvant chemotherapy (POST-TEXT). The central surgical review will be performed on an ongoing basis by the team of study surgeons by web access to imaging coordinated through IROC RI (QARC) and completed by the team of surgeons and radiologists. A bi-annual group review of imaging will be held to achieve consensus on imaging where central review is divergent amongst the reviewers

### 13.3 Surgical Management of Pulmonary Metastasis

Patients presenting with pulmonary metastatic disease (Stage IV) will receive the "up-front" window chemotherapy described above for high-risk patients. If metastases disappear with chemotherapy, no pulmonary surgical intervention will be performed. If metastases are persistent after 4 total cycles of C5VD chemotherapy and the patient is considered a candidate for liver transplant at that time, metastases are to be resected to render the patient free of extrahepatic disease prior to transplant. Transplant may then be undertaken.

If the liver tumor can be primarily resected after either Cycles 4 or 7 in high risk responders and after Cycles 4 or 6 in high-risk non-responders without transplant, this should be performed and the final cycles of chemotherapy should be administered. If the metastases are still present, they should then be resected. Pulmonary metastectomy may be performed earlier in the course of therapy if it can be done without resulting in delays in the administration of scheduled chemotherapy.

### 13.4 Liver Transplant or Extreme Liver Resection

Two distinct cohorts of unresectable patients are expected. Patients identified as potentially unresectable based on preoperative radiographic imaging that are either: 1) successfully referred for evaluation at a transplant center in a timely fashion, or 2) not successfully referred for evaluation at a transplant center in a timely fashion. Within the first cohort there are further possible subgroups: 1a) prove to be resectable at the time of surgery; 1b) remain unresectable and primary transplant performed, 1c) remain unresectable, no surgery performed due to persistent metastatic disease unresponsive to chemotherapy or surgical resection, or 1d) do not proceed to surgery because of refusal or deteriorating patient condition.

Post surgery/transplant chemotherapy will be based on the chemotherapy received preoperatively. For patients with disease confined to the liver, 2 additional post operative/transplant cycles of the same chemotherapy given preoperatively (4 cycles) will be given postoperatively for a total of 6 cycles. For patients with metastatic disease, additional cycles of the same chemotherapy given pre-operatively will be given post-operatively. The number of post operative cycles may vary depending upon the point in treatment during which resection occurred for a total of 8 cycles for patients who did not respond to window therapy and a total of 10 cycles for patients who did respond to window therapy.

Patient management guidelines will follow the same format that has been discussed and agreed upon by an international committee of liver transplant surgeons in the preparation of the Pediatric Liver Unresectable Tumor Observatory (PLUTO). All patients treated by liver transplantation will be asked to sign a consent within one month (optimally) post transplant giving permission for registration on the PLUTO multi-center international cooperative database for children who receive a liver transplant for hepatoblastoma or hepatocellular carcinoma. The consent is usually obtained by the liver transplant team, but may also be obtained by the oncology team. Medical information is entered via a secure internet connection with a remote data entry system accessible at www.pluto.cineca.org. The organization called CINECA is an information management organization with a contract with SIOPEL (the liver tumor study group of the Societe International Oncologie Pediatric (SIOP)) to collect and manage the information. Other children's liver study groups that participate in the registry include the Children's Oncology Group (COG), the German Pediatric Oncology Group (GPOH), the Study Pediatric Liver International Transplant group (SPLIT), and several independent liver transplant centers throughout the USA, Europe, South America, and Japan.

The database collects information about type of liver tumor, tumor size, number and location of tumors in and outside of the liver, involvement of blood vessels, chemotherapy medications used, lymphocyte blood count, immunosuppression medications used after transplant, side effects of the medications, at what point in the treatment was the transplant performed, complications from the transplant surgery, and outcome of the transplant and the disease free survival. The registry plans to enroll patients for a minimum of ten years with an enrollment of approximately 300. The registry currently plans to keep the entered data indefinitely. If subjects do not want to continue participating in the database, their data will be removed upon request. This database can be accessed via the PLUTO Registry Website: http://pluto.cineca.org/access.htm. In order to be authorized to use the transplant database, it is necessary to register with PLUTO. The link to the required participation form is found using the same PLUTO access link provided above.

The registry on the internet has a home page with basic information about what it is and about the organizations that have cooperated to make the registry possible. Access to the main part of the registry where the patient information is collected and stored is strictly controlled and requires a secure password which is available only to the research doctors approved by the registry. The registry is maintained by CINECA (www.cineca.it), a nonprofit consortium made up of 32 Italian Universities, the Italian National Institute of Oceanography and Experimental Geophysics, the Italian National Research Council, and the Italian Ministry of University and Research. CINECA supports the research activities of the scientific community through supercomputing and its applications. By contract with SIOPEL (International Childhood Liver Tumour Strategy Group), CINECA serves as the data management group for all SIOPEL studies. The PLUTO registry data are available to scientists/clinicians whose centers regularly contribute to PLUTO. Data can be used to perform scientific studies which have been approved by the PLUTO steering committee. To obtain access to data, a written request is addressed to the chairperson of PLUTO steering committee serving as custodian of the registry. The request must contain title, objectives and description of study, supporting letter of program director, name and affiliation of investigator, and a disclosure statement disclosing any potential conflicts of interest.

## 14.0 PATHOLOGY GUIDELINES AND SPECIMEN REQUIREMENTS

Before entering patients on this trial, clinicians should discuss this protocol with their pathologist and provide them with pathology section of the protocol and list of the required materials that will need to be submitted. (Requirements are listed on the Data Submission Schedule in the CRF packet.)

It is the responsibility of the Principal Investigator at the institution to ensure that the pathologist is informed of each patient enrolled on AHEP0731 and to request that patients' materials be forwarded to the COG Biopathology Center (BPC), as required. The BPC will NOT request materials.

### 14.1 Pathology Evaluation

The pathologic classification of liver tumors is becoming increasingly complex. Because of limited biopsy specimens for review, the diagnosis of hepatoblastoma is sometimes difficult to make. Central review is therefore critical to ensuring that the diagnosis is accurate and that patients are treated appropriately. Central pathologic review will be performed on all diagnostic specimens (whether resected or biopsied). Results of the review will only be given to the treating institution for Stage I and II patients who receive rapid central pathology review.

If there is a discrepancy between the institutional diagnosis and the diagnosis on the central review of a Stage I or II patient, then a discussion between the local and study pathologists will take place to attempt to reach a consensus. If a consensus cannot be reached, then the institutional diagnosis will be accepted. An assessment of the influence of the exclusion of cases for whom there is a discrepancy in diagnosis between institutional and central review, or for whom there is an exceptional or unusual histological presentation will be addressed statistically.

Please label all materials with the patient's COG Patient Identification Number and the surgical pathology number and block number from the corresponding institutional pathology report(s).

There are 2 study pathologists: Drs. Milton Finegold and Sarangarajan Ranganathan.
There are 2 JPLT study pathologists: Drs. Yukichi Tanaka and Takeshi Inoue.

#### 14.1.1 Central Pathology Review

Central pathologic review will be performed for all resected/biopsied specimens (liver and/or lung) to assess for the presence of positive surgical margins, microscopic satellite nodules, and microscopic venous invasion. Specimens should be submitted at the time of diagnosis and from all subsequent biopsies or resections or explants.

- **Stage I and II Specimens at Diagnosis**

Rapid central pathology review of all Stage I and II patient specimens is required. Rapid central pathology review was utilized on the P9645 study and was shown to be feasible. Two sets of duplicate slides of the entire specimen must be SUBMITTED to the COG Biopathology Center (BPC) no later than 14 calendar days from resection (7 days preferred). The BPC will immediately forward one set to one of the study pathologists. **Enrollment on this study of Stage I or II patients must not occur until results of rapid central pathologic review are known.** The study pathologists will review all slides and will communicate results to the contact person noted on the Rapid Review Transmittal Form for Stage I and II patients. If there is > 1 week delay from submission of specimens for rapid review and receipt of pathology review, the study chair should be contacted.

