April 2, 2018

Martha Kruhm, MS RAC
Head, Protocol and Information Office
Quality Assurance Section
CTEP, DCT, NCI
6130 Executive Blvd, EPN Room 7000
Bethesda, MD 20892

Dear Ms. Kruhm:

Enclosed is Addendum #11 to E1208, *A Phase III Randomized, Double-Blind Trial of Chemoembolization with or without Sorafenib in Unresectable Hepatocellular Carcinoma (HCC) in Patients with and without Vascular Invasion*.

The following revisions to E1208 protocol have been made in this addendum:

	Section	Change
1.	Cover Page	Updated Study Chair and updated Version Date.
2.	Contact Page	Updated Study Chair contact information.

The following revisions to E1208 Informed Consent Document have been made in this addendum:

	Section	Change
1.	Cover Page	Updated Version Date.

If you have any questions regarding this addendum, please contact spiers.madeline@jimmy.harvard.edu or 857-504-2900.

We request review and approval of this addendum to E1208 so ECOG-ACRIN may activate it promptly.

Thank you.

Sincerely,

Pamela Cogliano

Protocol Development Manager

28 State Street, Suite 1100, Boston, MA 02109 p: 857.504.2900 f: 617. 589.0914 ecog-acrin.org

Enclosure

CC: Al B. Benson, III, MD
Michael Soulen, MD
Mark Rosen, MD, PhD
Michael Choti, MD
Gregory Gores, MD
Kim Olthoff, MD
Jill Kolesar, PharmD
Paul Catalono, ScD
Peter O'Dwyer, MD
Bert O'Neil, MD
Melanie Thomas, MD
Mitesh Borad, MD
George Carro, RPh., MS, BCOP
Carol Chami,RN
Melinda Flood
Bruce Giantonio, MD
Kerry Higgins
Gayle Ipock
Jean MacDonald
Madeline Spiers
Lauren Lambert
Becky Fillingham
Stephanie C. Friedman, RPh
Ivan Reveles
Brad Hughes, PharmD

ECOG-ACRIN
cancer research group
Reshaping the future of patient care

E1208

A Phase III Randomized, Double-Blind Trial of Chemoembolization with or without Sorafenib in Unresectable Hepatocellular Carcinoma (HCC) in Patients with and without Vascular Invasion

Rev. 6/14
Rev.Add11

STUDY CHAIR:	Al B. Benson, III, M.D.
INTERVENTIONAL RADIOLOGY CO-CHAIR:	Michael Soulen, M.D.
DIAGNOSTIC RADIOLOGY CO-CHAIR:	Mark Rosen, M.D., Ph.D.
SURGERY CO-CHAIR:	Michael Choti, M.D.
GASTROENTEROLOGY CO-CHAIR:	Gregory Gores, M.D.
TRANSPLANT SURGERY CO-CHAIR:	Kim Olthoff, M.D.
PHARMACOGENOMIC CO-CHAIR:	Jill Kolesar, Pharm.D
STUDY STATISTICIAN:	Paul Catalano, Sc.D.
GI COMMITTEE CHAIR:	Al B. Benson, III, MD
CALGB CO-CHAIR:	Bert O'Neill, M.D.
SWOG CO-CHAIR:	Melanie Thomas, M.D.
Rev. 9/10 NCCTG CO-CHAIR	Mitesh Borad, M.D.

Version Date: April 2, 2018
NCI Update Date: December 22, 2010

Sorafenib/Placebo (NSC #724772) Supplied by the NCI for This Study

Rev. 9/10
6/14

STUDY PARTICIPANTS

ALLIANCE / Alliance for Clinical Trials in Oncology
NCIC-CTG / NCIC Clinical Trials Group
NRG / NRG Oncology Foundation, Inc
SWOG / SWOG

NOTE: This study is supported by the NCI Cancer Trials Support Unit (CTSU). Institutions not aligned with ECOG-ACRIN will participate through the CTSU mechanism.

ACTIVATION DATE

October 28, 2009

Update #1 – Incorporated prior to activation
Addendum #1 – 3/10
Addendum #2 – 9/10
Addendum #3 – 12/10
Update #2 – 12/10
Update #3 – 12/10
Addendum #4 – 5/11
Addendum #5 – 5/12
Addendum #6 – 6/14
Addendum #7 – 9/14
Addendum #8 – 12/14
Addendum #9 – 9/15
Addendum #10- 3/16
Addendum #11

Table of Contents

Rev. 6/14
Rev.Add11

STUDY CHAIR

Al Benson III, M.D.
Northwestern University, Suite 850
676 North St. Clair Street
Chicago, IL 60611
PI Phone: 312-695-6180
PI Fax: 312-695-6189
PI E-mail: a-benson@northwestern.edu

STUDY CO-CHAIRS

INTERVENTIONAL RADIOLOGY CO-CHAIR

Michael Soulen, M.D.
University of Pennsylvania
3400 Spruce Street
Philadelphia, PA 19104
Office: 215-662-7111
Fax: 215-662-7448
Email: Michael.Soulen@uphs.upenn.edu

Rev. 6/14

SWOG CO-CHAIR

Melanie Thomas, M.D.
Medical College of South Carolina
Hollings Cancer Center
86 Jonathan Lucas St.
MSC 955
Charleston, SC 29425
Office: 843-792-5329
Fax: 843-792-4233
Email: thomasmb@musc.edu

CALGB CO-CHAIR

Bert O'Neil, M.D.
University of North Carolina
Division of Hem/Onc
3009 Old Clinic Bldg
Chapel Hill, NC 27599-7305
Office: 919-843-7180
Fax: 919-966-6735
Bert_oneil@med.unc.edu

TRANSPLANT SURGERY CO-CHAIR

Kim Olthoff, M.D.
HUP – 2nf Floor Dulles Pvln
3400 Spruce St.
4283
Philadelphia, PA 19104
Office: 215-662-6136
Fax: 215-662-2244
Kim.olthoff@uphs.upenn.edu

DIAGNOSTIC RADIOLOGY CO-CHAIR

Mark Rosen, M.D., Ph.D.
University of Pennsylvania
Department of Radiology
1 Silverstein
3400 Spruce Street
Philadelphia, PA 19104
Office: 215-662-3107
Fax: 215-662-3013
Email: Mark.rosen@uphs.upenn.edu

SURGERY CO-CHAIR

Michael Choti, M.D.
Johns Hopkins Hospital
Department of Surgery
600 N. Wolfe Street
Blalock 665
Baltimore, MD 21287
Phone: 410-955-7113
Fax: 410-614-4667
Email: mchoti@jhmi.edu

HEPATOLOGY CO-CHAIR

Gregory Gores, M.D.
200 First Street Southwest
Rochester, MN 55905
Phone: 507-284-0686
Email: gores.gregory@mayo.edu

Rev. 6/14

PHARMACOLOGY CO-CHAIR

Jill Kolesar, Pharm,D.
UWCCC Analytical Instrumentation Lab
600 Highland Avenue, Room K6/571
Madison, WI 53792-5669
Phone: 608-262-5549
Fax: 608-265-5421
Email: jmkolesar@pharmacy.wisc.edu

Rev. 9/10

NCCTG CO-CHAIR

Mitesh Borad, M.D.
13400 Shea Boulevard
Scottsdale, AZ 85259
Phone: 480-301-8000
Fax: 507-284-5280
Email: borad.mitesh@mayo.edu

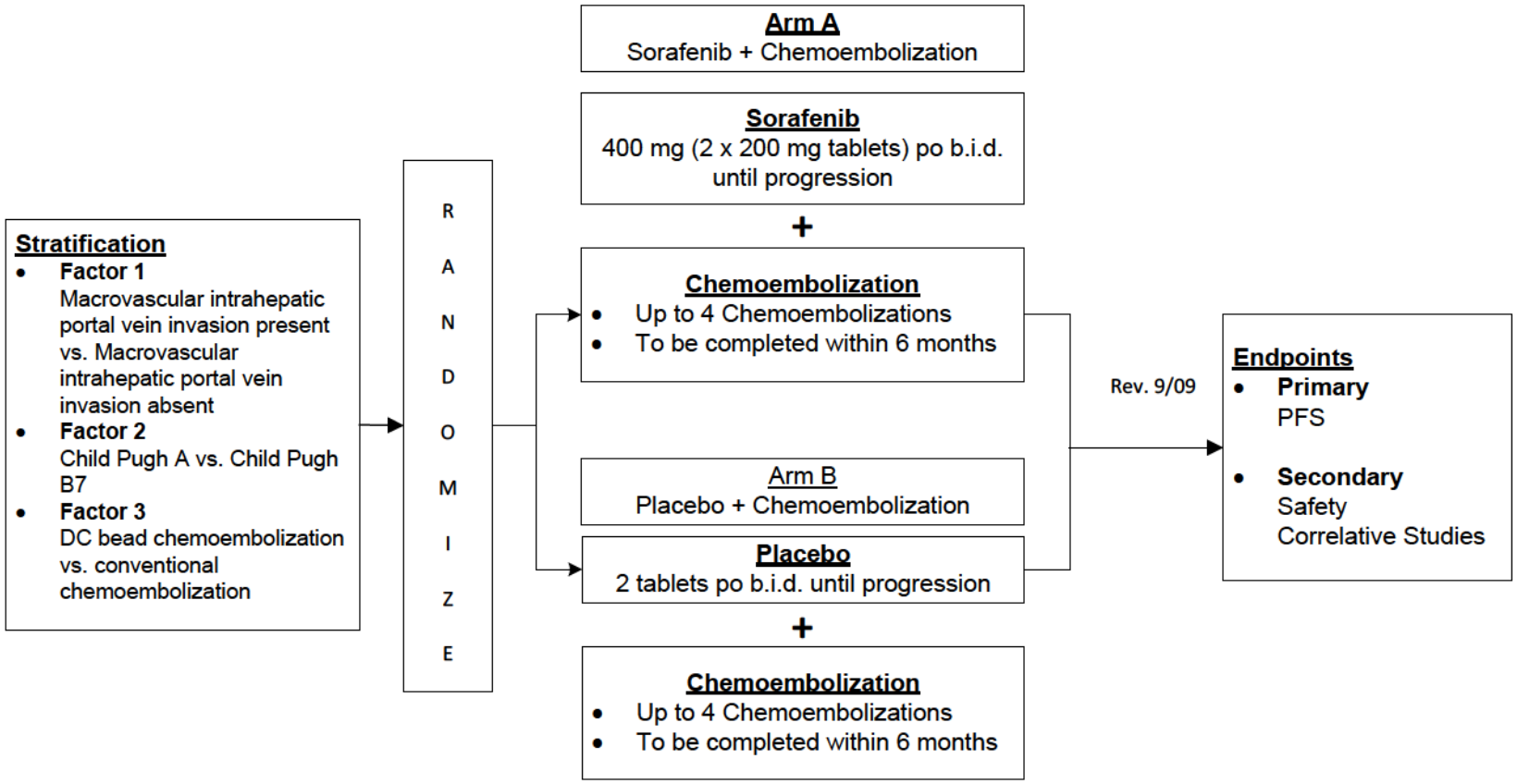
Rev. 6/14

Rev. 6/14

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

To submit site registration documents:	**For patient enrollments:**	**Submit study data directly to the Lead Cooperative Group unless otherwise specified in the protocol:**
CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA 19103 Phone – 1-866-651-CTSU Fax – 215-569-0206 Email: CTSURegulatory@ctsu.coccg.org (for submitting regulatory documents only)	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com	ECOG-ACRIN Operations Office – Boston, FSTRF 900 Commonwealth Avenue Boston, MA 02215 (ATTN: DATA). Phone # 617-632-3610 Fax # 617-632-2990 Data should be sent via postal mail (preferred), however fax is accepted. Do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password.		
For clinical questions (i.e. patient eligibility or treatment-related) contact the Study PI of the Lead Protocol Organization.		
For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
For detailed information on the regulatory and monitoring procedures for CTSU sites please review the CTSU Regulatory and Monitoring Procedures policy located on the CTSU members' website https://www.ctsu.org > education and resources tab > CTSU Operations Information >CTSU Regulatory and Monitoring Policy		
The CTSU Web site is located at https://www.ctsu.org		

Schema



Rev. 12/10

Accrual goal = 400 patients

1. Introduction

1.1 Hepatocellular Carcinoma Background

Hepatocellular carcinoma (HCC) is the fifth most common solid organ cancer worldwide, and causes more than 600,000 deaths every year.[1] The incidence of HCC is increasing in the United States (U.S.). From 1976 to 1980, 1.4 cases of HCC were diagnosed per 100,000 population; however from 1991 to 1995 the incidence rose to 2.4 per 100,000.[2] The incidence is even higher for men, in particular African American men, who are affected at a rate of 6.1 per 100,000. The increasing number of cases of HCC is attributable to the rise in hepatitis B (HBV) and chronic hepatitis C (HCV) viral infections that occurred in the late twentieth century. Through HBV vaccination and better HCV screening in banked blood products, these rates have come down significantly, but the damage is already done, and we are likely to see increasing incidence of primary liver cancer for the next 20 years.

1.2 Hepatocellular Carcinoma Management

Currently, the only potentially curative options available to patients with HCC are partial hepatectomy (PH) or orthotopic liver transplantation (OLT), but only 15% of patients are likely to benefit from such options due to concomitant cirrhosis and donor organ shortages.[3] For patients who undergo OLT, a 5-year survival of 70% is possible, provided they meet Milan criteria (one lesion less than 5 cm or up to three lesions less than 3 cm).[4-7]

For patients with HCC limited to the liver that are not candidates for curative resection or OLT, loco-regional therapies such as radiofrequency ablation (RFA) or chemoembolization offer tumor control while minimizing systemic toxicity and are felt to be reasonable alternatives to systemic therapy according to the National Comprehensive Cancer Network guidelines (version 2.2008).[8] RFA utilizes high frequency electrical currents administered through a probe inserted into a tumor to cause thermal injury leading to tumor necrosis. The efficacy of RFA is limited by several factors such as tumor size, tumor number, location of tumor, and proximity to vasculature and other vital structures. RFA is generally felt to result in more consistent tumor necrosis with tumors less than 3cm in size due to diminished heat transfer over increasing distances.[9] For tumors less than 3 cm RFA offer excellent 3 year disease free survival (DFS) rates up to 80% to 90%.[10-12]

For localized HCC not amenable to RFA, chemoembolization offers an alternative treatment strategy. Tumor directed hepatic artery chemoembolization is possible because normal liver receives blood flow from both the hepatic artery and the portal vein, whereas HCC receives almost all blood flow from the hepatic artery.[13,14] By inserting an angiographic catheter into the branches of the hepatic artery supplying the tumor and injecting cytotoxic chemotherapeutic agents (e.g. doxorubicin, cisplatin) followed by the injection of embolic particles leading to cessation of blood flow in the hepatic artery branch, tumor necrosis may result from both exposure to cytotoxic agents as well as ischemia.[15,16] A theoretical advantage to the combination of chemotherapy and embolization is the ischemia induced by embolization may overcome drug resistance by causing cell membrane pumps to fail. A newer method of chemoembolization utilizes DC

Rev. 12/10

beads, which are nonresorbable polyvinyl alcohol (PVA) hydrogel beads capable of being loaded with doxorubicin. These beads are then injected into the hepatic artery which will lead to occlusion of tumor vasculature while also exposing tumors to doxorubicin as the doxorubicin disassociates from the DC beads. A randomized phase II trial demonstrated no difference in response rates (52% vs. 44%), between DC bead chemoembolization and conventional chemoembolization respectively, however, a statistically significant lower rate of liver toxicity and doxorubicin related toxicity was noted in favor of DC bead chemoembolization. (Lammer et al Cardiovasc Intervent radiol (2010) 33:41-52).