Required materials for Stage I and II are:
Paraffin-embedded blocks are preferred; if all blocks with tumor are not available, then send 2 H&E and 2 unstained slides per block.

- A **minimum** of 1 block of tissue for each 1 cm of maximum tumor diameter should be sampled
- **Sections of tumor should measure approximately 2.5 x 1.5 cm per paraffin block**
- Include the surgical margin (1 section for each cm of resection margin)
- Include the peri-or intra-hilar portal vein and hepatic vein at margin of resection

- Include any well-defined encapsulated circular foci of tumor suggestive of intravenous growth
- Representative sections of grossly diverse appearing areas (most closely resembling normal liver and moderately firm to capture 'fetal" histology; softer more pale, pinkish and moist areas for 'embryonal' or 'small cell' components; more firm and even calcified areas for fibrous and 'osteoid' mesodermal derivatives; dark brown foci for melanotic 'teratoid' elements). Some or all of these sections may also meet the requirement for marginal material. It is very desirable to photograph the gross specimen and to diagram {map} the precise source of the samples.

**Special Instructions:** It should be noted on the AHEP0731 Rapid Review Transmittal Form for Stage I and II patients that the specimen is for a Stage I or II rapid review at diagnosis.

- **All Other Specimens (**all surgeries except initial Stage I and II surgery**)**

Histologic sections of all remaining pathology specimens will be sent to the BPC (see address below). Slides must be submitted following **all** other surgical biopsies/resections including:

- Non-Stage I or II diagnostic biopsy
- Primary upfront resection
- Delayed surgical resection
- Liver explant at time of orthotopic liver transplant
- Pulmonary metastectomy

Slides must be submitted within **4 weeks** of surgical procedure. Required materials for all surgeries (except initial Stage I and II surgery) are:
Paraffin-embedded blocks are preferred; if all blocks with tumor are not available, then send 2 H&E and 2 unstained slides per block.

- **A minimum** of 1 block for each 1 cm of maximum tumor diameter
- **Sections of tumor should measure approximately 2.5 x 1.5 cm per paraffin block**
- Include the surgical margin (1 section for each cm of resection margin)
- Include the peri- or intra-hilar portal vein and hepatic vein at margin of resection
- Include any well-defined encapsulated circular foci of tumor suggestive of intravenous growth
- Representative sections of grossly diverse appearing areas (most closely resembling normal liver and moderately firm to capture 'fetal' histology; softer more pale, pinkish and moist areas for 'embryonal' or 'small cell' components; more firm and even calcified areas for fibrous and 'osteoid' mesodermal derivatives; dark brown foci for melanotic 'teratoid' elements). Some or all of these sections may also meet the requirement for marginal material. It is very desirable to photograph the gross specimen and to diagram {map} the precise source of the samples.

14.1.2 Pathology Submission Requirements

All materials must be submitted with the following identification:

- COG Registration Number
- Surgical Pathology ID (SPID) Number
- Block Number

The following items from each surgical procedure must also be submitted:

Pathology Report
Pathology Checklist
Operative report
Specimen Transmittal Form (Stage I & II tumors use specific form for rapid review submission available on AHEP0731 protocol page on COG website; all other submissions use the COG Generic Specimen Transmittal form)
Any gross image with mapping if performed

14.1.3 Shipping Addresses

Please see the link below for guidelines on which courier account to use when sending rapid central pathology review materials: https://members.childrensoncologygroup.org/_files/reference/FEDEXmemo.pdf. All other materials should be sent by regular mail or using your own courier account.

BPC Shipment Address:
COG Biopathology Center
Nationwide Children's Hospital
700 Children's Drive, Room WA 1340
Columbus, OH 43205
Phone: (614) 722-2894
Email:BPCParaffinTeam@nationwidechildrens.org

Shipping address for JPLT Institutions Only:
Japanese Children Cancer Group (JCCG) Pathology Center
National Center for Child Health and Development
National Medical Center for Children and Mothers Research Institute
2-10-1 Okura Setagaya-ku Tokyo, 157-8535 Japan
Phone: 03-3416-0181
Email: nakagawa-a@ncchd.go.jp

14.2 **Biology Studies**

The submission of diverse tumor and corresponding normal tissue for biologic studies is strongly encouraged. Please submit biology specimens using ABTR01B1 or other appropriate study.

## 15.0 IMAGING STUDIES REQUIRED AND GUIDELINES FOR OBTAINING

15.1 **Primary Site Imaging**

The same modality used at baseline should be used for all follow-up imaging.

15.1.1 Primary Site Computed Tomography

1. All CT scans should be done with technical factors using the lowest radiation exposure possible (ALARA principle) that allow optimal image quality.
2. CT slice *acquisition* thickness should be 1.5 mm or less.
3. Post-contrast IV enhanced portal venous phase abdominal and pelvic CT should be performed from just above the diaphragm to the symphysis pubis. Dual phase (arterial and portal venous) abdominal CT is strongly recommended.
4. Oral contrast is strongly recommended.

15.1.2 Primary Site Magnetic Resonance Imaging

Axial images and coronal images of the liver tumor should be acquired with at least two pulse sequences, including T1 and either fat-suppressed T2, STIR, or fat-suppressed fast/turbo imaging. Gadolinium should be given if appropriate and if there is normal renal function. After contrast administration T1W, fat-suppressed, axial images should be obtained. Based on patient age, images may be non-breath-hold or breath-hold, including respiratory triggered or respiratory gated.

Dual phase MRI may be performed at the discretion of the local radiologist. To perform dual phase MR, gadolinium-enhanced imaging is performed in combination with dynamic gradient echo sequences. After

contrast agent injection, images are obtained through the liver during the arterial phase (20 to 30 seconds post injection), portal venous phase (60 to 80 seconds after injection), and at equilibrium (3 to 5 minutes after injection). Delayed images can be obtained if needed for further lesion characterization.

### 15.2 Metastatic Site Imaging

Chest CT is required to evaluate metastatic disease. Chest CT may be performed without intravenous contrast material. The diameter of a "measurable" nodule should be at least twice the reconstructed slice thickness. Smaller nodules are considered detectable, but will be counted as "non-measurable. Bone scan is not required but should be considered in symptomatic patients with bone pain or bone lesions. Metastatic disease to bone and bone marrow is extremely rare and should only be considered if the patient is symptomatic with unexplained bone pain or unexplained cytopenias.

### 15.3 Timing of Imaging

Real Time Review:

- The Stratum 4 (upfront window therapy) patients will have a real-time central review of response using RECIST by one of the study committee radiologists. This review will be performed after Cycle 2. Baseline and post cycle 2 images must be submitted to IROC RI (QARC) as soon as the post Cycle 2 imaging is acquired. Baseline imaging can be submitted when performed or included with the post Cycle 2 imaging.

Retrospective Reviews:

- PRETEXT at diagnosis for all patients (to establish concordance between local and central grouping) will be performed by a panel of pediatric surgeons and radiologists.
- POST-TEXT for Stage III and IV patients after window therapy and after all subsequent imaging (to compare concordance between local and central grouping and compare with surgical/pathologic staging) will be performed by a panel of pediatric surgeons and radiologists.

All patients with tumors that are only biopsied initially will have CT and/or MRI scans performed at the time points noted below. Patients will all have abdominal ultrasounds performed at diagnosis (to evaluate the IVC and portal vein) if reconstructed CT MIP or VRT images of the portal vein are inadequate to exclude thrombus. Patients with tumor/thrombus in blood vessels at diagnosis should have repeat examinations using the same confirmatory imaging modality after Cycles 2 and 4 of C5VD.

Imaging studies as noted below for **all** Stratum 4 patient (high risk) should be submitted **immediately** after acquisition of the post Cycle 2 scans as further treatment will be determined by central review. Results of the central review will be entered into the COG eRDE system.

All other imaging studies should be submitted to IROC RI (QARC) **within 1 month** of obtaining the scans. These scans will be reviewed retrospectively. Therapy decisions at these time points are not based on central review.

The following imaging studies with the corresponding radiology reports should be submitted as noted below:

| **Stratum 1** Radiologic Studies to be Submitted | Baseline |
|---|---|
| Primary tumor evaluation (CT and/or MRI)[1] | X[3] |
| Metastatic tumor evaluation (CT chest) | X[3] |
| Abdominal ultrasound[2] | X[3] |

| **Stratum 2** Radiologic Studies to be Submitted | Baseline | End of Therapy |
|---|---|---|
| Primary tumor evaluation (CT and/or MRI)[1] | X[3] | X |
| Metastatic tumor evaluation (CT chest) | X[3] | X |
| Abdominal ultrasound[2] | X[3] | |

| **Stratum 3** Radiologic Studies to be Submitted | Baseline | End of Cycle 2 | End of Cycle 4 | End of Therapy |
|---|---|---|---|---|
| Primary tumor evaluation (CT and/or MRI)[1] | X[3] | X[4] | X[4] | X |
| Metastatic tumor evaluation (CT chest) | X[3] | | X[4] | |
| Abdominal ultrasound[2] | X[3] | X[2] | X[2] | |

| **All Stratum 4** patients Radiologic Studies to be Submitted | Baseline | **End of Cycle 2 (submitted for real time review of response)** |
|---|---|---|
| Primary tumor evaluation (CT and/or MRI)[1] | X[3] | X[4] |
| Metastatic tumor evaluation (CT chest) | X[3] | X[4] |
| Abdominal ultrasound[2] | X[3] | X[2] |

| **Stratum 4 Non Responders** Additional Radiologic Studies to be Submitted | End of Cycle 4 | End of Cycle 6 | End of Therapy |
|---|---|---|---|
| Primary tumor evaluation (CT and/or MRI)[1] | X[4] | X[4] | X[4] |
| Metastatic tumor evaluation (CT chest) | X[4] | X[4] | X[4] |
| Abdominal ultrasound[2] | X[2] | X[2] | X[2] |

| **Stratum 4 Responders** Additional Radiologic Studies to be Submitted | End of Cycle 4 | End of Cycle 6 | End of Therapy |
|---|---|---|---|
| Primary tumor evaluation (CT and/or MRI)[1] | X[4] | X[4] | X[4] |
| Metastatic tumor evaluation (CT chest) | X[4] | X[4] | X[4] |
| Abdominal ultrasound[2] | X[2] | X[2] | X[2] |

1 The same modality should be used each time for consistency.

2 Ultrasound only needs to be repeated if initial U/S showed tumor thrombus & does not need to be performed once thrombus has resolved or surgery performed.

3 Tumor evaluation, including ultrasound, may be done within 28 days prior to enrollment and must be submitted within one month from diagnosis.
4 Tumor disease evaluation performed after VIT Cycle 2 and after Cycles 4, 6 & 8 for non-responders and after Cycles 4, 6, and 10 for responders until tumor removed. No scans required once all tumor has been removed or resolved until the end of therapy. Scans should be submitted immediately after VIT Cycle 2 for central review while all other timepoints should be submitted within 1 month of each set of scans

### 15.4 Image Submission and Review

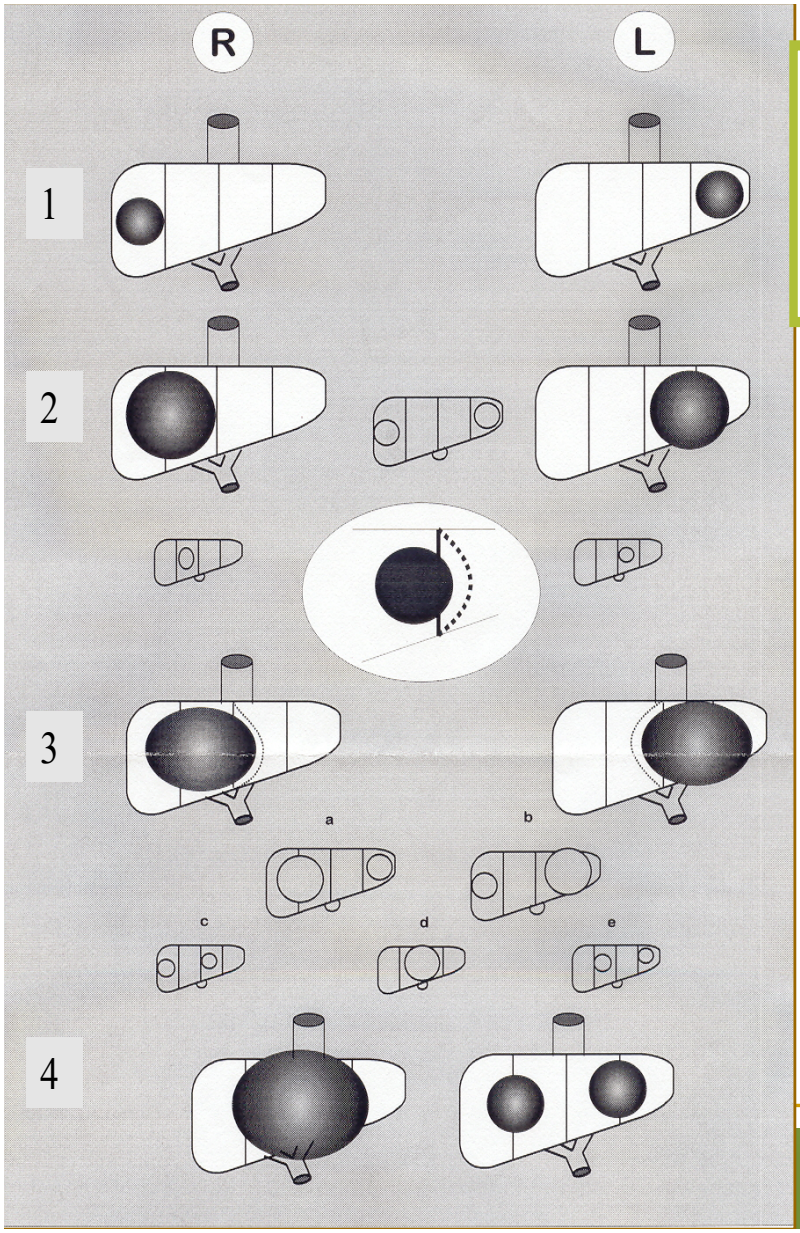
Submission of Diagnostic Imaging data in digital format is required. Digital files must be in DICOM format. These files can be submitted via sFTP. Information for obtaining an sFTP account and submission instructions can be found at www.QARC.org. Follow the link labeled digital data. Alternatively, if sFTP is not feasible, the imaging may be burned to a CD and mailed to IROC RI (QARC). Multiple studies for the same patient may be submitted on one CD; however, please submit only one patient per CD. Sites using DICOMmunicator may submit imaging via that application. Contact IROC RI (QARC) with questions or for additional information. Diagnostic Imaging reports may be submitted with the scans or electronically.

**Note for JPLT sites:** do not submit material directly to IROC-RI, instead send materials to the _JPLT Center shipping address provided below.