While there have been multiple randomized trials of chemoembolization that have failed to demonstrate a survival advantage in favor of chemoembolization, all these studies were performed in the 1980's to mid 1990's.[17-19] Since then, interventional techniques have improved and two randomized trials reported in 2002 demonstrated a survival advantage for chemoembolization.[16,20] Llovet and colleagues randomized 112 patients to chemoembolization, bland embolization, or best supportive care (BSC) and reported a statistically significant result in favor of chemoembolization. One and 2 year survival probabilities were 82% and 63% for chemoembolization; 63% and 27% for BSC; p=0.009. In a single institution study from Hong Kong, Lo and colleagues randomized 80 patients to either cisplatin based chemoembolization or BSC. Survival for the chemoembolization arm (1 year, 57%; 2 years, 31%; 3 years, 26%) was superior to the BSC arm (1 year, 32%; 2 years, 11%; 3 years, 3%; p =0.002). A subsequent metaanalysis of randomized trials in HCC conducted between 1978 and 2002 with a combined total of 545 patients by Llovet and colleagues reported a significant improvement of 2 year survival in favor of chemoembolization, Odds Ratio (OR) 0.42; 95% CI, 0.20 – 0.88. Chemoembolization has become accepted worldwide as an effective standard treatment option for unresectable HCC. The National Comprehensive Cancer Network (NCCN), The American Association for the Study of Liver Diseases (AASLD), and the Barcelona Clinic Liver Cancer Group, all recognize chemoembolization as a reasonable treatment option for select patients with unresectable HCC.[8,21,22]

1.3 Rationale

There are pre-clinical and clinical data suggesting hepatic artery embolization leads to increase VEGF expression and neo-angiogenesis. Gupta and colleagues reported a rat model study where mammary cancer (13762 NF) tumor cells were inoculated into the livers of male rats, then transcatheter arterial embolization (TAE) was performed 12 – 14 days after tumor inoculation.[23] The rats were then sacrificed 3 – 6 hours or 2 to 3 days after TAE. Tumors treated with TAE had varying levels of central necrosis with residual viable tumor at the periphery and TAE treated animals also demonstrated significantly higher tumor microvascular density as well as circulating levels of Vascular Endothelial Growth Factor (VEGF). Kim and colleagues reported a case series in which surgically resected HCC tumor specimens, which underwent pre-operative TAE (3 to 4 weeks prior to liver resection), were examined for Ki67 proliferative index and found increased proliferative index of endothelial cells in the area 0.5mm from the necrotic margin compared to areas greater than 0.5mm from the necrotic margin. The Ki67 proliferative index was also found to be higher than in control samples which were obtained from resected HCC that did not undergo pre-operative TAE. The authors concluded that their results suggest that the

proliferative activity of intratumoral endothelial cells and tumor cells may be increased by ischemic necrosis induced by TAE. Lastly, Sergio and colleagues reported a case series of 71 HCC patients undergoing Trans-Arterial Chemoembolization (TACE) who had blood samples obtained at three time points: pre-TACE, 3 days post-TACE, 4 weeks post-TACE.[24]. CT imaging confirmed responses were noted in 27% of patients and serum VEGF levels were noted to be higher in non-responders compared to responding patients (p=0.01). In addition below median VEGF levels were associated with longer survival (p=0.008). The investigators concluded, "when TACE is not totally effective, it may induce a significant neo-angiogenetic reaction." These data suggest an anti-angiogenic approach in combination with chemoembolization for HCC may lead to additive or synergistic effects.

No single oncogenic event leading to the development of HCC has been discovered. It is likely that an amalgamation of multiple aberrant signaling pathways promotes carcinogenesis. Two crucial pathways that have been implicated in HCC carcinogenesis are ras/raf/MEK/ERK and VEGF.[25,26] Given that HCC tumors are rich in vascular supply, an anti-VEGF strategy to attack HCC seemed rational.

Sorafenib is a small molecule inhibitor of multiple tyrosine kinases, including: Vascular Endothelial Growth Factor Receptor (VEGFR)-2, VEGFR-3, raf, c-kit, FLT3, RET, and Platelet Derived Growth Factor (PDGFR)-β. Based on preclinical data, a published phase II trial of sorafenib in 137 patients with unresectable HCC reported 46 (33.6%) patients had stable disease and 8 (8%) patients had either partial or minor responses.[3] A subsequent international randomized, placebo controlled phase III trial of sorafenib, entitled "Sorafenib HCC Assessment Randomized Protocol" (SHARP), randomized 602 patients to either sorafenib or placebo. The primary objectives of the study was to compare OS and time to symptom progression (TTSP).[27] The SHARP trial was unblinded at the second planned interim analysis by the data monitoring committee (DMC) as the study met its primary endpoint, 40% improvement in survival; median OS sorafenib 10.7 months vs. placebo 7.9 months, P = 0.00058, Hazard ratio 0.69 (95% CI 0.55 – 0.88). Subset analysis of the SHARP study demonstrated an even bigger benefit for patients with liver limited disease, OS HR 0.55 (95% CI 0.39 – 0.77). In addition, a recently reported phase II study of single agent doxorubicin or the combination of sorafenib and doxorubicin revealed superior OS and TTP in favor of the combination; OS (13.7 vs. 6.5 months), TTP (8.6 vs. 4.8 months) suggesting possible synergism between sorafenib and doxorubicin.

Given these clinical trial results and the correlative data suggesting an increase in neo-angiogenesis following embolization, incorporation of an anti-angiogenic agent such as sorafenib with chemoembolization is a reasonable approach to advance the treatment of localized hepatocellular carcinoma.

2. Objectives

2.1 Primary Objective

2.1.1 To compare Progression-Free Survival (PFS) of chemoembolization alone to sorafenib in combination with chemoembolization.

2.2 Secondary Objectives

Rev. 9/10

2.2.1 To compare overall survival (OS) of chemoembolization alone to sorafenib in combination with chemoembolization.

2.2.2 To evaluate extra-hepatic versus intra-hepatic patterns of failure.

Rev. 9/10

2.2.3 To determine the rates of toxicity related to Sorafenib in combination with chemoembolization.

2.2.4 Pharmacogenetic and Pharmacokinetic Ancillary (PG0107) Objective

To analyze the pharmacogenetic and pharmacokinetic properties of Sorafenib including angiogenesis, monooxygenases, polymorphisms and MDR.

Rev. 9/10

2.2.5 ECOG-ACRIN secondary imaging objective: Site vs. Central evaluation of PFS

2.2.6 Correlative Imaging Science Objectives

2.2.6.1 To determine the inter-reader concordance for response characterization at four and eight months by the European Association for the Study of Liver (EASL) criteria.

2.2.6.2 To determine the value of objective tumor response at four and eight months by the EASL criteria to predict PFS (by RECIST) and OS.

2.2.6.3 To evaluate the effects of intra-hepatic vs. extra-hepatic progression on OS.

3. Selection of Patients

Each of the criteria in the checklist that follows must be met in order for a patient to be considered eligible for this study. Use the checklist to confirm a patient's eligibility. For each patient, this checklist must be photocopied, completed and maintained in the patient's chart.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday four weeks later would be considered Day 28.

ECOG-ACRIN Patient No. _____

Patient's Initials (L, F, M) _____

Physician Signature and Date _____

NOTE: All questions regarding eligibility should be directed to the study chair or study chair liaison.

NOTE: Institutions may use the eligibility checklist as source documentation if it has been reviewed, signed, and dated prior to registration/randomization by the treating physician.

3.1 Eligibility Criteria

_____ 3.1.1 Patients must have a diagnosis of hepatocellular carcinoma by at least one criterion listed below:

i. Histologically confirmed

ii. Magnetic Resonance Imaging (MRI) or Computerized Tomography (CT) consistent with liver cirrhosis **AND** at least one solid liver lesion > 2cm with early enhancement and delayed enhancement washout regardless of alpha-feto protein levels (AFP).

iii. AFP > 400ng/mL **AND** evidence of at least one solid liver lesion > 2cm regardless of specific imaging characteristics on CT or MRI

_____ 3.1.2 Patients must have HCC limited to the liver. There must be no clinical or radiographic evidence of extrahepatic HCC.

Yes: _____ No:_____

_____ 3.1.3 Portal Lymphadenopathy IS permitted for patients with HBV or HCV – as lymphadenopathy is commonly associated with hepatitis unrelated to malignancy.

_____ 3.1.4 Staging CT of the Chest and CT or MRI of the Abdomen and Pelvis must have been completed within 4 weeks of study registration.

Date of Chest CT: _____

Date of Abdominal CT/MRI: _____

_____ 3.1.5 Patients must have measurable disease as defined in Section 6.1.1 constituting < 50% of liver parenchyma within 4 weeks of registration

Yes: _____ No:_____

Rev. 12/10 _____ 3.1.6 Patients may not have ascites detectable on physical examination.

Patient has ascites detectable on physical examination?

Yes: _____ No:_____

_____ 3.1.7 Patients must not be candidates for curative resection, orthotopic liver transplantation, or radiofrequency ablation (RFA).

Has the patient deemed not to be a candidate for resection, OLT or RFA?

Yes: _____ No:_____

_____ 3.1.8 Patients may have been treated with RFA in the past, but no sooner than 4 weeks before study registration.

Has the patient been treated with RFA in past:

Yes: ____ No: ____

If Yes, date of RFA: ____

_____ 3.1.9 Patients may have undergone previously attempted curative liver resection.

_____ 3.1.10 Patients may NOT have been previously treated with brachytherapy such as Yttrium-90 microsphere.

Rev. 9/10 Prior treatment with brachytherapy

Yes: _____ No:_____

_____ 3.1.11 Patients may **NOT** have been previously treated with sorafenib, chemoembolization, or systemic chemotherapy including cytotoxic agents or molecularly targeted agents.

Prior treatment with sorafenib, chemoembolization, or systemic therapy:

Yes: _____ No:_____

_____ 3.1.12 Branch portal vein invasion by tumor is permitted but patients with main portal vein invasion by tumor are not eligible.

Portal Vein invasion by tumor present: Yes: _____ No:_____

_____ 3.1.13 Patients must have Child-Pugh score of A or B7 within 4 weeks prior to study registration. Please Refer to Appendix IX for Child-Pugh scoring.

Child-Pugh Score: _____ Date: _____

_____3.1.14 Patients must have the following baseline laboratories obtained within 4 weeks prior to study registration:

i. Serum Total Bilirubin ≤ 2.0 mg/dL.

Total bilirubin: _____ Date of test: _____

Rev. 12/10

ii. Alkaline Phosphatase, AST, ALT < 5x ULN.

Alkaline Phos: _____ ULN: _____ Date of test: _____

AST: _____ ULN: _____ Date of test: _____

ALT: _____ ULN: _____ Date of test: _____

iii. Serum Creatinine ≤ 1.5 mg/dL.

Serum Creatinine: _____ Date of test: _____

Rev. 12/10

iv. Platelet count ≥ 50,000/mm^3.

Platelet count: _____ Date of test: _____

_____3.1.15 Patients must not have any evidence of bleeding diathesis or active gastrointestinal bleeding.

_____3.1.16 Patients must have no clinical signs of heart failure and meet New York Heart Association functional classification I or II defined as:

i. Class I – Patients with no limitation of activities; they suffer no symptoms from ordinary activities.

ii. Class II – Patients with slight, mild limitation of activity; they are comfortable with rest or with mild exertion

Yes: _____ No:_____

_____3.1.17 Patients must have an ECOG performance status of 0 or 1.

Yes: _____ No:_____

_____3.1.18 Patients must have a life expectancy of at least 3 months.

Yes: _____ No:_____

_____3.1.19 Patients must not be known to be HIV positive; drug-drug interactions with study medication and HIV medications is not well-characterized and could lead to unwanted side effects.

Yes: _____ No:_____

_____3.1.20 Patients must not have other uncontrolled intercurrent illnesses excluding HBV or HCV, including, but not limited to: uncontrolled hypertension, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia or psychiatric illness/addictive disorders that would limit compliance with study requirements.

Uncontrolled hypertension is defined as optimally treated baseline blood pressure that exceeds 150/90 mm Hg.

Uncontrolled illness Yes: _____ No:_____

Blood Pressure: _____ Date: _____

_____3.1.21 Patients must not be taking cytochrome P450 enzyme inducing drugs. Refer to a list of agents listed in Appendix VIII.

Yes: _____ No:_____

_____3.1.22 Age ≥ 18 years.

Yes: _____ No:_____

_____3.1.23 Women must not be pregnant or breast-feeding due to teratogenic effects of agents used in this trial.

All females of childbearing potential must have a blood test or urine study within 2 weeks prior to registration to rule out pregnancy.

Female? _____ (Yes or No)

Date of blood test or urine study: _____

_____3.1.24 Women of childbearing potential and sexually active males must be strongly advised to use an accepted and effective method of contraception.

Patient CounseledYes: _____ No:_____

_____ 3.1.25 Patients must not have an allergy to iodine or gadolinium contrast that can not be safely controlled with premedication.

Rev. 9/10

Allergic to iodine contrast Yes: _____ No:_____

Allergic to iodine controlled with premedication

Yes: _____ No:_____

Allergic to Gadolinium contrast Yes: _____ No:_____

Rev. 9/10

Allergic to Gadolinium controlled with premedication

Yes: _____ No:_____

_____3.1.26 Patient must be able to swallow pills, as study medications can not be crushed.

4. Registration Procedures

Rev. 6/14

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

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>.

CTSU Registration Procedures

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

IRB Approval:

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. 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' website by entering credentials at https://www.ctsu.org. For sites under the CIRB initiative, IRB data will automatically load to RSS.