If submitted via CD send to:
IROC Rhode Island QA Center
Building B, Suite 201
640 George Washington Highway
Lincoln, Rhode Island 02865-4207
Phone: (401) 753-7600
Fax: (401) 753-7601 or E-mail to DataSubmission@QARC.org

Shipping address for JPLT Institutions Only:
JPLT Center
National Center for Basic Research and Development (NBRAD)
Hiroshima University
1-2-3, Kasumi, Minami-ku Hiroshima, 734-8551 Japan
Phone: 082-257-5416
Email: jplt@hiroshima-u.ac.jp

## APPENDIX I: PRETEXT SURGICAL RESECTION GUIDELINES




# PRETEXT

or

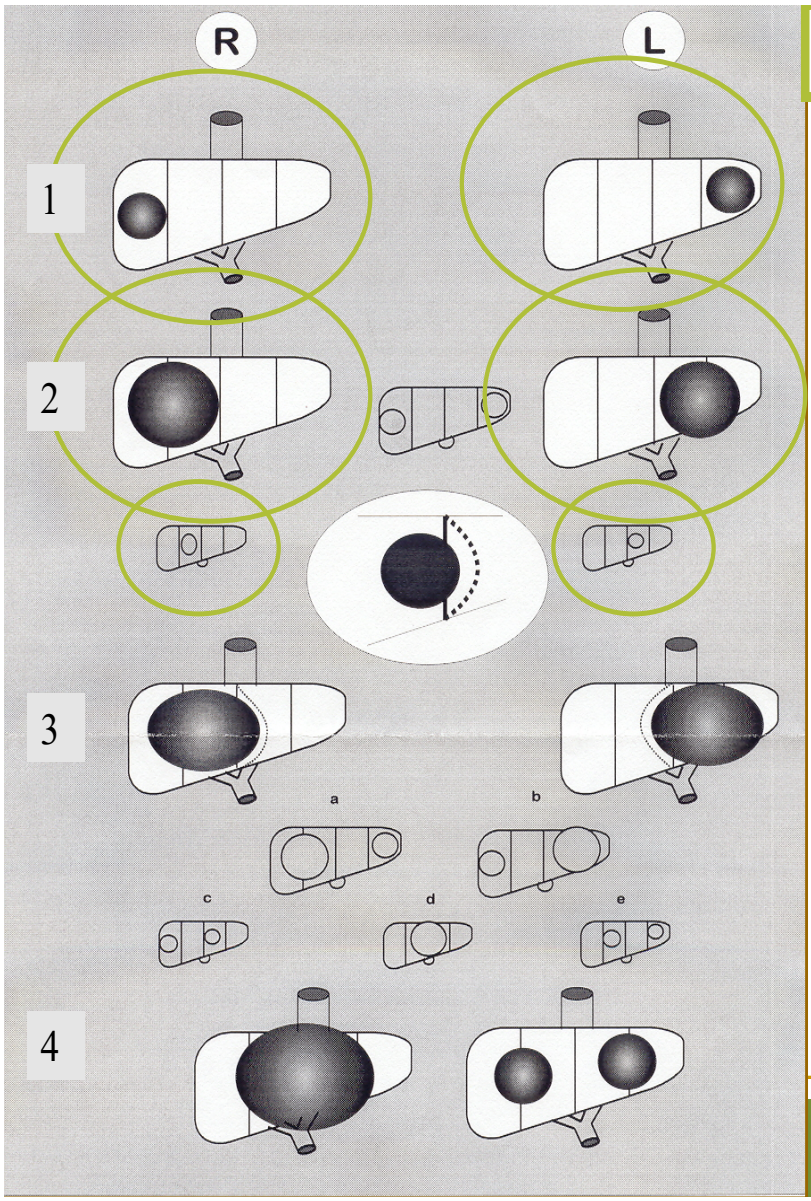
POST-TEXT if assigned after chemotherapy

| | |
|---|---|
| 1 | 3 contiguous free sections |
| 2 | 2 contiguous free sections |
| 3 | 1 contiguous free section |
| 4 | no free sections |

Any group may have **involvement of:**

| | |
|---|---|
| V | vena cava or all 3 hepatic veins |
| P | main portal or portal bifurcation vein |
| C | caudate |
| E | extrahepatic, contiguous |
| M | distant metastatic |

CureSearch Children's Oncology Group




AHEP 0731 Surgical Resection Guidelines

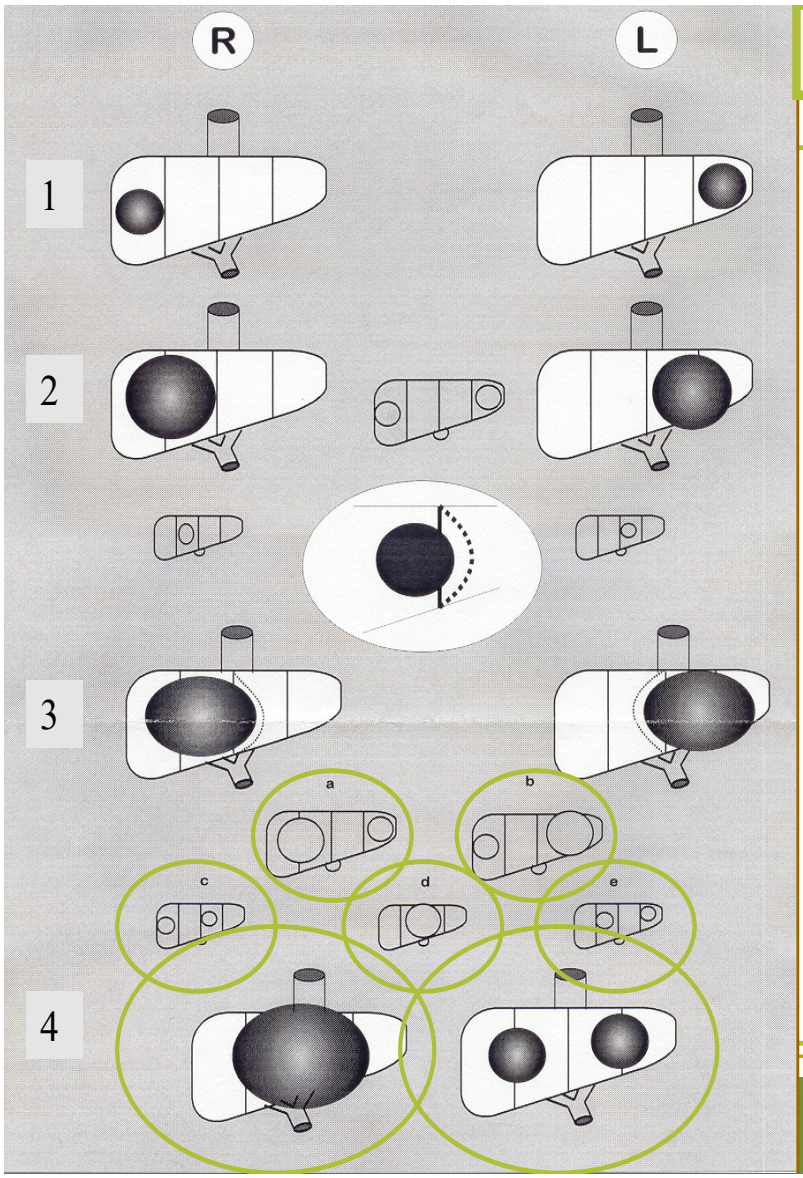
## Resect at Diagnosis

Easy lobectomy with > 1 cm margin:

- PRETEXT 1
- PRETEXT 2

Diagnosis CT shows unifocal tumor with at least 1cm clear radiographic margin from middle hepatic vein and portal bifurcation

CureSearch Children's Oncology Group




AHEP 0731 Surgical Resection Guidelines

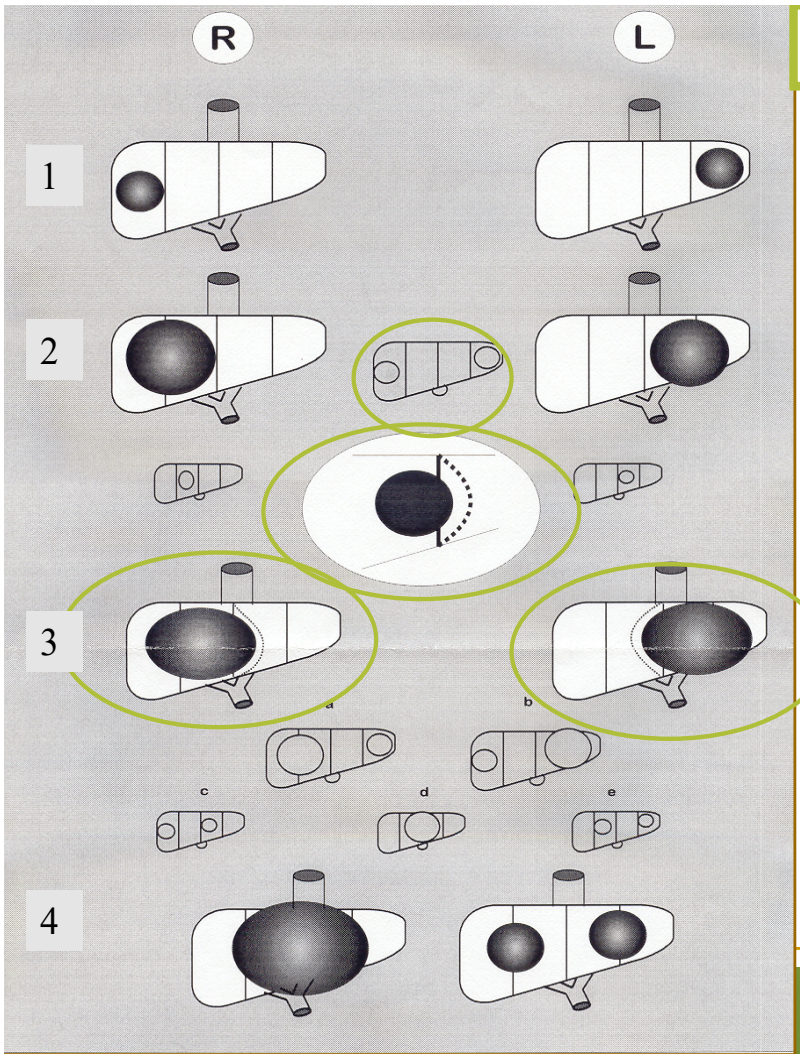
## Biopsy and Refer at Diagnosis

Tumor expected to require liver transplantation or extreme, complex liver resection

- multifocal PRETEXT 3 or 4
- PRETEXT 3 +V, +P
- PRETEXT 4

Consultation with liver program to complete transplant evaluation and listing with goal of transplant on or before completion of four cycles neoadjuvant chemotherapy

CureSearch Children's Oncology Group




AHEP 0731 Surgical Resection Guidelines

## Biopsy at Diagnosis Neoadjuvant Chemotherapy

POST-TEXT => Repeat CT Scan after 2nd cycle chemotherapy

* Resect after 2nd cycle chemo
  - POST-TEXT 1
  - POST-TEXT 2 if there is > 1cm radiographic margin on middle hepatic vein and portal bifurcation

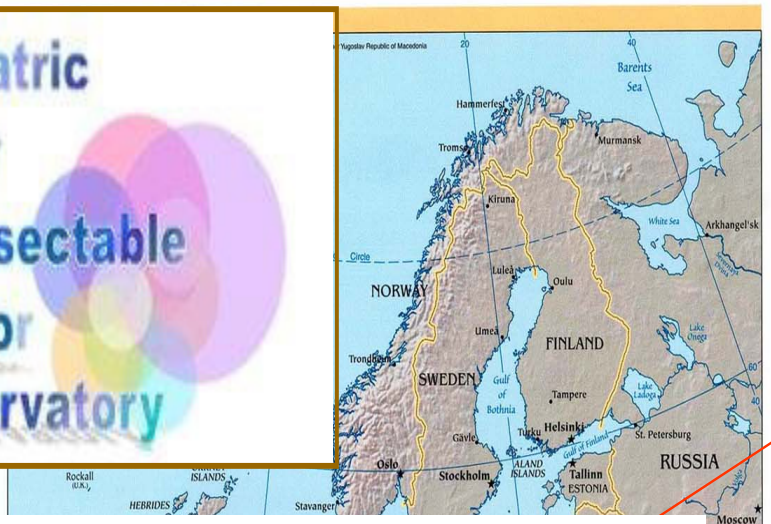
** Resect after 4th cycle chemo
  - POST-TEXT 2 < 1 cm margin
  - POST-TEXT 3

*** Refer to liver center
  - POST-TEXT 3 +V, +P

Consultation with liver program to complete transplant evaluation and listing with goal of transplant on or before completion of four cycles neoadjuvant chemotherapy

CureSearch Children's Oncology Group

Pediatric Liver Unresectable Tumor Observatory



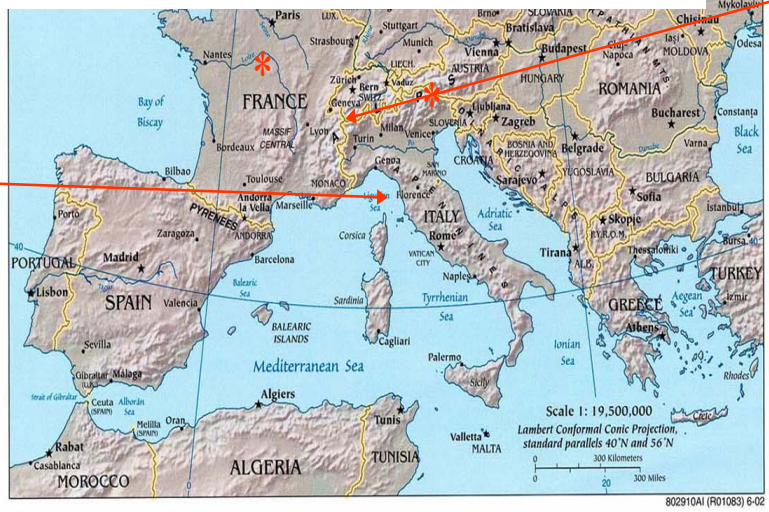

# Liver Transplant for Tumor Data Base - Registry
# http://pluto.cineca.org

PLUTO Project Director Jean-Bernard Otte, Brussels, Belgium

Statistical office: Berne, Switzerland

CINECA
Consorzio Interuniversitario

WEB System headquarter: Bologna, Italy




SIOPEL
Childhood Liver Tumours Strategy Group - SIOPEL

IPTA

Astellas

CureSearch
Children's Cancer Group

CureSearch
Children's Oncology Group

## APPENDIX II: YOUTH INFORMATION SHEET

### INFORMATION SHEET REGARDING RESEARCH STUDY AHEP0731
### (for children from 7 through 12 years of age)

*Special Studies to Learn More About a Liver Tumor called Hepatoblastoma and How to Treat It*

1. We have been talking with you about hepatoblastoma. Hepatoblastoma is a type of cancer (tumor) that grows in the liver, which is on the upper right side of your belly area. After doing tests, we have found that you have this type of cancer.

2. We are asking you to take part in a research study because you have hepatoblastoma. A research study is when doctors work together to try out new ways to help people who are sick. This study is trying to safely change the amount of treatment that children with hepatoblastoma need. This is why we are doing this study.

3. Some children, who have surgery to remove their entire tumor, may not need any further treatment. Other children will need treatment with chemotherapy. (Chemotherapy is a type of strong medicine that destroys cancer cells). If the cancer cannot be removed when it is first discovered or has spread to other organs you may need more chemotherapy medicines over a longer period of time.

4. Some children who are part of this study will have surgery and then will need blood tests occasionally to make sure they are doing OK. Some children will be treated with chemotherapy. The chemotherapy may be given for 6 to 36 weeks, depending on the features of your cancer. If the tumor cannot be removed when it is first discovered you will be treated with chemotherapy and have frequent blood tests and scans to see if the tumor is getting smaller.

5. Sometimes good things can happen to people when they are in a research study. These good things are called “benefits”. We hope that being part of this study may have benefits for you.

6. Sometimes bad things can happen to people when they are in a research study. These bad things are called “risks”. Other things may happen to you that we don’t yet know about. Depending on the kind of tumor you have, your study doctors may give you less or more treatment than has been normally given to adolescents and children with hepatoblastoma. It is possible that giving less treatment may not work as well at getting rid of your cancer. It is possible that giving more treatment may cause more side effects.

7. Your family can choose to be part of this study or not. Your family can also decide to stop being in this study at any time once you start. There may be other treatments for your illness. Your doctor can tell you about them. Ask your doctors any questions that you have.