Downloading Site Registration Documents:

Site registration forms may be downloaded from the **E1208** protocol page located on the CTSU members' website.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Protocols tab in the upper left of your screen
- Click on the **ECOG-ACRIN** link to expand, then select trial protocol **E1208**
- Click on the Site Registration Documents link

Requirements for E1208 site registration:

- CTSU IRB Certification (for sites not participating via the NCI IRB)
- CTSU IRB/Regulatory Approval Transmittal Sheet (for sites not participating via the NCI IRB)

Submitting Regulatory Documents:

Submit completed forms along with a copy of your IRB Approval and Model Informed Consent to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103
PHONE: 1-866-651-2878
FAX: (215) 569-0206
E-mail: CTSURegulatory@ctsu.coccg.org (for regulatory document submission only)

Rev. 12/10

NOTE: It is the responsibility of each site to submit the E1208 Declaration of Chemoembolization Administration Method Form to the CTSU prior to registration of new patients to this study after activation of addendum #3.

Required Protocol Specific Regulatory Documents:

1. **CTSU Regulatory Transmittal Form.**
2. **Copy of IRB Informed Consent Document.**

   NOTE: Any deletion or substantive modification of information concerning risks or alternative procedures contained in the sample informed consent document must be justified in writing by the investigator and approved by the IRB.

3. **A. CTSU IRB Certification Form.**
   Or
   B. HHS OBM No. 0990-0263 (replaces form 310).
   Or
   C. IRB Approval Letter

Rev. 12/10

4. Declaration of Chemoembolization Administration Method Form

NOTE: The above submissions must include the following details:

- **Indicate all sites approved for the protocol under an assurance number.**
- **OHRP assurance number of reviewing IRB**
- **Full protocol title and number**
- **Version Date**
- **Type of review (full board vs. expedited)**
- **Date of review.**
- **Signature of IRB official**

Checking Your Site's Registration Status:

Check the status of your site's registration packets by querying the RSS site registration status page of the members' section of the CTSU website. (Note: Sites will not receive formal notification of regulatory approval from the CTSU Regulatory Office.)

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab at the top of your screen
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

Patient Enrollment:

Patients must not start protocol treatment prior to registration.

Treatment should start within 10 working days after registration.

NOTE: No blinded starter supplies will be available for this study. Blinded, patient-specific clinical supplies will be shipped from the Pharmaceutical Management Branch to the registering investigator at the time of patient randomization and should arrive within seven to ten working days (see Section 8.0).

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at <https://eapps-ctep.nci.nih.gov/iam/index.jsp>) and a 'Registrar' role on either the LPO or participating organization roster.

All site staff (Lead Group and CTSU Sites) will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org

Prior to accessing OPEN, site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes.

- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

NOTE: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

NOTE: To receive site reimbursement for specific tests and/or bio-specimen submissions, completion dates must be entered in the OPEN Funding screen post registration. Please refer to the protocol specific funding page on the CTSU members' website for additional information. Timely entry of completion dates is recommended as this will trigger site reimbursement.

Further instructional information is provided on the OPEN tab of the CTSU members' side of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

Rev. 6/14

4.1 Registration

The following information will be requested at the time of registration:

4.1.1 Protocol Number

4.1.2 Investigator Identification

4.1.2.1 Institution and affiliate name

4.1.2.2 Investigator's first and last name

4.1.2.3 NCI investigator number

4.1.3 Patient Identification

4.1.3.1 Patient's initials and chart number

4.1.3.2 Patient's Social Security number

4.1.3.3 Patient demographics

4.1.3.3.1 Sex

4.1.3.3.2 Birth date (mm/yyyy)

4.1.3.3.3 Race

4.1.3.3.4 Ethnicity

4.1.3.3.5 Nine-digit ZIP code

4.1.3.3.6 Method of payment

4.2 Eligibility Verification

Patients must meet all of the eligibility requirements listed in Section 3.0. An eligibility checklist has been appended to the protocol. A confirmation of registration will be forwarded by the ECOG-ACRIN Operations Office – Boston.

4.2.1 Stratification Factors

- Macrovascular intrahepatic portal vein invasion present vs. Macrovascular intrahepatic portal vein invasion absent

4.2.2 Stratification Factor 2

- Child Pugh A vs. Child Pugh B7

Rev. 12/10

4.2.3 Stratification Factor 3

Rev. 5/11

- LC bead chemoembolization vs. conventional chemoembolization.

4.3 Additional Requirements

4.3.1 Patients must provide a signed and dated, written informed consent form.

Rev. 9/10, 12/10

4.3.2 CT and MRI imaging must be submitted to ACRIN as outlined in Section 5.3.4 and Appendix X.

4.3.3 From patients consenting to participate in the "Pharmacogenetic and Pharmacokinetic Laboratory Studies" (PG0107, Appendix IV) specimens are to be submitted as outlined in Section 11.

Rev. 12/14

NOTE: ECOG-ACRIN requires that biological specimens submitted to the ECOG-ACRIN Central Biorepository and Pathology Facility from patients participating in E1208 be entered and tracked via the online ECOG-ACRIN Sample Tracking System (STS). Any case reimbursements associated with specimen submissions may not be captured if specimens are not logged into STS. See Section 10.3.

Rev. 12/10

4.3.4 It is the responsibility of each site to submit the E1208 Declaration of Chemoembolization Administration Method Form to the CTSU prior to registration of new patients to this study after activation of addendum #3.

4.4 Instructions for Patients who Do Not Start Assigned Protocol Treatment

If a patient does not receive any assigned protocol treatment, baseline and follow-up data will still be collected and must be submitted according to the instructions in the E1208 Forms Packet. Document the reason for not starting protocol treatment on the off-treatment form. forms. Also report the date and type of the first non-protocol treatment that the patient receives.

4.5 Emergency Unblinding

NOTE: The information provided below is for the use by a physician, nurse, CRA or pharmacist treating the patient. These contact numbers should not be used by patients. Patients should be instructed to call their doctor's office in the event of an emergency or adverse event that may result in the need to unblind the patient.

Rev. 6/14

In the event of an emergency or severe adverse reaction necessitating identification of the medication for the welfare of the patient, please contact the Study Chair, Dr. Jeff Geschwind, at 410-614-6597, first to ensure the reason for unblinding is valid. Then call a member of the ECOG-ACRIN Operations Office – Boston drug team at 617-632-3610 Monday through Friday between 9:00AM and 5:00PM Eastern Time. For unblinding outside of these hours, contact

AnswerConnect at 1-866-296-8940. This service will request the reason for unblinding and then page the on-call ECOG-ACRIN staff who will return your call and provide the unblinded treatment assignment if applicable. **Remember, AnswerConnect should only be contacted outside of normal business hours and only in the event of an emergency.** The ECOG-ACRIN Operations Office – Boston or AnswerConnect will require the protocol number (i.e., "E1208"), the patient ID number (e.g., "99999"), and the patient initials (e.g., "FL") to unblind the patient. Please note that if a patient is emergently unblinded he/she is considered to be off-therapy and must discontinue protocol treatment. However, follow-up according to the protocol schedule is still required.

5. Treatment Plan

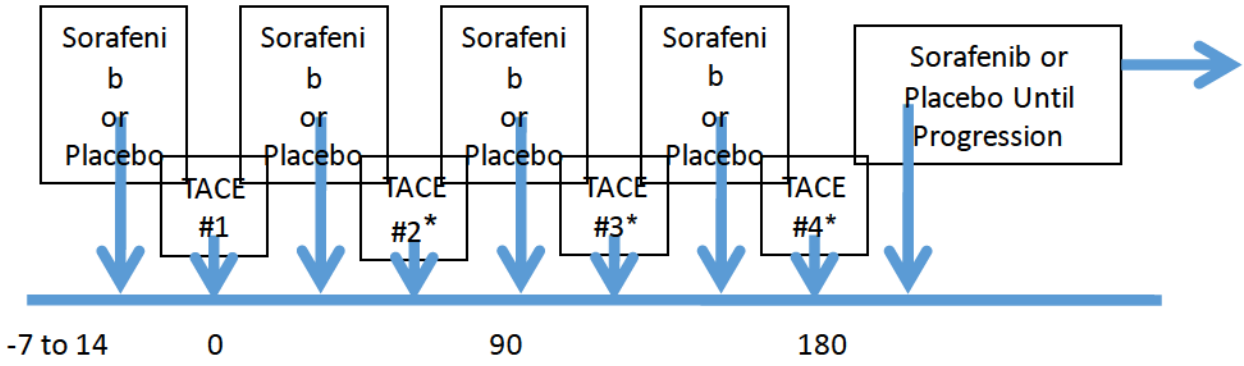
5.1 Overview

Study subjects will be randomized to sorafenib or placebo. Once a stable dose of sorafenib/placebo is reached study subjects will then undergo chemoembolization. Up to a total of 4 chemoembolization treatments as deemed necessary by the treating interventional radiologist may be administered as outline in section 5.3. All chemoembolization treatments must be completed within 6 months of the first chemoembolization. Sorafenib/placebo dosing will be halted 24 to 48 hours prior to chemoembolization and sorafenib/placebo will not be reinitiated until serum chemistries return to acceptable levels listed below in Section 5.2.10.2.

NOTE: No blinded starter supplies will be available for this study. Blinded, patient-specific clinical supplies will be shipped from the Pharmaceutical Management Branch to the registering investigator at the time of patient randomization and should arrive within seven to ten working days (see Section 8.0).

At the conclusion of study participation, the treating physician or their coordinator should call a member of the ECOG-ACRIN Operations Office – Boston drug team at (617) 632-3610 Monday through Friday between 9:00 AM and 5:00 PM Eastern Time to determine if a study subject receive sorafenib or placebo. For emergency unblinding please refer to section 8.1.6 of the protocol.

Figure 5.1



* If deemed necessary by treating interventional radiologist, up to 4 chemoembolization treatments may be administered. All Chemoembolizations must be completed within 6 months of initial chemoembolization.

Treatment must start within 10 working days after registration.

NOTE: **Patients treated with placebo on study will not be provided sorafenib once their participation on E1208 ends, since sorafenib**

is a commercially available agent approved for the treatment of hepatocellular carcinoma.

5.2 Sorafenib/placebo Administration Schedule / Dose Adjustments.

THE FOLLOWING SECTIONS ARE A DETAILED TREATMENT ALGORITHM INCLUDING DOSE ADJUSTMENT FOR SORAFENIB/PLACEBO. FOR FURTHER EXPLANATION OF DOSE ADJUSTMENTS PLEASE REFER TO SECTION 5.5 AND FIGURE 5.2.

5.2.1 Screening Laboratories and baseline imaging < 4 weeks prior to registration.

5.2.1.1 Abdominal/pelvic imaging modality can be either MRI or CT, but MRI is the PREFERRED imaging modality. All subsequent imaging studies must be of the same modality as the baseline imaging study.

5.2.1.2 Chest imaging must be performed by CT throughout the study.

5.2.2 To confirm patient eligibility to begin sorafenib treatment safely within 10 to 14 days of planned start date of sorafenib/placebo, obtain the following laboratory studies: CBC, Chemistry Panel, bilirubin, Alkaline Phosphatase AST, ALT, PT/INR.

5.2.3 Start sorafenib/placebo 400mg p.o. twice a day. Monitor toxicity as outlined below until stable dose of sorafenib/placebo established.

5.2.4 Assess toxicity of sorafenib/placebo 10 to 14 days after starting sorafenib/placebo. Study subjects may proceed to chemoembolization (Section 5.3) provided the following criteria in Sections 5.2.4.1 and 5.2.4.2 are met, otherwise adjust doses of sorafenib/placebo as directed below in Section 5.2.5:

Rev. 12/10

5.2.4.1 ≤ grade 2 hematologic toxicity.

5.2.4.2 ≤ grade 1 non-hematologic toxicity with the exception of:

- Serum Creatinine ≤ 1.5 mg/dL
- Serum bilirubin ≤ 2.0 mg/dL

Rev. 12/10

- Serum albumin > 2 g/dL
- AST ≤ 5X upper limit of normal (ULN)
- ALT ≤ 5X ULN
- Alkaline Phosphatase ≤ 5X ULN

5.2.5 If the above criteria in Sections 5.2.4 are not met, sorafenib/placebo therapy must be held until criteria in Section 5.2.4 are fulfilled. Sorafenib/placebo may be held up to 21 days. If criteria in Section 5.2.4 are not met within 21 days of holding sorafenib/placebo then the study subject is to be removed from the study. Once criteria in Sections 5.2.4.1 and 5.2.4.2 are met, sorafenib/placebo should be resumed at 200mg p.o. twice a day and toxicity re-evaluated after 10-14 days of therapy. To proceed with chemoembolization, subjects must meet the criteria listed below in Sections 5.2.5.1 and 5.2.5.2:

Rev. 12/10

5.2.5.1 ≤ grade 2 hematologic toxicity.

5.2.5.2 ≤ grade 1 non-hematologic toxicity with the exception of:

- Serum Creatinine ≤ 1.5 mg/dL
- Serum bilirubin ≤ 2.0 mg/dL

Rev. 12/10

- Serum albumin > 2 g/dL
- AST ≤ 5X ULN
- ALT ≤ 5X ULN
- Alkaline Phosphatase ≤ 5X ULN

5.2.6 If the above criteria in Section 5.2.5 are not met, sorafenib/placebo therapy must be held until criteria in Section 5.2.5 are fulfilled. Sorafenib/placebo may be held up to 21 days, if criteria in Section 5.2.4 are not met within 21 days of holding sorafenib/placebo then the study subject is to be removed from the study. Once criteria in Sections 5.2.4.1 and 5.2.4.2 are met, sorafenib/placebo should be resumed at 200mg p.o. once a day and toxicity re-evaluated after 10-14 days of therapy. To proceed with chemoembolization, subjects must meet the criteria listed below in Sections 5.2.6.1 and 5.2.6.2:

Rev. 12/10

5.2.6.1 ≤ grade 2 hematologic toxicity.

5.2.6.2 ≤ grade 1 non-hematologic toxicity with the exception of:

- Serum Creatinine ≤ 1.5 mg/dL
- Serum bilirubin ≤ 2.0 mg/dL

Rev. 12/10

- Serum albumin > 2 g/dL
- AST ≤ 5X ULN
- ALT ≤ 5X ULN
- Alkaline Phosphatase ≤ 5X ULN

5.2.7 If the criteria in Section 5.2.6 are not met despite two dose reductions of sorafenib/placebo as outlined in Sections 5.2.5 and 5.2.6, then sorafenib/placebo will be permanently discontinued and the study subject will be removed from the study.

5.2.8 If a patient is unable to reach a stable dose of sorafenib within 28 days after the first dose of sorafenib, or within 42 days after chemoembolization, they are to be removed from the study.

5.2.9 Provided the study subject meets the criteria outlined in Section 5.2.4.1 and 5.2.4.2. Chemoembolization is to be performed within two weeks of reaching a stable dose of sorafenib as outlined in Sections 5.2.4, 5.2.5, and 5.2.6. 24 to 48 hours before planned chemoembolization, sorafenib/placebo dosing will be suspended. Then study subjects are to undergo chemoembolization per guidelines outlined in Section 5.3.