**INFORMATION SHEET REGARDING RESEARCH STUDY AHEP0731**
**(for teens from 13 through 17 years of age)**

*Special Studies to Learn more About a Liver Tumor called Hepatoblastoma and How to Treat It*

1. We have been talking with you about hepatoblastoma. Hepatoblastoma is a type of cancer that grows in the liver, which is on the upper right side of your abdomen. After doing tests, we have found that you have this type of cancer.

2. We are asking you to take part in a research study because you have hepatoblastoma. A research study is when doctors work together to try out new ways to help people who are sick. This study is trying to safely reduce the amount of treatment that children and teens with low-risk hepatoblastoma need. This study is also trying to improve the treatment for children and teens with high-risk hepatoblastoma by adding a new medication to the regular treatment. The term, risk, refers to the chance of the cancer coming back after treatment This is why we are doing this study.

3. Some children and teens, who have surgery to remove their entire tumor, may not need any further treatment. Other children will need treatment with chemotherapy. (Chemotherapy is a type of strong medicine that destroys cancer cells). If the cancer cannot be removed when it is first discovered or has spread to other organs you may need more chemotherapy medicines over a longer period of time. If all of the tumor could not be removed when you were diagnosed, you may need a second surgery or maybe even a liver transplant. You may need to go to another hospital, where there are doctors who specialize in liver surgery or liver transplant.

4. Some children and teens who are part of this study will have surgery and then will need blood tests occasionally to make sure they are doing OK. Some teens and children will be treated with chemotherapy. The chemotherapy may be given for about 6 to 36 weeks, depending on the features of your cancer. If the tumor cannot be removed when it is first discovered you will be treated with chemotherapy and have frequent blood tests and scans to see if the tumor is getting smaller.

5. Sometimes good things can happen to people when they are in a research study. These good things are called “benefits”. We hope that being part of this study may have benefits for you. We don’t know for sure if there is any benefit of being part of this study.

6. Sometimes bad things can happen to people when they are in a research study. These bad things are called “risks”. Things may happen to you that we don’t yet know about. Depending on the kind of tumor you have, your study doctors may give you less or more treatment than has been normally given to adolescents and children with hepatoblastoma. It is possible that giving less treatment may not work as well at getting rid of your cancer. It is possible that giving more treatment may cause more side effects.

7. Your family can choose to be part of this study or not. Your family can also decide to stop being in this study at any time once you start. There may be other treatments for your illness that your doctor can tell you about. Ask your doctors any questions that you have.

## APPENDIX III: SURGICAL STAGING OF PRIMARY TUMOR AT TIME OF INITIAL SURGERY

Patients are staged for risk classification and treatment using COG staging guidelines as listed below:

**Stage I:** completely resected tumors.
Note: all Stage I tumors require rapid pathology review prior to enrollment.

**Stage II:** grossly resected tumors with evidence of microscopic residual.
Resected tumors with microscopic positive margins or pre-operative (intra-operative) rupture.
Note: all Stage II tumors require rapid pathology review prior to enrollment.

**Stage III:** unresectable tumors
Partially resected tumors with measurable tumor left behind or patients with abdominal lymph node involvement.

**Stage IV:** metastatic disease to lungs, other organs or sites distant from the abdomen.

PFH tumors are entirely composed of a purely fetal histologic pattern with a low mitotic index defined as ≤ 2 mitoses/10 high power fields

SCU tumors are tumors with any amount of small cell undifferentiated cells detected.

## APPENDIX IV: UNACCEPTABLE ENZYME INDUCING AND RECOMMENDED NON-ENZYME INDUCING ANTICONVULSANTS

Note: This concomitant medication restriction is applicable only for Stratum 4 (High Risk) patients.

| **Recommended Non-enzyme inducing anticonvulsants** | |
|---|---|
| *Generic Name* | *U.S. Trade Name* |
| Gabapentin | Neurontin |
| Lamotrigine | Lamictal |
| Levetiracetam | Keppra |
| Tigabine | Gabitril |
| Topiramate | Topamax |
| Valproic Acid | Depakote, Depakene |
| Zonisamide | Zonegran |
| **Unacceptable Enzyme inducing anticonvulsants** | |
| *Generic Name* | *U.S.Trade Name* |
| Carbamazepine | Tegretol |
| Felbamate | Felbatol |
| Phenobarbital | Phenobarbital |
| Phenytoin | Dilantin |
| Primidone | Mysoline |
| Oxcarbazepine | Trileptal |

## APPENDIX V: CYP3A4 INDUCERS AND INHIBITORS

Note: This concomitant medication restriction is applicable only for Stratum 4 (High Risk) patients.

The use of the following medications should be discontinued prior to initiation of protocol therapy and should be avoided during protocol therapy if reasonable alternatives exist. This list may not be comprehensive. Additional information about this list can be found at the following site: http://medicine.iupui.edu/clinpharm/ddis/table.aspx

| Strong Inhibitors | Moderate Inhibitors | Weak Inhibitors | Other Inhibitors | Inducers |
|---|---|---|---|---|
| Clarithromycin<br>Indinavir<br>Itraconazole<br>Ketoconazole<br>Posaconazole<br>Nefazodone<br>Nelfinavir<br>Ritonavir<br>Saquinavir<br>Telithromycin | Aprepitant<br>Diltiazem<br>Erythromycin<br>Fluconazole<br>Grapefruit<br>Juice<br>Verapamil | Cimetidine | Amiodarone<br>Boceprevir<br>Chloramphenicol<br>Ciprofloxacin<br>Delaviridine<br>Fluvoxamine<br>Imatinib<br>Norfloxacin<br>Norfluoxetine<br>(fluoxetine)<br>Starfruit<br>Telaprevir<br>Voriconazole | Barbiturates<br>Carbamazepine<br>Efavirenz<br>Glucocorticoids<br>Modanfinil<br>Nevirapine<br>Oxcarbazepine<br>Phenobarbital<br>Phenytoin<br>Pioglitazone<br>Rifabutin<br>Rifampin<br>St. John's wort<br>Troglitazone |

# APPENDIX VI: CTEP REGISTRATION PROCEDURES

## CTEP Investigator Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all investigators participating in any NCI-sponsored clinical trial to register and to renew their registration annually.

Registration requires the submission of:

- a completed ***Statement of Investigator Form*** (FDA Form 1572) with an original signature
- a current Curriculum Vitae (CV)
- a completed and signed ***Supplemental Investigator Data Form*** (IDF)
- a completed ***Financial Disclosure Form*** (FDF) with an original signature

Fillable PDF forms and additional information can be found on the CTEP website at <http://ctep.cancer.gov/investigatorResources/investigator_registration.htm>. For questions, please contact the ***CTEP Investigator Registration Help Desk*** by email at <pmbregpend@ctep.nci.nih.gov>.

## CTEP Associate Registration Procedures / CTEP-IAM Account

The Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) application is a web-based application intended for use by both Investigators (i.e., all physicians involved in the conduct of NCI-sponsored clinical trials) and Associates (i.e., all staff involved in the conduct of NCI-sponsored clinical trials).

Associates will use the CTEP-IAM application to register (both initial registration and annual re-registration) with CTEP and to obtain a user account.

Investigators will use the CTEP-IAM application to obtain a user account only. (See CTEP Investigator Registration Procedures above for information on registering with CTEP as an Investigator, which must be completed before a CTEP-IAM account can be requested.)

An active CTEP-IAM user account will be needed to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications, including the CTSU members' website.

Additional information can be found on the CTEP website at <http://ctep.cancer.gov/branches/pmb/associate_registration.htm>. For questions, please contact the ***CTEP Associate Registration Help Desk*** by email at <ctepreghelp@ctep.nci.nih.gov>.

## APPENDIX VII: JPLT SITE SPECIFIC INFORMATION

Japanese Data Safety Committee

Serious Adverse Reaction (SAR) Reports will be reviewed by the Japanese Data Safety Committee (DSC) for patients enrolled on AHEP0731 in Japan. Review of SAR reports is in addition to COG Data Safety Committee review of Serious Adverse Events (SAE) Reports. The Japanese DSC serves as a local advisory committee to ensure Japanese patient safety according to the Independent Data Monitoring Guideline in Japan.

**REFERENCES**

1. Exelby PR, Filler RM, Grosfeld JL: Liver tumors in children in the particular reference to hepatoblastoma and hepatocellular carcinoma: American Academy of Pediatrics Surgical Section Survey--1974. J Pediatr Surg 10:329-37, 1975
2. Katzenstein HM, London WB, Douglass EC, et al: Treatment of unresectable and metastatic hepatoblastoma: a pediatric oncology group phase II study. J Clin Oncol 20:3438-44, 2002
3. Perilongo G, Shafford E, Maibach R, et al: Risk-adapted treatment for childhood hepatoblastoma. final report of the second study of the International Society of Paediatric Oncology--SIOPEL 2. Eur J Cancer 40:411-21, 2004
4. Haas JE, Muczynski KA, Krailo M, et al: Histopathology and prognosis in childhood hepatoblastoma and hepatocarcinoma. Cancer 64:1082-95, 1989
5. Haas JE, Feusner JH, Finegold MJ: Small cell undifferentiated histology in hepatoblastoma may be unfavorable. Cancer 92:3130-4, 2001
6. Ortega JA, Douglass EC, Feusner JH, et al: Randomized comparison of cisplatin/vincristine/fluorouracil and cisplatin/continuous infusion doxorubicin for treatment of pediatric hepatoblastoma: A report from the Children's Cancer Group and the Pediatric Oncology Group. J Clin Oncol 18:2665-75, 2000
7. Fuchs J, Rydzynski J, Von Schweinitz D, et al: Pretreatment prognostic factors and treatment results in children with hepatoblastoma: a report from the German Cooperative Pediatric Liver Tumor Study HB 94. Cancer 95:172-82, 2002
8. Pritchard J, Brown J, Shafford E, et al: Cisplatin, doxorubicin, and delayed surgery for childhood hepatoblastoma: a successful approach--results of the first prospective study of the International Society of Pediatric Oncology. J Clin Oncol 18:3819-28, 2000
9. Douglass EC, Green AA, Wrenn E, et al: Effective cisplatin (DDP) based chemotherapy in the treatment of hepatoblastoma. Med Pediatr Oncol 13:187-90, 1985
10. Black CT, Cangir A, Choroszy M, et al: Marked response to preoperative high-dose cis-platinum in children with unresectable hepatoblastoma. J Pediatr Surg 26:1070-3, 1991
11. Fuchs J, Bode U, von Schweinitz D, et al: Analysis of treatment efficiency of carboplatin and etoposide in combination with radical surgery in advanced and recurrent childhood hepatoblastoma: a report of the German Cooperative Pediatric Liver Tumor Study HB 89 and HB 94. Klin Padiatr 211:305-9, 1999
12. Evans AE, Land VJ, Newton WA, et al: Combination chemotherapy (vincristine, adriamycin, cyclophosphamide, and 5-fluorouracil) in the treatment of children with malignant hepatoma. Cancer 50:821-6, 1982
13. Ortega JA, Krailo MD, Haas JE, et al: Effective treatment of unresectable or metastatic hepatoblastoma with cisplatin and continuous infusion doxorubicin chemotherapy: a report from the Childrens Cancer Study Group. J Clin Oncol 9:2167-76, 1991
14. Brown J, Perilongo G, Shafford E, et al: Pretreatment prognostic factors for children with hepatoblastoma-- results from the International Society of Paediatric Oncology (SIOP) study SIOPEL 1. Eur J Cancer 36:1418-25, 2000
15. Perilongo G, Brown J, Shafford E, et al: Hepatoblastoma presenting with lung metastases: treatment results of the first cooperative, prospective study of the International Society of Paediatric Oncology on childhood liver tumors. Cancer 89:1845-53, 2000
16. Tomlinson GE, Douglass EC, Pollock BH, et al: Cytogenetic evaluation of a large series of hepatoblastoma:numerical abnormalities with recurring aberrations involving 1q12-q21. Genes Chromosomes Cancer 44(2):177-84, 2005

17. Terracciano LM, Bernasconi B, Ruck P, et al: Comparative genomic hybridization analysis of hepatoblastoma reveals high frequency of X-chromosome gains and similarities between epithelial and stromal components. Hum Pathol 34(9):864-71, 2003
18. Surace C, Leszl A, Perilongo G, et al: Fluorescent in situ hybridization (FISH) reveals frequent and recurrent numerical and structural abnormalities in hepatoblastoma with no informative karyotype. Med Pediatr Oncol 39(5):536-9, 2002
19. Yeh YA, Rao PH, Cigna CT, et al: Trisomy 1q, 2, and 20 in a case of hepatoblastoma: possible significance of 2q35-q37 and 1q12-q21 rearrangements. Cancer Genet Cytogenet 123(2):140-3, 2000
20. Tomlinson GE, Chen T, Zhang J, et al: NOTCH2, a developmental gene involved in hepatic maturation, is disrupted in hepatoblastoma. AACR Ann. Meeting, 2006
21. Zsiros J, Maibach R, Brock P, et al: Initial low AFP level predicts a bad prognosis in high-risk hepatoblastoma: Treatment results of two consecutive Trials – SIOPEL-2 and 3. 37th annual meeting of SIOP. 2005
22. Hansen K, Bagtas J, Mark HF, et al: Undifferentiated small cell hepatoblastoma with a unique chromosomal translocation: a case report. Pediatr Pathol 12:457-62, 1992
23. Gunawan B, Schafer KL, Sattler B, et al: Undifferentiated small cell hepatoblastoma with a chromosomal translocation t(22;22)(q11;q13). Histopathology 40:485-7, 2002
24. Trobaugh-Lotrario AD, Tomlinson GE, Finegold MJ, et al: Small cell undifferentiated variant of hepatoblastoma: Adverse clinical and molecular features similar to rhabdoid tumors. Ped Blood Cancer 2008
25. Stringer MD, Hennayake S, Howard ER, et al: Improved outcome for children with hepatoblastoma. Br J Surg 82:386-91, 1995
26. Malogolowkin MH, Katzenstein H, Krailo MD, et al: Intensified platinum therapy is an ineffective strategy for improving outcome in pediatric patients with advanced hepatoblastoma. J Clin Oncol 24:2879-84, 2006
27. von Schweinitz D, Byrd DJ, Hecker H, et al: Efficiency and toxicity of ifosfamide, cisplatin and doxorubicin in the treatment of childhood hepatoblastoma. Study Committee of the Cooperative Paediatric Liver Tumour Study HB89 of the German Society for Paediatric Oncology and Haematology. Eur J Cancer 33:1243-9, 1997
28. Simpson C, Herr H, Courville KA: Concurrent therapies that protect against doxorubicin-induced cardiomyopathy. Clin J Oncol Nurs 8:497-501, 2004
29. Wexler LH: Ameliorating anthracycline cardiotoxicity in children with cancer: clinical trials with dexrazoxane. Semin Oncol 25:86-92, 1998
30. Lipshultz SE, Giantris AL, Lipsitz SR, et al: Doxorubicin administration by continuous infusion is not cardioprotective: the Dana-Farber 91-01 Acute Lymphoblastic Leukemia protocol. J Clin Oncol 20:1677-82, 2002
31. von Schweinitz D, Hecker H, Harms D, et al: Complete resection before development of drug resistance is essential for survival from advanced hepatoblastoma--a report from the German Cooperative Pediatric Liver Tumor Study HB-89. J Pediatr Surg 30:845-52, 1995
32. Zsiros J, Maibach R, Shafford E, et al: Successful treatment of childhood high-risk hepatoblastoma with dose-intensive multiagent chemotherapy and surgery: final results of the SIOPEL-3HR study. J Clin Oncol 28:2584-90, 2010
33. Furman WL, Stewart CF, Poquette CA, et al: Direct translation of a protracted irinotecan schedule from a xenograft model to a phase I trial in children. J Clin Oncol 17:1815-24, 1999
34. Rodriguez-Galindo C, Radomski K, Stewart CF, et al: Clinical use of topoisomerase I inhibitors in anticancer treatment. Med Pediatr Oncol 35:385-402, 2000
35. Ma MK, Zamboni WC, Radomski KM, et al: Pharmacokinetics of irinotecan and its metabolites SN-38 and APC in children with recurrent solid tumors after protracted low-dose irinotecan. Clin Cancer Res 6:813-9, 2000