5.2.10 Seven to 14 days following chemoembolization:

5.2.10.1 Subjects are to be evaluated for toxicity with:

- Physical examination

- Serum chemistries including: bilirubin, albumin, AST, ALT, Alkaline Phosphatase, PT/INR
- CBC

5.2.10.2 Reinitiate sorafenib/placebo therapy at dose administered prior to chemoembolization if the following criteria are met:

- Serum Bilirubin elevation < Grade 2. If serum bilirubin ≥ grade 2 then assess weekly and resume sorafenib/placebo at dose administered prior to chemoembolization once bilirubin < Grade 2.
- Serum Albumin < Grade 3. If serum albumin ≥ grade 3 then assess weekly and resume sorafenib/placebo at dose administered prior to chemoembolization once serum albumin < Grade 3.
- Resolution of grade < 3 non-hematologic toxicity (other than bilirubin and albumin criteria above), If non-hematologic toxicity ≥ grade 3 then assess weekly and resume sorafenib/placebo at dose administered prior to chemoembolization once non-hematologic toxicity < Grade 3.
- Hematologic toxicity resolved of ≤ 2. If hematologic toxicity ≥ grade 3 then assess weekly and resume sorafenib/placebo at dose administered prior to chemoembolization once the hematologic toxicity is ≤ Grade 2.

Rev. 12/10

Rev. 5/12

- ECOG performance status ≤ 1.

5.2.10.3 Evaluate for repeat chemoembolization of incompletely or untreated HCC identified by the treating interventional radiologist no sooner than 4 weeks from prior chemoembolization. To proceed with additional chemoembolization procedures, subject must meet initial study eligibility criteria.

5.2.10.4 Repeat chemoembolization up to a total of 4 as deemed necessary by treating interventional radiologist to adequately treat HCC tumor burden. All chemoembolizations must be completed within 6 months of first chemoembolization.

Rev. 9/10

5.2.11 After final chemoembolization is complete, the patient will begin maintenance therapy of sorafenib/placebo until progression. Dosage continues at 2 tablets p.o. b.i.d. Maintenance cycles are 28 days in length.

Rev. 12/10, 5/11

5.3 <u>Chemoembolization - Individual sites have the option of utilizing one of 3 chemoembolization options:</u>

a. <u>Conventional chemoembolization utilizing doxorubicin, mitomycin, and cisplatin (this option may only be utilized for patients registered prior to addendum #3).</u>

b. Conventional chemoembolization utilizing doxorubicin only

c. Chemoembolization utilizing LC bead and doxorubicin

NOTE: Once a site chooses a chemoembolization option, ALL patients treated at that particular site must receive chemoembolization utilizing the same treatment.

5.3.1 Conventional Chemoembolization Protocol (or per institutional standards) utilizing doxorubicin, mitomycin, and cisplatin

Rev. 12/10

NOTE: This method of chemoembolization may only be utilized for patients registered prior to the activation of addendum #3).

Rev. 12/10

5.3.1.1 Chemotherapy Formulation

Table 5.1 SUMMARY OF CHEMOTHERAPEUTIC AGENTS IN CHEMOEMBOLIZATION EMULSION

CHEMOTHERAPEUTIC AGENTS	DOSE
Doxorubicin	50 mg
Mitomycin	10 mg
Cisplatin	100 mg

a) The entire chemotherapy solution in a sterile container is delivered to the Angiography suite. The final dosages of the individual chemotherapy agents in solution are doxorubicin 50 mg, mitomycin-C 10 mg and cisplatin 100mg. (Please calculate mg of each agent/cc). Final drug concentrations should be:

- Cisplatin 10 mg/mL
- Doxorubicin 5 mg/mL
- Mitomycin 1 mg/mL

b) Reconstitute chemotherapy per institutional standard. An example is listed below:

Rev. 10/11

i) Draw up 8.5 cc of the sterile contrast, omnipaque 350 plus 1.5 cc of sterile water in a 10 cc sterile syringe.

ii) Reconstitute two 5 mg bottles of mitomycin by injecting 5 cc into each bottle.

iii) Use the mitomycin solution to reconstitute 50 mg of doxorubicin (needs vigorous shaking).

iv) Use the mitomycin/doxorubicin solution to reconstitute two 50 mg bottles of cisplatin.

Rev. 12/10

5.3.1.2 Patient Pre-Procedural Preparation

a) IV Normal Saline per institutional standard.

b) Pre-meds (or institutional standard):

i. cephazolin 1 gm IV

ii. metronidazole 500 mg IV
iii. diphenhydramine 50 mg IV
iv. dexamethazone 10 mg IV
v. dolasetron 100mg or ondansetron 24mg IV

c) Place Foley catheter, if ordered.

Rev. 12/10

5.3.1.3 Chemoembolization Procedural Preparation

a) The patient is prepped and draped in a sterile fashion.

b) Equipment: 2x 20 cc and 2x10 cc syringes; three 3 cc syringes, and two 1 cc Luer-Lok syringes (for microcatheter system) or two 5 cc syringes (for standard catheters); needles, one 3-way stopcock, the embolic agent, 10 cc of lipiodol (Ethiodol), chemotherapy (cisplatin 100 mg, doxorubicin 50 mg and mitomycin C 10 mg dissolved in Omnipaque 350 in pharmacy and delivered directly to angiography suite immediately before procedure), 15ml of 1% lidocaine divided among five 3-ml syringes.

c) 100-500 um Embospheres (Biosphere Medical), and radiographic contrast.

d) Access the common femoral artery using Seldinger technique. A 5-French vascular sheath is then placed. Under fluoroscopic guidance, a visceral-shape catheter is used to perform diagnostic visceral arteriogram (celiac and SMA) to depict arterial flow to the tumor, hepatic arterial anatomy, and portal vein blood flow. The diagnostic catheter or a microcatheter is advanced into the target hepatic artery branch, depending on tumor location. Angiography is performed to confirm safety of the location to delivery the chemoembolic emulsion. An additional disposable drape is placed under the exposed end of the catheter for possible spillage of the chemotherapy.

Based on the operator's assessment of tumor size and vascularity, 25%-50% of the chemotherapeutic solution is emulsified with iodized oil in a 1:1-2:1 oil:chemotherapy solution ratio using the pumping technique through the 3-way stopcock. Five ml of the emulsion is slowly infused under continuous fluoroscopic monitoring, followed by a 3 ml lidocaine flush under fluoroscopic monitoring. If forward flow in the main vessel remains unchanged, the emulsion ratio between the iodized oil and the chemotherapy is kept. Otherwise, the amount of lipiodol is reduced in subsequent aliquots to decrease the viscosity of the mixture with the goal of delivering the entire dose of chemotherapy to the tumor. Forward flow into the vessel must always be present otherwise reflux into a non-target area can occur.

The end point of the procedure is achieved when the entire amount of chemotherapeutic agents are delivered to the tumor or when there is slowing of flow with pruning of the tumor-feeding branches (the "tree-in-winter" appearance) or transit time of contrast in the feeding artery takes 4 heartbeats. 2-4 mL of Embosphere particles (Biosphere Medical, Boston, MA) measuring 100-500 microns in size are mixed into the final aliquot of the emulsion or injected immediately after the final aliquot depending upon institutional protocol, to slow down arterial inflow and prevent washout of the chemotherapeutic agents.

Rev. 12/10

5.3.1.4 Chemoembolic Administration

a) Draw up 10ml of Ethiodol (lipiodol) in a 20 cc polycarbonate syringe and connect to the 3-way stopcock.
b) Draw up the chemotherapy retrieved from the pharmacy in another 20ml polycarbonate syringe.
c) Use two 10 ml polycarbonate syringes to emulsify 25%-50% of the lipiodol with chemotherapy in a 1:1 to 2:1 ratio with the 3 way stopcock.
d) Administer the chemotherapy/ethiodol mixture (without embolic agents) into the target vessel.
e) Flush the micro catheter with 1% lidocaine solution after each aliquot of chemotherapy is given.
f) After each aliquot of emulsion has been administered, check for patency of artery and flow. If flow remains unchanged, then continue with the initial ratio between chemotherapy and lipiodol and infuse the entire amount in this way. If the flow is diminished, then reduce the oil:chemotherapy ratio in subsequent aliquots.
g) Flow through the main tumor vessel should always be preserved. A small amount of Embospheres (1-4 cc) should be administered with the final aliquot or after the entire chemotherapy/oil mixture.

Rev. 12/10

5.3.1.5 Post-chemoembolization Procedure Orders and Care

a) Post-Procedure Orders.
b) Patients admitted for overnight observation.
c) Hydration with IV NSS at 150 cc/hr x 3 liters; then D 5 ½ NSS at 80 cc/hr or per institutional standard.
d) Medications Administered post-chemoembolization procedure (or per institutional protocol).
    i. Cefazolin 1 Gram IV q 8 hours
    ii. Metronidazole 500 mg IV q 12 hours
    iii. Morphine Sulfate 1-2 mg IV q 1-2 hours, PRN pain

iv. Tylenol #3, 2 tablets pox. q 4 hours, PRN moderate pain
v. Tylenol 650 mg pox. or p.r.n. q 4 hours, PRN fever
vi. Prochlorperazine 25 mg p.r.n. q 8 hours, PRN nausea
vii. Dolasetron 12.5mg q12h X 4 doses or ondansetron 8mg q8h IV x 2 days
viii. Dexamethasone 8 mg IV q 8 hours x 2 days

e) Foley catheter discontinued morning after if urine output adequate, if ordered prior to procedure.

Rev. 12/10

5.3.1.6 Post-Procedure Care

a) Post-arteriography bedrest with monitoring of vital signs and pulses per institutional protocol.
b) Patient can be discharged as soon as they demonstrate adequate oral intake or liquids, and no longer require parenteral narcotics or antiemetics. (Average length of stay is 1.5 days).
c) Fevers <103^0 are normal in the first week and do not require cultures.
d) Discharge medications:
   i. Antibiotics per institutional protocol if felt to be medically necessary by treating physicians.
   ii. Tylenol #3 PRN for pain
   iii. Prochlorperazine suppositories PRN for nausea
e) CBC, creatinine, liver function panel, INR, and AFP three weeks post-chemoembolization to assure continued eligibility for additional chemoembolization.
f) Patient returns in approximately 4 weeks for repeat treatment based on anatomy and tumor burden (remaining lobe of the liver or retreat same territory if incompletely embolized).
g) **Optional Based upon Institutional Practice.** Based on institutional practice tumor response within the liver may be assessed by CT or MR imaging studies (chest imaging must be performed by CT), and tumor markers at intervals other than those specified by the study are optional. However, for the purposes of defining progression free survival, only the tumor imaging obtained at the study specified time points (refer to Section 5.3.4) should be used. Please contact study chairs for questions regarding the interpretation of imaging as it relates to determining progression.

Rev. 12/10

Rev. 12/10

5.3.2 Conventional Chemoembolization Protocol (or per institutional standards) utilizing single agent doxorubicin.

5.3.2.1 Chemotherapy Formulation

Table 5.2 DOXORUBICIN DOSING BASED ON SERUM BILIRUBIN LEVELS	
Serum Total Bilirubin level (mg/dL)	**DOSE**
<1.5 mg/dL	75 mg/m^2
1.5 to 2.0 mg/dL	50 mg/m^2

The entire chemotherapy solution in a sterile container is delivered to the Angiography suite.

5.3.2.2 Patient Pre-Procedural Preparation

a) IV Normal Saline per institutional standard.
b) Pre-meds (or institutional standard):
   i. cephazolin 1 gm IV
   ii. metronidazole 500 mg IV
   iii diphenhydramine 50 mg IV
   iv. dexamethazone 10 mg IV
   v. dolasetron 100mg or ondansetron 24mg IV
c) Place Foley catheter, if ordered.

5.3.2.3 Chemoembolization Procedural Preparation

a) The patient is prepped and draped in a sterile fashion.
b) Equipment: 2x 20 cc and 2x10 cc syringes; three 3 cc syringes, and two 1 cc Luer-Lok syringes (for microcatheter system) or two 5 cc syringes (for standard catheters); needles, one 3-way stopcock, the embolic agent, 10 cc of ethiodized poppyseed oil (e.g., Lipiodol®), chemotherapy (doxorubicin dissolved in Omnipaque 350 in pharmacy and delivered directly to angiography suite immediately before procedure), 15ml of 1% lidocaine divided among five 3-ml syringes.
c) 100-500 um Embospheres (Biosphere Medical), and radiographic contrast.
d) Access the common femoral artery using Seldinger technique. A 5-French vascular sheath is then placed. Under fluoroscopic guidance, a visceral-shape catheter is used to perform diagnostic visceral arteriogram (celiac and SMA) to depict arterial flow to the tumor, hepatic arterial anatomy, and portal vein blood flow. The diagnostic catheter or a microcatheter is advanced into the target hepatic artery branch, depending on tumor location. Angiography is performed to confirm safety of the location to delivery the chemoembolic emulsion. An additional disposable drape is placed under the exposed end of the catheter for possible spillage of the chemotherapy.

Based on the operator's assessment of tumor size and vascularity, 25%-50% of the chemotherapeutic solution is emulsified with iodized oil in a 1:1-2:1 oil:chemotherapy solution ratio using the pumping technique through the 3-way stopcock. Five ml of the emulsion is slowly infused under continuous fluoroscopic monitoring, followed by a 3 ml lidocaine flush under fluoroscopic monitoring. If forward flow in the main vessel remains unchanged, the emulsion ratio between the iodized oil and the chemotherapy is kept. Otherwise, the amount of lipiodol is reduced in subsequent aliquots to decrease the viscosity of the mixture with the goal of delivering the entire dose of chemotherapy to the tumor. Forward flow into the vessel must always be present otherwise reflux into a non-target area can occur.

The end point of the procedure is achieved when the entire amount of chemotherapeutic agents are delivered to the tumor or when there is slowing of flow with pruning of the tumor-feeding branches (the "tree-in-winter" appearance) or transit time of contrast in the feeding artery takes 4 heartbeats. 2-4 mL of Embosphere particles (Biosphere Medical, Boston, MA) measuring 100-500 microns in size are mixed into the final aliquot of the emulsion or injected immediately after the final aliquot depending upon institutional protocol, to slow down arterial inflow and prevent washout of the chemotherapeutic agents.