36. Palmer RD, Williams DM: Dramatic response of multiply relapsed hepatoblastoma to irinotecan (CPT-11). Med Pediatr Oncol 41:78-80, 2003
37. Katzenstein HM, Rigsby C, Shaw PH, et al: Novel therapeutic approaches in the treatment of children with hepatoblastoma. J Pediatr Hematol Oncol 24:751-5, 2002
38. Bjornsti M-A, Houghton PJ: The TOR pathway: a target for cancer therapy. Nat Rev Cancer 4:335-348, 2004
39. Jacinto E, Hall MN: Tor signalling in bugs, brain and brawn. Nat Rev Mol Cell Biol 4:117-126, 2003
40. Wan X, Shen N, Mendoza A, et al: CCI-779 inhibits rhabdomyosarcoma xenograft growth by an antiangiogenic mechanism linked to the targeting of mTOR/Hif-1alpha/VEGF signaling. Neoplasia 8:394-401, 2006
41. Land SC, Tee AR: Hypoxia-inducible factor 1alpha is regulated by the mammalian target of rapamycin (mTOR) via an mTOR signaling motif. J Biol Chem 282:20534-20543, 2007
42. Abraham RT: mTOR as a positive regulator of tumor cell responses to hypoxia. Curr Top Microbiol Immunol 279:299-319, 2004
43. Hosoi H, Dilling MB, Liu LN, et al: Studies on the mechanism of resistance to rapamycin in human cancer cells. Mol Pharmacol 54:815-824, 1998
44. Misawa A, Hosoi H, Tsuchiya K, et al: Rapamycin inhibits proliferation of human neuroblastoma cells without suppression of MycN. Int J Cancer 104:233-237, 2003
45. Mondesire WH, Jian W, Zhang H, et al: Targeting mammalian target of rapamycin synergistically enhances chemotherapy-induced cytotoxicity in breast cancer cells. Clin Cancer Res 10:7031-7042, 2004
46. Geoerger B, Kerr K, Tang CB, et al: Antitumor activity of the rapamycin analog CCI-779 in human primitive neuroectodermal tumor/medulloblastoma models as single agent and in combination chemotherapy. Cancer Res 61:1527-1532, 2001
47. Wagner F, Henningsen B, Lederer C, et al: Rapamycin blocks hepatoblastoma growth in vitro and in vivo implicating new treatment options in high-risk patients. Eur J Cancer, 2012
48. Spunt SL, Grupp SA, Vik TA, et al: Phase I study of temsirolimus in pediatric patients with recurrent/refractory solid tumors. J Clin Oncol 29:2933-2940, 2011
49. Pencreach E, Guerin E, Nicolet C, et al: Marked activity of irinotecan and rapamycin combination toward colon cancer cells in vivo and in vitro is mediated through cooperative modulation of the mammalian target of rapamycin/hypoxia-inducible factor-1alpha axis. Clin Cancer Res 15:1297-307, 2009
50. Rochelle Bagatell, Robin Elizabeth Norris, Ashish M Ingle, et al: Phase I trial of temsirolimus (TEM), irinotecan (IRN), and temozolomide (TMZ) in children with refractory solid tumors: A Children's Oncology Group study. Journal of Clinical Oncology, 2012 ASCO Annual Meeting Proceedings (Post-Meeting Edition) Vol 30, No 15_suppl (May 20 Supplement), 2012: 9540
51. Van Tornout JM, Buckley JD, Quinn JJ, et al: Timing and magnitude of decline in alpha-fetoprotein levels in treated children with unresectable or metastatic hepatoblastoma are predictors of outcome: a report from the Children's Cancer Group. J Clin Oncol 15:1190-7, 1997
52. von Schweinitz D: Identification of risk groups in hepatoblastoma--another step in optimising therapy. Eur J Cancer 36:1343-6, 2000
53. von Schweinitz D: Management of liver tumors in childhood. Semin Pediatr Surg 15:17-24, 2006
54. Aronson DC, Schnater JM, Staalman CR, et al: Predictive value of the pretreatment extent of disease system in hepatoblastoma: results from the International Society of Pediatric Oncology Liver Tumor Study Group SIOPEL-1 study. J Clin Oncol 23:1245-52, 2005
55. Dicken BJ, Bigam DL, Lees GM: Association between surgical margins and long-term outcome in advanced hepatoblastoma. J Pediatr Surg 39:721-5, 2004
56. Tiao GM, Bobey N, Allen S, et al: The current management of hepatoblastoma: a combination of chemotherapy, conventional resection, and liver transplantation. J Pediatr 146:204-11, 2005

57. Fuchs J, Rydzynski J, Hecker H, et al: The influence of preoperative chemotherapy and surgical technique in the treatment of hepatoblastoma--a report from the German Cooperative Liver Tumour Studies HB 89 and HB 94. Eur J Pediatr Surg 12:255-61, 2002
58. Towu E, Kiely E, Pierro A, et al: Outcome and complications after resection of hepatoblastoma. J Pediatr Surg 39:199-202; discussion 199-202, 2004
59. Czauderna P, Otte JB, Aronson DC, et al: Guidelines for surgical treatment of hepatoblastoma in the modern era--recommendations from the Childhood Liver Tumour Strategy Group of the International Society of Paediatric Oncology (SIOPEL). Eur J Cancer 41:1031-6, 2005
60. Reynolds M, Douglass EC, Finegold M, et al: Chemotherapy can convert unresectable hepatoblastoma. J Pediatr Surg 27:1080-3; discussion 1083-4, 1992
61. Ehrlich PF, Greenberg ML, Filler RM: Improved long-term survival with preoperative chemotherapy for hepatoblastoma. J Pediatr Surg 32:999-1002; discussion 1002-3, 1997
62. Seo T, Ando H, Watanabe Y, et al: Treatment of hepatoblastoma: less extensive hepatectomy after effective preoperative chemotherapy with cisplatin and adriamycin. Surgery 123:407-14, 1998
63. Otte JB, de Ville de Goyet J, Reding R, et al: Living related donor liver transplantation in children: the Brussels experience. Transplant Proc 28:2378-9, 1996
64. Otte JB, Pritchard J, Aronson DC, et al: Liver transplantation for hepatoblastoma: results from the International Society of Pediatric Oncology (SIOP) study SIOPEL-1 and review of the world experience. Pediatr Blood Cancer 42:74-83, 2004
65. Pimpalwar AP, Sharif K, Ramani P, et al: Strategy for hepatoblastoma management: Transplant versus nontransplant surgery. J Pediatr Surg 37:240-5, 2002
66. Schnater JM, Aronson DC, Plaschkes J, et al: Surgical view of the treatment of patients with hepatoblastoma: results from the first prospective trial of the International Society of Pediatric Oncology Liver Tumor Study Group. Cancer 94:1111-20, 2002
67. Vos A: Primary liver tumours in children. Eur J Surg Oncol 21:101-5, 1995
68. Feusner JH, Krailo MD, Haas JE, et al: Treatment of pulmonary metastases of initial stage I hepatoblastoma in childhood. Report from the Childrens Cancer Group. Cancer 71:859-64, 1993
69. Jassem N, Jones CM, Briscoe T, et al: The hook effect: a need for constant vigilance. Ann Clin Biochem 43:314-317, 2006
70. Kaplan EL, Meier P: Nonparametric estimation from incomplete observations. J Amer Statist Assoc 53 (282):457-481, 1958