5.3.2.4 Chemoembolic Administration

a) Draw up 10ml of Ethiodol (lipiodol) in a 20 cc polycarbonate syringe and connect to the 3-way stopcock.

b) Draw up the chemotherapy retrieved from the pharmacy in another 20ml polycarbonate syringe.

c) Use two 10 ml polycarbonate syringes to emulsify 25%-50% of the lipiodol with chemotherapy in a 1:1 to 2:1 ratio with the 3 way stopcock.

d) Administer the chemotherapy/ethiodol mixture (without embolic agents) into the target vessel.

e) Flush the micro catheter with 1% lidocaine solution after each aliquot of chemotherapy is given.

f) After each aliquot of emulsion has been administered, check for patency of artery and flow. If flow remains unchanged, then continue with the initial ratio between chemotherapy and lipiodol and infuse the entire amount in this way. If the flow is diminished, then reduce the oil:chemotherapy ratio in subsequent aliquots.

g) Flow through the main tumor vessel should always be preserved. A small amount of Embospheres (1-4 cc) should be administered with the final aliquot or after the entire chemotherapy/oil mixture.

5.3.2.5 Post-chemoembolization Procedure Orders and Care

a) Post-Procedure Orders.

b) Patients admitted for overnight observation.

c) Hydration with IV NSS at 150 cc/hr x 3 liters; then D 5 ½ NSS at 80 cc/hr or per institutional standard.

d) Medications Administered post-chemoembolization procedure (or per institutional protocol).

i. Cefazolin 1 Gram IV q 8 hours

ii. Metronidazole 500 mg IV q 12 hours

iii. Morphine Sulfate 1-2 mg IV q 1-2 hours, PRN pain

iv. Tylenol #3, 2 tablets pox. q 4 hours, PRN moderate pain

v. Tylenol 650 mg pox. or p.r.n. q 4 hours, PRN fever

vi. Prochlorperazine 25 mg p.r.n. q 8 hours, PRN nausea

vii. Dolasetron 12.5mg q12h X 4 doses or ondansetron 8mg q8h IV x 2 days

viii. Dexamethasone 8 mg IV q 8 hours x 2 days

e) Foley catheter discontinued morning after if urine output adequate, if ordered prior to procedure.

5.3.2.6 Post-Procedure Care

a) Post-arteriography bedrest with monitoring of vital signs and pulses per institutional protocol.

b) Patient can be discharged as soon as they demonstrate adequate oral intake or liquids, and no longer require parenteral narcotics or antiemetics. (Average length of stay is 1.5 days).

c) Fevers $<103^0$ are normal in the first week and do not require cultures.

d) Discharge medications:

i. Antibiotics per institutional protocol if felt to be medically necessary by treating physicians.

ii. Tylenol #3 PRN for pain

iii. Prochlorperazine suppositories PRN for nausea

e) CBC, creatinine, liver function panel, INR, and AFP three weeks post-chemoembolization to assure continued eligibility for additional chemoembolization.

f) Patient returns in approximately 4 weeks for repeat treatment based on anatomy and tumor burden (remaining lobe of the liver or retreat same territory if incompletely embolized).

g) **Optional Based upon Institutional Practice.** Based on institutional practice tumor response within the liver may be assessed by CT or MR imaging studies (chest imaging must be performed by CT), and tumor markers at intervals other than those specified by the study are optional. However, for the purposes of defining progression free survival, only the tumor imaging obtained at the study specified time points (refer to Section 5.3.4) should be used. Please contact study chairs for questions regarding the interpretation of imaging as it relates to determining progression.

Rev. 12/10

5.3.3 LC bead Chemoembolization Protocol (or per institutional standard)

5.3.3.1 LC bead Description

a) LC bead comprise a range of hydrogel microspheres that are biocompatible, hydrophilic, non resorbable, precisely calibrated and capable of loading doxorubicin. LC bead is produced from polyvinyl alcohol and are available in the following size ranges:

Rev. 10/11

Nominal Bead Size	Label Colour	***Upon loading with doxorubicin, LC Bead undergo a slight decrease in size, up to 20% when loading at 25mg/ml***
100 – 300 µm	Yellow	
300 – 500 µm	Blue	
500 – 700 µm	Red	
700 – 900 µm	Green	

b) How supplied:

i. 10 ml glass vial

ii. Each vial contains approximately 2 mL of LC bead in non-pyrogenic, sterile physiological buffered saline. Total volume of saline and LC bead is approximately 8ml.

iii. The vial is stopper sealed by an aluminum cap equipped with a color-coded lid.

iv. Each vial is intended for single patient use only. Do not resterilize. Discard any unused material.

c) Contraindications:

i. Patients intolerant to vascular occlusion procedures.

ii. Vascular anatomy that precludes catheter placement or emboli injection

iii. Presence or likely onset of vasospasm.

iv. Presence or likely onset of hemorrhage.

v. Presence of severe atheromatous disease.
vi. Presence of feeding arteries smaller than distal branches from which they emerge.
vii. Presence of patent extra-to-intracranial anastomoses or shunts.
viii. Presence of collateral vessel pathways potentially endangering normal territories during embolization.
ix. Presence of end arteries leading directly to cranial nerves.
x. Presence of arteries supplying the lesion not large enough to accept LC bead.
xi. Vascular resistance peripheral to the feeding arteries precluding passage of LC bead into the lesion.
xii. Do not use LC bead for embolization of large diameter arteriovenous shunts (i.e. where the blood does not pass through the arterial/capillary/venous transition but directly from artery to vein).
xiii. Do not use LC bead for embolization in any vasculature where LC bead Embolic Agent could pass directly into the internal carotid artery or other non-target territories

5.3.3.2 Drug Loading Instructions:

LC bead is suitable for loading doxorubicin-HCL ONLY. Liposomal formulations of doxorubicin are not suitable for loading into LC bead.

To obtain final loading of 50 to 75mg doxorubicin per 2mL vial of LC bead;

I. Reconstitute a vial containing 50 to 75mg of doxorubicin with 2mL of sterile water for injection. Mix well to obtain a clear red solution (25 to 37.5mg/mL).
II. Remove as much saline as possible from vial of LC bead using a syringe with a small gauge needle.
III. Using a syringe and needle add the 2mL of reconstituted doxorubicin solution directly to the vial of LC bead.
IV. Agitate the LC bead/doxorubicin solution occasionally to encourage mixing until the LC bead is red. Although the solution retains a red color, the doxorubicin will be loaded.
V. Loading will take a minimum of 20 minutes for the smallest size LC bead and up to 120 minutes for the largest size LC bead.
VI. Prior to use, transfer the LC bead loaded with doxorubicin to a syringe and add 1 to 4 times the

Rev. 10/11

volume of the non-ionic contrast media, Omnipaque 350. Invert the syringe gently to obtain an even suspension of DEC bead. A dose of up to 37.5 doxorubicin per mL LC bead can be loaded.

VII. THE MAXMIUM RECOMMENDED TOTAL DOSE OF DOXORUBICIN PER PROCEDURE IS 150MG.

LC bead loaded with doxorubicin may be stored for up to 24 hours in a fridge at 2 - 8ºC in the presence or absence of non-ionic contrast media.;

5.3.3.3 Patient Pre-Procedural Preparation

a) IV Normal Saline per institutional standard.

b) Pre-meds (or institutional standard):

i. cephazolin 1 gm IV

ii. metronidazole 500 mg IV

iii. diphenhydramine 50 mg IV

iv. dexamethazone 10 mg IV

v. dolasetron 100mg or ondansetron 24mg IV

c) Place Foley catheter, if ordered.

5.3.3.4 Chemoembolization Procedural Preparation

a) The patient is prepped and draped in a sterile fashion.

b) Carefully evaluate the vascular network associated with the lesion with high resolution imaging prior to beginning the embolization procedure.

c) LC beads are available in a range of sizes, but only 100 to 500 µm particles should be utilized. Care should also be take to choose the appropriate size of LC bead that best matches the pathology (i.e. vascular target/vessel size) and provides the desired clinical outcome.

d) Choose a delivery catheter based on the size of the target vessel. LC bead can tolerate temporary compression of 20% to 30% in order to facilitate passage through the delivery catheter.

e) Introduce the delivery catheter into the target vessel according to standard techniques. Position the catheter tip as close as possible to the treatment site to avoid inadvertent occlusion of normal vessels.

f) LC beads are not radio-opaque. It is recommended to monitor the embolization under fluoroscopic visualization by adding the desired amount of contrast medium to the suspension fluid.

i. Take care to ensure proper suspension of the LC bead in the contrast medium to enhance distribution during injection.

ii. Draw the LC bead into a syringe needle of a size greater than or to 19 gauge (1.07 mm).
iii. At a rate no faster that 1mL/minute, slowly inject LC bead into the delivery catheter under fluoroscopic visualization while observing the contrast flow rate. Exercise conservative judgment in determining the embolization endpoint.

g) Upon completion of the treatment, remove the catheter while maintaining gentle suction so as not to dislodge LC bead still within the catheter lumen.
h) Discard any unused LC bead loaded with doxorubicin.

5.3.3.5 Post-chemoembolization Procedure Orders and Care

a) Post-Procedure Orders.
b) Patients admitted for overnight observation.
c) Hydration with IV NSS at 150 cc/hr x 3 liters; then D 5 ½ NSS at 80 cc/hr or per institutional standard.
d) Medications Administered post-chemoembolization procedure (or per institutional protocol).
   i. Cefazolin 1 Gram IV q 8 hours
   ii. Metronidazole 500 mg IV q 12 hours
   iii. Morphine Sulfate 1-2 mg IV q 1-2 hours, PRN pain
   iv. Tylenol #3, 2 tablets pox. q 4 hours, PRN moderate pain
   v. Tylenol 650 mg pox. or p.r.n. q 4 hours, PRN fever
   vi. Prochlorperazine 25 mg p.r.n. q 8 hours, PRN nausea
   vii. Dolasetron 12.5mg q12h X 4 doses or ondansetron 8mg q8h IV x 2 days
   viii. Dexamethasone 8 mg IV q 8 hours x 2 days
e) Foley catheter discontinued morning after if urine output adequate, if ordered prior to procedure.

5.3.3.6 Post-Procedure Care

a) Post-arteriography bedrest with monitoring of vital signs and pulses per institutional protocol.
b) Patient can be discharged as soon as they demonstrate adequate oral intake or liquids, and no longer require parenteral narcotics or antiemetics. (Average length of stay is 1.5 days).
c) Fevers $<103^0$ Fare normal in the first week and do not require cultures.
d) Discharge medications:
   i. Antibiotics per institutional protocol if felt to be medically necessary by treating physicians.
   ii. Tylenol #3 PRN for pain

iii. Prochlorperazine suppositories PRN for nausea

e) CBC, creatinine, liver function panel, INR, and AFP three weeks post-chemoembolization to assure continued eligibility for additional chemoembolization.

f) Patient returns in approximately 4 weeks for repeat treatment based on anatomy and tumor burden (remaining lobe of the liver or retreat same territory if incompletely embolized).

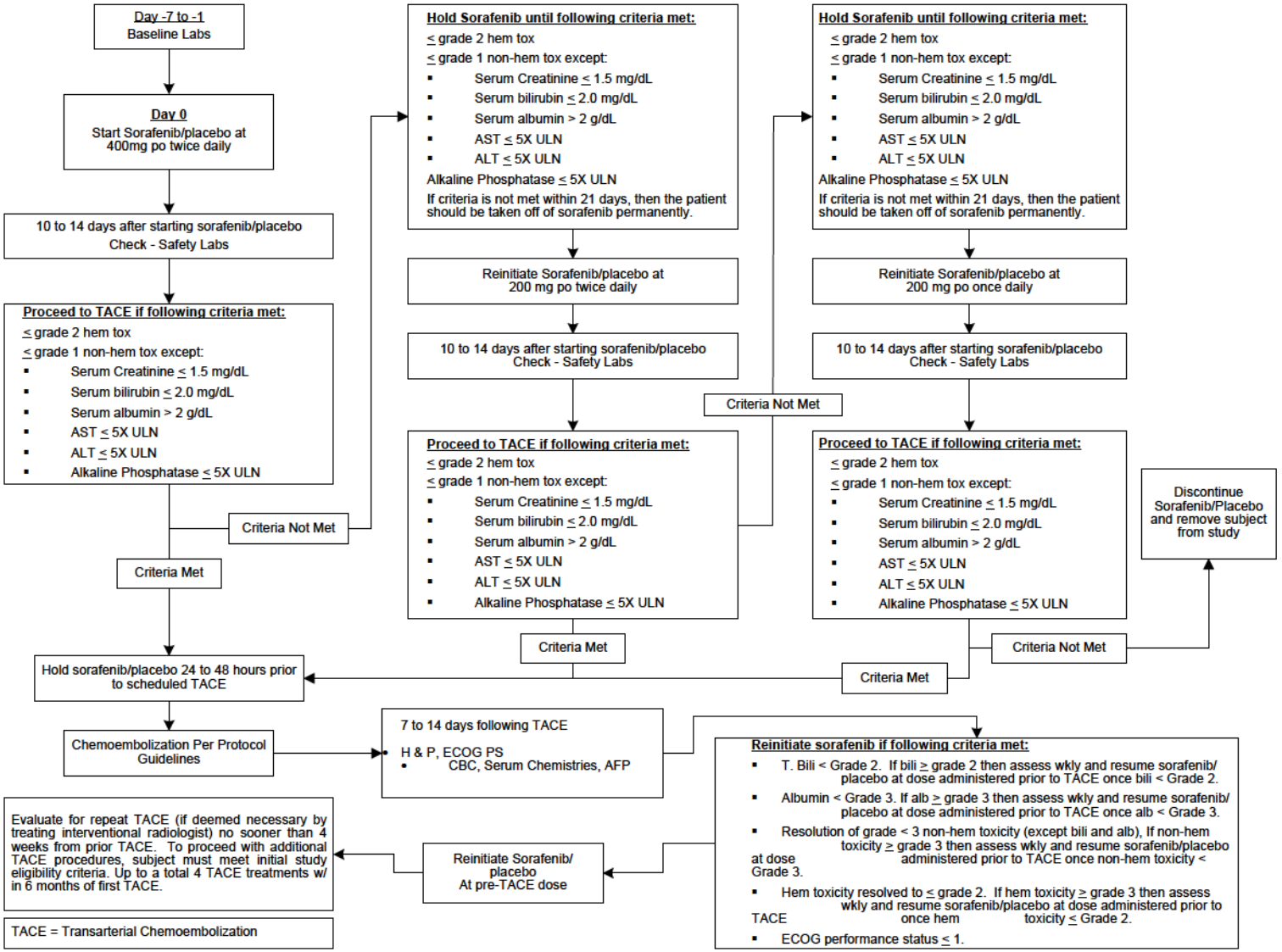
g) **Optional Based upon Institutional Practice.** Based on institutional practice tumor response within the liver may be assessed by CT or MR imaging studies (chest imaging must be performed by CT), and tumor markers at intervals other than those specified by the study are optional. However, for the purposes of defining progression free survival, only the tumor imaging obtained at the study specified time points (refer to Section 5.3.4) should be used. Please contact study chairs for questions regarding the interpretation of imaging as it relates to determining progression.

Rev. 12/10

Rev. 12/10

Rev. 5/12

Figure 5.2 - Treatment Algorithm



Rev. 10/10 NOTE: If a patient is unable to reach a stable dose of Sorafenib within 28 days after the first dose of Sorafenib, or within 42 days after chemoembolization, they are to be removed from the study.

5.3.4 Tumor imaging studies for the purposes of determining PFS are to be performed as follows:

- Baseline (chest CT, Abdomen/pelvis CT or MRI)
- 4 months after first chemoembolization (chest CT, Abdomen/pelvis CT or MRI)
- 8 months after first chemoembolization (chest CT, Abdomen/pelvis CT or MRI)
- Every 2 months beginning at 10 months post baseline

It is recognized that there is regional variability for the follow up care of chemoembolization that may result in additional tumor imaging outside of the required imaging scans. Please follow the recommended guidelines for scan interpretation to assist in determining disease progression. For questions regarding scan interpretation in relation to disease progression, investigators are urged to contact the study chairs.

Rev. 9/10

All CT and MRI images must be submitted to ACRIN for all study participants. Imaging guidelines and image submission instructions are detailed in Appendix X.

Chest Imaging

Chest imaging is required at baseline by computer tomography in all patients. Imaging protocol is detailed below. Repeat chest imaging is required at 4 months and 8 months after first chemoembolization. Chest CT should be performed every 2 months thereafter until patient is no longer on-study.

Abdominal/Pelvic Imaging

Abdominal/Pelvic imaging may be performed by CT or MRI. Contrasted enhanced imaging is required. Detailed imaging protocols are indicated below. Repeat abdominal-pelvic imaging is required at 4 months and 8 months after first chemoembolization. After 8 months, abdominal imaging is required every two month until patient is no longer on-study. If there is no evidence of pelvic disease. Pelvic imaging need not be performed

Rev. 9/10

The same imaging modality MUST be used throughout the course of the trial, unless a change in modality is mandated.

Clinical management and treatment decisions will be made by the treating physician based on local site assessments and other clinically appropriate considerations.

Rev. 6/14

5.4 Adverse Event Reporting Requirements

5.4.1 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. Adverse events are reported in a routine manner

at scheduled times during a trial (please refer to the E1208 Forms Packet for the list of forms with directions for routine adverse event reporting). Additionally, certain adverse events must be reported in an expedited manner for more timely monitoring of patient safety and care. The following sections provide information about expedited reporting.

5.4.2 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 arm includes both investigational and commercial agents, the following rules apply.

- *Concurrent administration:* When an investigational agent(s) is used in combination with a commercial agent(s), the combination is considered to be investigational and expedited reporting of adverse events would follow the guidelines for investigational agents.

Steps to determine if an adverse event is to be reported in an expedited manner:

Rev. 12/10

Step 1: *Identify the type of event*. The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) v4.0 will be utilized for AE reporting. The Version 4.0 of the CTCAE is identified and located on the CTEP website at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTEP version 4.0 of CTCAE.

Rev. 12/10

Step 2: *Grade the event using the NCI CTCAE* v4.0.

Step 3: *Determine whether the adverse event is related to the protocol therapy (investigational or commercial).* Attribution categories are as follows: Unrelated, Unlikely, Possible, Probable, and Definite.

Rev. 5/12

Step 4: *Determine the prior experience of the adverse event*. *Expected* events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered *unexpected*, for expedited reporting purposes only, when either the type of event or the severity of the event is NOT listed in:

- **Arm X** – the current NCI Specific Protocol Exceptions to Expedited Reporting (SPEER) for Sorafenib or package insert/protocol for the commercial agents

NOTE: The NCI SPEER for Sorafenib is included in Section 5.5 of the protocol.

- FOR THIS PROTOCOL, events listed in the SPEER for Sorafenib should be considered EXPECTED if the grade being reported is the same or lower than the grade noted in the parentheses next to the AE in the SPEER. Events listed in the SPEER column should be considered UNEXPECTED if the grade being reported exceeds the grade noted in parentheses next to the AE in the SPEER.
- If the event being reported is listed in **EITHER** the SPEER for Sorafenib or the package insert/protocol for the commercial agents, then it is considered 'expected' for CTEP-AERS adverse event reporting purposes, regardless of the grade.

The SPEER is presented in the last column of the CAEPR and identified with ***bold*** and ***italicized*** text.

Step 5: *Review the "Additional instructions, requirements, and exceptions for protocol E1208" table in section 5.4.6 for protocol and/or ECOG-ACRIN specific requirements for expedited reporting of specific adverse events that require special monitoring.*

NOTE: For general questions regarding expedited reporting requirements, please contact the AEMD Help Desk at aemd@tech-res.com or 301-897-7497.

Rev. 5/12

5.4.3 Reporting Procedure

This study requires that expedited adverse event reporting use CTEP's Adverse Event Reporting System (CTEP-AERS). CTEP's guidelines for CTEP-AERS can be found at http://ctep.cancer.gov. A CTEP-AERS report must be submitted electronically to ECOG-ACRIN and the appropriate regulatory agencies via the CTEP-AERS Web-based application located at http://ctep.cancer.gov.

In the rare event when Internet connectivity is disrupted a 24-hour notification is to be made by telephone to

- the AE Team at ECOG-ACRIN (617-632-3610)
- the NCI (301-897-7497)

An electronic report MUST be submitted immediately upon re-establishment of internet connection.

Supporting and follow up data: Any supporting or follow up documentation must be faxed to ECOG-ACRIN (617-632-2990), Attention: AE within 48-72 hours. In addition, supporting or follow up documentation must be faxed to the NCI (301- 230-0159) in the same timeframe.

NCI Technical Help Desk: For any technical questions or system problems regarding the use of the CTEP-AERS application, please contact the NCI Technical Help Desk at ncictephelp@ctep.nci.nih.gov or by phone at 1-888-283-7457.

5.4.4 When to Report an Event in an Expedited Manner

Some adverse events require 24-hour notification (refer to Section 5.4.6). Please complete a 24-Hour Notification Report via the CTEP-AERS website (http://ctep.cancer.gov) within 24 hours of learning of the event. The full CTEP-AERS report must be completed and submitted via CTEP-AERS within 5 calendar days.

If the CTEP-AERS system is down, a 24-hour notification call must be made to ECOG-ACRIN (617-632-3610) and to NCI (301-897-7497). Once the system is restored, a 24-hour Notification Report must be entered into the CTEP-AERS system by the original submitter of the report at the site.

When an adverse event requires expedited reporting, submit a full CTEP-AERS report within the timeframes outlined in Section 5.4.6.

NOTE: Adverse events that meet the reporting requirements in Section 5.4.6 and occur within 30 days of the last dose of protocol treatment must be reported on an expedited adverse event report form (using CTEP-AERS). For any adverse events that occur more than 30 days after the last dose of treatment, only those that have an attribution of possibly, probably, or definitely AND meet the reporting requirements in Section 5.4.6 must be reported on an expedited adverse event report form (using CTEP-AERS).

5.4.5 Other Recipients of Adverse Event Reports

DCTD/NCI will notify ECOG-ACRIN/pharmaceutical collaborator(s) of all AEs reported to FDA. Any additional written AE information requested by ECOG-ACRIN MUST be submitted to BOTH the NCI and ECOG-ACRIN.

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

5.4.6 Expedited Reporting for Investigational Agents

Phase 2 and 3 Trials Utilizing an Agent under a CTEP IND: CTEP-AERS Reporting Requirements for Adverse Events That Occur Within 30 Days[1] of the Last Dose of Investigational Agent (Sorafenib/Placebo) in this Study (Arm X) OR Within 30 Days of the Last Dose of Any Protocol Treatment.

Attribution	Grade 1	Grade 2	Grade 2	Grade 3		Grade 3		Grades 4 & 5[2]	Grades 4 & 5[2]
	Unexpected and Expected	Unexpected	Expected	Unexpected		Expected		Unexpected	Expected
				with Hospitalization	without Hospitalization	with Hospitalization	without Hospitalization		
Unrelated Unlikely	Not Required	Not Required	Not Required	10 Calendar Days	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days
Possible Probable Definite	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days	10 Calendar Days	Not Required	24-Hour; 5 Calendar Days	10 Calendar Days

[1] **Adverse events with attribution of possible, probable, or definite that occur <u>greater</u> than 30 days after the last dose of treatment with an agent under a CTEP IND require reporting as follows:**

CTEP-AERS 24-hour notification followed by complete report within 5 calendar days for:

- Grade 4 and Grade 5 unexpected events

CTEP-AERS 10 calendar day report:

- Grade 3 unexpected events with hospitalization or prolongation of hospitalization
- Grade 5 expected events

[2] Although an CTEP-AERS 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table.

Please see additional information below under section entitled "Additional instructions, requirements, and exceptions for protocol E1208"

March 2005

NOTE: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause should be provided.

- **Expedited AE reporting timelines:**
  - **24 Hours; 5 calendar days** – The investigator must initially report the AE via CTEP-AERS within <u>24 hours</u> of learning of the event followed by a complete CTEP-AERS report within <u>5 calendar days</u> of the initial 24-hour report.

- **10 calendar days** – A complete CTEP-AERS report on the AE must be submitted within 10 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 disability/incapacity, congenital anomaly, or birth defect** 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.

*Hospitalizations are defined as lasting 24 hours or longer and these events must be reported via CTEP-AERS.

Additional instructions, requirements and exceptions for protocol E1208

1. Additional Instructions:

- With respect to determining the specific day by which the event must be reported, the day the reporter learns of the adverse event constitutes "Day 0"
- For grade 2 and 3 unexpected events, CTEP-AERS reporting is only required if the event is related to the investigational agent(s); it is not required if the event is related only to the commercial agent(s) included in the protocol treatment.

  NOTE: For grade 3 unexpected events with hospitalization lasting ≥ 24 hours (or prolonged hospitalization), an CTEP-AERS report is required even if the event is unrelated to the investigational agent(s).
- For instructions on how to specifically report events that result in persistent or significant disability/incapacity, congenital anomaly, or birth defect events via CTEP-AERS, please contact the AEMD Help Desk at aemd@tech-res.com or 301-897-7497. This will need to be discussed on a case-by-case basis.

2. ECOG-ACRIN and Protocol Specific expedited reporting requirements:

The adverse events listed below also require expedited reporting for this trial:

ECOG-ACRIN specific expedited reporting requirements:

- **Hospitalizations:** Any grade 1 or 2 adverse event which precipitates a hospitalization lasting ≥ 24 hours (or prolongs hospitalization) must be reported via CTEP-AERS within 10 calendar days of learning of the event regardless of the attribution and designation as expected or unexpected.

3. Protocol specific expedited reporting exceptions:

For study arm X, the adverse events listed below **do not** require expedited reporting via CTEP-AERS:

- Grade 4 expected myelosuppresion (unless it results in a hospitalization, in which case, a CTEP-AERS report is required).

Rev. 9/10, 5/12

5.4.7 Reporting Second Primary Cancers

All cases of second primary cancers, including acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS), that occur following treatment on NCI-sponsored trials must be reported to ECOG-ACRIN:

- **A second malignancy is a cancer that is UNRELATED to any prior anti-cancer treatment (including the treatment on this protocol). Second malignancies require ONLY routine reporting as follows:**
  1. Submit a completed Second Primary Form within 30 days to ECOG-ACRIN at

     ECOG-ACRIN Operations Office – Boston
     FSTRF
     900 Commonwealth Avenue
     Boston, MA 02215
  2. Submit a copy of the pathology report to ECOG-ACRIN confirming the diagnosis.
  3. If the patient has been diagnosed with AML/MDS, submit a copy of the cytogenetics report (if available) to ECOG-ACRIN
- **A secondary malignancy is a cancer CAUSED BY any prior anti-cancer treatment (including the treatment on this protocol). Secondary malignancies require both routine and expedited reporting as follows:**
  1. Submit a completed Second Primary Form within 30 days to ECOG-ACRIN at

     ECOG-ACRIN Operations Office – Boston
     FSTRF
     900 Commonwealth Avenue
     Boston, MA 02215
  2. Report the diagnosis via CTEP-AERS at http://ctep.cancer.gov

     Report under a.) leukemia secondary to oncology chemotherapy, b.) myelodysplastic syndrome, or c.) treatment related secondary malignancy
  3. Submit a copy of the pathology report to ECOG-ACRIN and NCI/CTEP confirming the diagnosis.
  4. If the patient has been diagnosed with AML/MDS, submit a copy of the cytogenetics report (if available) to ECOG-ACRIN and NCI/CTEP.

NOTE: The Second Primary Form and the CTEP-AERS report should not be used to report recurrence or development of metastatic disease.

NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the Second Primary Form must be submitted for the most recent trial. ECOG-ACRIN must be provided with a copy of the form and the associated

pathology report and cytogenetics report (if available) even if ECOG-ACRIN was not the patient's most recent trial.

NOTE: Once data regarding survival and remission status are no longer required by the protocol, no follow-up data should be submitted via CTEP-AERS or by the Second Primary Form.

Rev. 9/10, 5/12, 6/14, 9/14, 3/16

5.5 Comprehensive Adverse Events and Potential Risks list (CAEPR) for Sorafenib (BAY 43-9006, NSC 724772)

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 2571 patients.* Below is the CAEPR for Sorafenib (BAY 43-9006; Nexavar).

NOTE: FOR THIS PROTOCOL, events listed in the SPEER column should be considered EXPECTED if the grade being reported is the same or lower than the grade noted in the parentheses next to the AE in the SPEER. Events listed in the SPEER column should be considered UNEXPECTED if the grade being reported exceeds the grade noted in parentheses next to the AE in the SPEER.

NOTE: If the event being reported is listed in **EITHER** the SPEER for Sorafenib or the package insert/protocol for the commercial agents, then it is considered 'expected' for CTEP-AERS adverse event reporting purposes, regardless of the grade.

Version 2.7, November 16, 2015[1]

Adverse Events with Possible Relationship to Sorafenib (BAY 43-9006; Nexavar) (CTCAE 4.0 Term) [n= 2571]			**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)***
CARDIAC DISORDERS			
		Acute coronary syndrome	
	Chest pain - cardiac		
		Heart failure	
		Left ventricular systolic dysfunction	
		Myocardial infarction	
GASTROINTESTINAL DISORDERS			
Abdominal pain			***Abdominal pain (Gr 3)***
	Ascites		
	Constipation		***Constipation (Gr 2)***
Diarrhea			***Diarrhea (Gr 3)***

Adverse Events with Possible Relationship to Sorafenib (BAY 43-9006; Nexavar) (CTCAE 4.0 Term) [n= 2571]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Gastrointestinal hemorrhage[2]		***Gastrointestinal hemorrhage[2] (Gr 3)***
		Gastrointestinal perforation[3]	
	Mucositis oral		
Nausea			***Nausea (Gr 3)***
	Vomiting		***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Edema limbs		
Fatigue			***Fatigue (Gr 3)***
	Fever		***Fever (Gr 2)***
HEPATOBILIARY DISORDERS			
		Hepatic failure	
IMMUNE SYSTEM DISORDERS			
		Anaphylaxis	
INFECTIONS AND INFESTATIONS			
	Infection[4]		
INVESTIGATIONS			
	Activated partial thromboplastin time prolonged		***Activated partial thromboplastin time prolonged (Gr 2)***
Alanine aminotransferase increased			***Alanine aminotransferase increased (Gr 3)***
Alkaline phosphatase increased			***Alkaline phosphatase increased (Gr 3)***
Aspartate aminotransferase increased			***Aspartate aminotransferase increased (Gr 3)***
Blood bilirubin increased			***Blood bilirubin increased (Gr 3)***
Creatinine increased			***Creatinine increased (Gr 3)***
		Electrocardiogram QT corrected interval prolonged	
	GGT increased		
INR increased			***INR increased (Gr 3)***
	Investigations - Other (bicarbonate-serum low)		

Adverse Events with Possible Relationship to Sorafenib (BAY 43-9006; Nexavar) (CTCAE 4.0 Term) [n= 2571]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
Lipase increased			***Lipase increased (Gr 3)***
Lymphocyte count decreased			***Lymphocyte count decreased (Gr 3)***
	Neutrophil count decreased		***Neutrophil count decreased (Gr 4)***
Platelet count decreased			***Platelet count decreased (Gr 4)***
Serum amylase increased			***Serum amylase increased (Gr 3)***
Weight loss			***Weight loss (Gr 2)***
White blood cell decreased			***White blood cell decreased (Gr 4)***
METABOLISM AND NUTRITION DISORDERS			
Anorexia			***Anorexia (Gr 3)***
	Hypercalcemia		
Hyperglycemia			***Hyperglycemia (Gr 3)***
	Hyperkalemia		***Hyperkalemia (Gr 3)***
	Hypernatremia		
Hypoalbuminemia			***Hypoalbuminemia (Gr 3)***
Hypocalcemia			***Hypocalcemia (Gr 3)***
	Hypoglycemia		***Hypoglycemia (Gr 2)***
	Hypokalemia		***Hypokalemia (Gr 3)***
Hyponatremia			***Hyponatremia (Gr 3)***
Hypophosphatemia			***Hypophosphatemia (Gr 3)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		***Arthralgia (Gr 3)***
	Back pain		***Back pain (Gr 3)***
	Bone pain		
	Musculoskeletal and connective tissue disorder - Other (muscle spasm)		
	Myalgia		
	Pain in extremity		***Pain in extremity (Gr 3)***

Adverse Events with Possible Relationship to Sorafenib (BAY 43-9006; Nexavar) (CTCAE 4.0 Term) [n= 2571]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			
	Treatment related secondary malignancy		
NERVOUS SYSTEM DISORDERS			
	Dizziness		
	Headache		***Headache (Gr 3)***
		Intracranial hemorrhage	
		Reversible posterior leukoencephalopathy syndrome	
PSYCHIATRIC DISORDERS			
	Insomnia		
RENAL AND URINARY DISORDERS			
	Acute kidney injury		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		***Dyspnea (Gr 3)***
	Respiratory hemorrhage[4]		
	Voice alteration		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
Alopecia			***Alopecia (Gr 2)***
	Dry skin		***Dry skin (Gr 2)***
		Erythema multiforme	
Palmar-plantar erythrodysesthesia syndrome			***Palmar-plantar erythrodysesthesia syndrome (Gr 3)***
	Pruritus		***Pruritus (Gr 3)***
Rash maculo-papular			***Rash maculo-papular (Gr 3)***
		Stevens-Johnson syndrome	
		Toxic epidermal necrolysis	
VASCULAR DISORDERS			
	Hypertension		***Hypertension (Gr 3)***
		Thromboembolic event	

[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] Gastrointestinal hemorrhage may include 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.

[3] Gastrointestinal perforation may include Colonic perforation, Duodenal perforation, Esophageal perforation, Gastric perforation, Ileal perforation, Jejunal perforation, Rectal perforation, and Small intestinal perforation under the GASTROINTESTINAL DISORDERS SOC.

[4] Infection may include any of the 75 infection sites under the INFECTIONS AND INFESTATIONS SOC.

[5] Respiratory hemorrhage may include bronchopulmonary hemorrhage, epistaxis, laryngeal hemorrhage, mediastinal hemorrhage, pharyngeal hemorrhage, and pleural hemorrhage under the RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS SOC.

[6] Febrile neutropenia is seen mostly in combination with other agents.

Adverse events reported on sorafenib (BAY 43-9006; Nexavar) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that sorafenib (BAY 43-9006; Nexavar) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (Thrombotic microangiopathy [e.g., TTP or HUS]); Febrile neutropenia[6]

CARDIAC DISORDERS - Atrial fibrillation; Atrial flutter; Cardiac arrest; Palpitations; Pericardial effusion; Pericarditis; Right ventricular dysfunction; Sinus bradycardia; Sinus tachycardia; Supraventricular tachycardia; Ventricular arrhythmia; Ventricular tachycardia

EAR AND LABYRINTH DISORDERS - Hearing impaired; Tinnitus

ENDOCRINE DISORDERS - Adrenal insufficiency; Hyperthyroidism; Hypothyroidism

EYE DISORDERS - Blurred vision; Cataract; Dry eye; Extraocular muscle paresis; Eye disorders - Other (color vision deficits); Eye disorders - Other (light to dark adaptation); Eye disorders - Other (retinal vein occlusion); Eye disorders - Other (retinal hemorrhage); Eye disorders - Other (visual field distortion); Flashing lights; Keratitis; Photophobia; Retinal detachment

GASTROINTESTINAL DISORDERS - Abdominal distension; Anal fistula; Anal mucositis; Anal pain; Anal ulcer; Cheilitis; Colitis; Colonic obstruction; Colonic ulcer; Dry mouth; Duodenal ulcer; Dyspepsia; Dysphagia; Enterocolitis; Esophageal pain; Esophagitis; Flatulence; Gastric ulcer; Gastritis; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (diverticulitis); Gastrointestinal disorders - Other (small bowel NOS fistula); Gastrointestinal fistula; Hemorrhoids; Ileal fistula; Ileus; Oral pain; Pancreatitis; Proctitis; Rectal fistula; Rectal mucositis; Rectal obstruction; Rectal pain; Small intestinal obstruction; Stomach pain

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Edema face; Facial pain; Flu like symptoms; Localized edema; Multi-organ failure; Non-cardiac chest pain; Pain

HEPATOBILIARY DISORDERS - Cholecystitis; Hepatic hemorrhage; Hepatobiliary disorders - Other (biliary obstruction secondary to multiple biliary stones)

IMMUNE SYSTEM DISORDERS - Allergic reaction; Cytokine release syndrome; Immune system disorders - Other (systemic inflammatory response syndrome)

INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Arterial injury; Fall; Fracture; Hip fracture; Vascular access complication; Wound complication; Wound dehiscence

INVESTIGATIONS - CPK increased; Cardiac troponin I increased; Cardiac troponin T increased; Cholesterol high; Ejection fraction decreased; Fibrinogen decreased; Investigations - Other (blood urea nitrogen high)

METABOLISM AND NUTRITION DISORDERS - Acidosis; Alkalosis; Dehydration; Hypermagnesemia; Hypertriglyceridemia; Hyperuricemia; Hypomagnesemia; Tumor lysis syndrome

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthritis; Chest wall pain; Generalized muscle weakness; Joint range of motion decreased; Muscle weakness left-sided; Muscle weakness lower limb; Muscle weakness right-sided; Muscle weakness upper limb; Musculoskeletal and connective tissue disorders - Other (cramping); Myositis; Neck pain

NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Leukemia secondary to oncology chemotherapy; Myelodysplastic syndrome; Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (tumor hemorrhage); Tumor pain

NERVOUS SYSTEM DISORDERS - Ataxia; Cognitive disturbance; Depressed level of consciousness; Dysgeusia; Dysphasia; Encephalopathy; Extrapyramidal disorder; Hydrocephalus; Ischemia cerebrovascular; Lethargy; Leukoencephalopathy; Memory impairment; Neuralgia; Peripheral motor neuropathy; Peripheral sensory neuropathy; Seizure; Stroke; Syncope; Tremor; Vasovagal reaction

PSYCHIATRIC DISORDERS - Agitation; Anxiety; Confusion; Depression; Libido decreased; Personality change; Psychosis

RENAL AND URINARY DISORDERS - Chronic kidney disease; Hematuria; Proteinuria; Renal and urinary disorders - Other (focal segmental glomerulosclerosis); Renal and urinary disorders - Other (nephrotic syndrome); Renal and urinary disorders - Other (right ureter rupture); Renal calculi; Renal hemorrhage; Urinary frequency; Urinary incontinence; Urinary retention; Urinary tract obstruction; Urine discoloration

REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Erectile dysfunction; Gynecomastia; Hematosalpinx; Menorrhagia; Ovarian hemorrhage; Prostatic hemorrhage; Spermatic cord hemorrhage; Testicular hemorrhage; Uterine hemorrhage; Vaginal fistula; Vaginal hemorrhage

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Allergic rhinitis; Bronchospasm; Hiccups; Hoarseness; Hypoxia; Laryngeal mucositis; Pharyngeal mucositis; Pharyngolaryngeal pain; Pleural effusion; Pneumonitis; Pneumothorax; Pulmonary edema; Pulmonary fibrosis; Respiratory, thoracic and mediastinal disorders - Other (nasal septal perforation); Tracheal mucositis

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Erythroderma; Hyperhidrosis; Nail loss; Pain of skin; Purpura; Rash acneiform; Scalp pain; Skin and subcutaneous tissue disorders - Other (folliculitis); Skin and subcutaneous tissue disorders - Other (non-life threatening squamous cell carcinoma of skin: keratoacanthoma type); Skin hyperpigmentation; Skin hypopigmentation; Skin ulceration; Urticaria

VASCULAR DISORDERS - Flushing; Hematoma; Hot flashes; Hypotension; Phlebitis; Vascular disorders - Other (ruptured aortic aneurysm); Vascular disorders - Other (visceral arterial ischemia); Vasculitis

NOTE: Sorafenib (BAY 43-9006; Nexavar) 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.

5.6 Dose Modifications

NOTE: Protocol treatment must be discontinued if the patient's treatment is interrupted or held for six continuous weeks for any reason.

Rev. 12/10

All toxicities should be graded according to the Common Terminology Criteria for Adverse Events v4.0 with the exception of Palmar-plantar erythrodysesthesia syndrome which is outlined below in Table 5.C. According to the following tables, the final dose modification should be based upon the worst grade of toxicity experienced.

Table 5.C Grading for Palmar-plantar erythrodysesthesia syndrome	
Grade 1	Numbness, dysesthesia/paresthesia, tingling, painless swelling or erythema of the hands and/or feet and/or discomfort, which does not disrupt normal activities.
Grade 2	Painful erythema and swelling of the hands and/or feet and/or discomfort affecting the subject's activities.
Grade 3	Moist desquamation, ulceration, blistering or severe pain of the hands and/or feet and/or severe discomfort that causes the subject to be unable to work or perform activities of daily living.

There will be no dose reductions for chemotherapeutic agents (mitomycin-C, doxorubicin, cisplatin) utilized during chemoembolization procedures.

Sorafenib doses will be interrupted or reduced for clinically significant toxicities that are related to protocol therapy as outlined in section 5.2 with the exception of Palmar-plantar erythrodysesthesia syndrome which is outlined in Table 5.E in Section 5.7.3. All dose modifications will follow predefined dose levels:

Table 5.D Dose modification levels for sorafenib/placebo treatment.	
Dose Level 1	**400 mg twice a day**
Dose Level -1	**200 mg twice a day**
Dose Level -2	**200 mg once a day**

If dose reduction beyond dose level -2 is required, the subject should be discontinued from the study.

5.7 Supportive Care

All supportive measures consistent with optimal patient care will be given throughout the study.

5.7.1 Antiemetics

Symptomatic nausea induced by agents utilized in E1208 may be treated with commercially available antiemetic agents.

5.7.2 Growth factor

Prophylactic use of G-CSF or GM-CSF is not permitted on this trial. Therapeutic G-CSF use in patients with serious neutropenic

complications may be given at the investigator's discretion and should follow ASCO guidelines for G-CSF use.

5.7.3 Palmar-plantar erythrodysesthesia syndrome

Providers are encouraged to refer study subjects with difficult to manage to a dermatologist for treatment. At the first occurrence of independent of grade, prompt institution of supportive measures such as topical emollients, low-potency steroids or urea-containing cream should be administered. For additional strategies to manage HFSR please refer to the following manuscript. Lacouture and colleagues, Evolving Strategies for the Management Associated with the Multitargeted Kinase Inhibitors Sorafenib and Sunitinib, The Oncologist 2008; 13:1001-1011

Table 5.E: Skin Toxicity Criteria for Dose Interruption and Dose Modification

Toxicity Grade		During a Course of Therapy	Dose for Next Cycle
Grade 1		Maintain dose level	Maintain dose level
Grade 2	1st appearance	Interrupt until resolved to grade 0-1	Maintain dose level
	2nd appearance	Interrupt until resolved to grade 0-1	Consider decreasing dose frequency or level.
	3rd appearance	Interrupt until resolved to grade 0-1	Consider decreasing dose frequency or level.
	4th appearance	Discontinue treatment permanently	
Grade 3	1st appearance	Interrupt until resolved to grade 0-1	Consider decreasing dose frequency or level.[a]
	2nd appearance	Interrupt until resolved to grade 0-1	Consider decreasing dose frequency or level.
	3rd appearance	Discontinue treatment permanently	

a For subjects who require a dose reduction for grade 3 rash or Palmar-plantar erythrodysesthesia syndrome, the dose of study drug may be increased to the starting dose after one full cycle of therapy has been administered at the reduced dose without the appearance of rash or Palmar-plantar erythrodysesthesia syndrome ≥ grade 1.

5.7.4 Post-Chemoembolization Procedure Caps

Please refer to Section 5.3.3.6.

5.8 Duration of Therapy

Patients will receive protocol therapy unless:

- Extraordinary Medical Circumstances: If at any time the constraints of this protocol are detrimental to the patient's health, protocol treatment should be discontinued. In this event, submit forms according to the instructions in the E1208 Forms packet.
- Patient withdraws consent
- Disease progression is documented

- Treatment is discontinued for toxicity as outlined in Section 5.2

5.9 Duration of Follow-up

For this protocol, all patients, including those who discontinue protocol therapy early, will be followed for response until progression, even if non-protocol therapy is initiated, and for survival for 4 years from the date of registration. All patients must also be followed through completion of all protocol therapy.

6. Measurement of Effect

Rev. 12/10

NOTE: Please refer to section 5.3.4 for detailed information regarding the schedule and interpretation of tumor imaging

6.1 Solid Tumor Response Criteria (RECIST)

6.1.1 Malignant Disease Evaluation

To assess objective response, it is necessary to estimate the overall tumor burden at baseline to which subsequent measurements will be compared. Measurable disease is defined by the presence of at least one measurable lesion.

All measurements should be recorded in metric notation by use of a ruler or calipers. The same method of assessment and the same technique should be used to characterize each identified lesion at baseline and during follow-up. All baseline evaluations should be performed as closely as possible to the beginning of treatment and **never more than four weeks** before registration.

The term evaluable in reference to measurability will not be used because it does not provide additional meaning or accuracy.

At baseline, tumor lesions will be characterized as either measurable or non-measurable.

6.1.1.1 Measurable

Lesions that can be accurately measured in at least one dimension (longest diameter to be recorded) as > 20 mm (2.0 cm) with conventional techniques or as > 10 mm (1.0 cm) with **spiral** CT scan.

If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

6.1.1.2 Non-Measurable

All other lesions, including small lesions [longest diameter < 20 mm (2.0 cm) with conventional techniques or < 10 mm (1.0 cm) with **spiral** CT scan] and truly non-measurable lesions.

Lesions considered to be truly non-measurable include the following: bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, abdominal masses that are not confirmed and followed by imaging techniques, and cystic lesions.

6.1.2 Definitions of Response

6.1.2.1 Target Lesions

All measurable lesions up to a maximum of five lesions per organ and 10 lesions in total, representative of all involved organs. Target lesions should be selected on the basis of their size (those with the longest diameters) and their suitability for accurate repeated measurements.

The sum of the longest diameters of all target lesions will be calculated at baseline and reported as the bas*eline sum longest diameter*. The *sum longest diameter* will be used to characterize the objective tumor response. For lesions measurable in 2 or 3 dimensions, always report the longest diameter at the time of each assessment.

6.1.2.2 Complete Response (CR)

The disappearance of all target lesions. To be assigned a status of complete response, changes in tumor measurements must be confirmed by repeat assessments performed **no less than four weeks** after the criteria for response are first met.

6.1.2.3 Partial Response (PR)

At least a 30% decrease in the sum of the longest diameters of target lesions, taking as reference the *baseline sum longest diameter*. To be assigned a status of partial response, changes in tumor measurements must be confirmed by repeat assessments performed **no less than four weeks** after the criteria for response are first met.

6.1.2.4 Progressive Disease (PD)

Rev. 12/10

NOTE: **Please refer to section 5.3.4 for detailed information regarding the schedule and interpretation of tumor imaging**

At least a 20% increase in the sum of the longest diameters of target lesions, taking as reference the *smallest sum longest diameter* recorded since the baseline measurements, or the appearance of one or more new lesion(s).

6.1.2.5 Stable Disease (SD)

Rev. 12/10

NOTE: **Please refer to section 5.3.4 for detailed information regarding the schedule and interpretation of tumor imaging**

Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease. To be assigned a status of stable disease, measurements must have met the stable disease criteria at least once

after study entry at a minimum interval (not less than 8 weeks).

6.1.3 Nontarget Lesions

All other lesions or sites of disease. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

6.1.3.1 Complete Response (CR)

The disappearance of all nontarget lesions and normalization of tumor marker levels, if applicable. To be assigned a status of complete response, changes in tumor measurements must be confirmed by repeat assessments performed **no less than four weeks** after the criteria for response are first met.

6.1.3.2 Incomplete Response/Stable Disease (SD)

Rev. 12/10

NOTE: **Please refer to section 5.3.4 for detailed information regarding the schedule and interpretation of tumor imaging**

The persistence of one or more nontarget lesion(s) and/**or** the maintenance of tumor marker levels above the normal limits. To be assigned a status of stable disease, measurements must have met the stable disease criteria at least once after study entry at a minimum interval (not less than 8 weeks).

6.1.3.3 Progressive Disease (PD)

Rev. 12/10

NOTE: **Please refer to section 5.3.4 for detailed information regarding the schedule and interpretation of tumor imaging**

The appearance of one or more new lesion(s) and/or unequivocal progression of existing nontarget lesions.

6.1.4 Symptomatic Deterioration

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having symptomatic deterioration.

6.2 Evaluation of Patient's Best Overall Response

The best overall response is the best response recorded from registration until disease progression/recurrence, taking as reference for progressive disease the smallest measurements recorded since registration. The table below provides overall responses for all possible combinations of tumor responses in target and nontarget lesions, with or without new lesions.

To be assigned a status of complete or partial response, changes in tumor measurements must be confirmed by repeat assessments performed **no less than four weeks** after the criteria for response are first met.

To be assigned a status of stable disease, measurements must have met the stable disease criteria at least once after study entry at a minimum interval (not less than 8 weeks).

Overall Response for all Possible Combinations of Tumor Response

Target Lesions	Nontarget Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease

6.2.1 First Documentation of Response

The time between initiation of therapy and first documentation of PR or CR.

6.2.2 Confirmation of Response

To be assigned a status of complete or partial response, changes in tumor measurements must be confirmed by repeat assessments performed **no less than four weeks** after the criteria for response are first met.

6.2.3 Duration of Response

Rev. 12/10

NOTE: **Please refer to section 5.3.4 for detailed information regarding the schedule and interpretation of tumor imaging**

Duration of overall response – the period measured from the time that measurement criteria are met for complete or partial response (whichever status is recorded first) until the first date that recurrent or progressive disease is objectively documented, taking as reference the smallest measurements recorded since treatment started.

6.2.3.1 Duration of Overall Complete Response

The period measured from the time measurement criteria are met for complete response until the first date that recurrent disease is objectively documented.

6.2.3.2 Duration of Stable Disease

A measurement from registration until the criteria for disease progression is met, taking as reference the smallest measurements recorded since registration. To be assigned a status of stable disease, measurements must

have met the stable disease criteria at least once after study entry at a minimum interval (not less than 8 weeks).

6.2.4 Survival

Survival will be measured from the date of entry on study.

6.2.5 Time to Progression

This interval will be measured from the date of entry on the study to the appearance of new metastatic lesions or objective tumor progression.

6.2.6 Methods of Measurement

Imaging based evaluation is preferred to evaluation by clinical examination. The same imaging modality must be used throughout the study to measure disease.

6.2.6.1 CT and MRI

CT and magnetic resonance imaging (MRI) are the best currently available and most reproducible methods for measuring target lesions. Conventional CT and MRI should be performed with contiguous cuts of 10 mm or less in slice thickness. Spiral CT should be performed by use of a 5 mm contiguous reconstruction algorithm. This specification applies to tumors of the chest, abdomen, and pelvis, while head and neck tumors, and those of the extremities require specific procedures.

6.2.6.2 Chest X-Ray

Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by an aerated lung. However, CT is preferable.

6.2.6.3 Tumor Markers

Tumor markers alone cannot be used to assess response. If initially above the upper normal limit, a tumor marker must return to normal levels for a patient to be considered in complete clinical response when all tumor lesions have disappeared.

6.2.6.4 Clinical Examination

Clinically detected lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For skin lesions, documentation by color photography, including a ruler to estimate size of the lesion, is recommended. Photographs should be retained at the institution.

6.2.6.5 Cytology and Histology

Cytologic and histologic techniques can be used to differentiate between complete and partial response in rare cases (e.g., after treatment to differentiate residual benign

lesions and residual malignant lesions in germ cell tumors). Cytologic confirmation of the neoplastic nature of any effusion that appears or worsens during treatment is required when the measurable tumor has met response or stable disease criteria.

6.2.6.6 Endoscopy and Laparoscopy

Endoscopy and laparoscopy have not been fully or widely validated, so their use should be limited to validation studies in specialized institutions, and to confirming complete histopathologic response when biopsy specimens have been obtained.

6.2.6.7 Ultrasound

Ultrasound may be used only as an alternative to clinical measurements for superficial palpable lymph nodes, subcutaneous lesions, and thyroid nodules, and for confirming complete disappearance of superficial lesions usually assessed by clinical examination.

7. Study Parameters

7.1 Therapeutic Parameters

7.1.1 Prestudy scans must be done within **4 weeks** prior to randomization/registration.

7.1.2 Prestudy CBC (with differential and platelet count) must be done ≤ **4 weeks** before randomization/ registration.

7.1.3 Prestudy Serum Chemistries (Creatinine, Total Bili, Alk Phos, AST, ALT, Albumin, PT/INR) must be done ≤ **4 weeks** before randomization/ registration.

7.1.4 Baseline history and physical, and ECOG performance status must be done ≤ 4 weeks before randomization/registration.

	Baseline	10 to 14 days after starting S/P	Within 14 days of reaching Stable S/P dose	7 to 14 days post-TACE	10 to 14 days after restarting S/P	4 months after initial TACE	8 months after initial TACE	Every 4 weeks beginning 10 months after initial TACE	Every 8 weeks beginning 10 months after initial TACE
History & Physical Exam	X	X		X	X			X	
ECOG Performance Status	X	X		X	X			X	
CBC with Differential[1]	X	X		X	X			X	
Serum Chemistries Including: Creatinine, Total Bili, Alk Phos, AST, ALT, Albumin	X	X		X	X	X		X	
Prothrombin Time/INR	X	X		X	X			X	
α-Feto Protein	X			X		X	X		X
Pregnancy Test	X								
Tumor Imaging[2,5]	X					X	X		X
Chemoembolization (TACE)			X[3,4]						

S/P = Sorafenib/placebo

1. CBCs (with differential and platelet count) which includes: WBC, ANC, Platelets, Hgb, and Hct
2. Chest evaluation must be performed by CT; abdomen-pelvis imaging may be performed by CT or MRI, although MRI is the preferred imaging modality. Imaging to be performed at baseline, 4 months post baseline following first chemoembolization, 8 months post baseline following first chemoembolization, then every 8 weeks, beginning at 10 months post baseline.

Rev. 6/14

3. Proceed to chemoembolization only if criteria in Sections 5.2.4.1 and 5.2.4.2 are met.

4. Chemoembolization may be repeated up to 4 times but must be completed within 6 months of the first chemoembolization procedure.
5. All CT and MRI images must be submitted to ACRIN for all study participants. Imaging guidelines and image submission instructions are detailed n Appendix X.

7.2 Biological Specimen Submissions

Specimens for the Pharmacogenetic/Pharmacokinetic laboratory research studies or banking are to be submitted only from patients who have given written consent for these submissions. Sample submissions are outlined in Section 10.

ECOG-ACRIN requires that all biological specimens submitted from patients participating in this study be logged and tracked via the online ECOG-ACRIN Sample Tracking System (STS). See Section 10.3.

NOTE: Institutions outside North America are not required to submit fresh specimens (blood) from consented patients due to the problems and costs of international shipping. If sites wish to participate in these studies, contact the ECOG-ACRIN CBPF to obtain alternative shipping guidelines.

Rev. 12/14

Rev. 12/10

	Baseline	Cycle 1 of S/P 1 hour post – sorafenib/placebo[2]	Day 8[1] of S/P treatment	Day 15[1] of S/P treatment	3-5 days prior to TACE #2[1]	3-5 days prior to TACE #3[1]
PHARMACOGENETIC/PHARMACOKINETIC ANCILLARY:						
Patient answers "Yes" to *"I agree to participate in the protein and DNA studies that are being done as part of this treatment trial"* or *"My specimens may be kept for use in research to learn about, prevent, treat, or cure cancer."*.						
Peripheral blood, PAXgene DNA	Sample may be drawn any time, although baseline (prior to treatment) preferred					
Tumor Tissue Block[3]	X					
Limited to sites with dry ice and Patient answers "Yes" to *"I agree to participate in the blood drug levels study that is being done as part of this treatment trial"*						
Plasma, two (2) 7mL heparin tubes	X	X[2]	X[1]	X[1]	X[1]	X[1]

S/P= Sorafenib / Placebo

Rev. 12/10

1 All draws are to be taken during the times the patient is taking S/P. Request patient bring the sorafenib/placebo to take AFTER the pharmacogenetic/pharmacokinetic and clinical blood draws. However, if patient has already taken the medication, draw the blood and note time of sorafenib/placebo administration and time of blood draw on the submission form. If blood draws can not be drawn on a specified day, draw as close to the designated day as possible. If patient is not available for the pre-TACE draws, the draws may be taken 10-14 days after S/P has been reinitiated, after any TACE treatment.

2 If this blood draw is not taken on day one, 1-hour post day 8 or day 15 sorafenib/placebo dose is requested. NOTE, however, that the pre-sorafenib/placebo blood draw on days 8 and 15 are more important than the 1 hour post- sorafenib/placebo.

3 From a previous biopsy or surgery. Submit with related pathology/surgical/immunological reports.

8. Drug Formulation and Procurement

Rev. 6/14

8.1 Sorafenib (NSC # 724772) / Placebo

Investigators with an affiliation with either ECOG-ACRIN or the CTSU may request an Investigator's Brochure by emailing the Pharmaceutical Management Branch's IB Coordinator at <ibcoordinator@mail.nih.gov> or by calling PMB at 240-276-6575 and providing:

- the investigator's full name (first, middle, last)
- the investigator's NCI investigator number
- the agent name (i.e., "sorafenib")
- the NSC (i.e., "724772")
- the protocol (i.e., "E1208")
- the requestor's name, email address, and phone number

8.1.1

Clinical Supplies: Sorafenib (NSC 724772) and matching Placebo will be provided free of charge by Bayer Pharmaceuticals and distributed by the Pharmaceutical Management Branch (PMB), Cancer Therapy Evaluation Program (CTEP), Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI).

Sorafenib and matching Placebo will be supplied in bottles containing 140 - 200mg tablets (Sorafenib) or 140 - 0mg tablets (Placebo for Sorafenib) of sorafenib with a child-resistant cap and a tamper-evident seal. Each blinded, patient-specific bottle will be labeled with:

- the protocol number (i.e., "E1208")
- the bottle number (i.e., "Bottle 1 of 2" and "Bottle 2 of 2")
- the number of tablets (i.e., "140 tablets")
- the patient ID number (e.g., "44444"; where "44444" represents the unique patient identifier assigned at randomization)
- the patient initials (i.e., first initial, last initial [e.g., "FL"])
- the agent identification (i.e., "Sorafenib 200mg or Placebo")
- a blank line for the pharmacist to enter the patient's name
- administration instructions (i.e., "Take ___ tablets every ___ hours.")
- storage instructions (i.e., "Store at room temperature (15ºC to 25ºC; 59ºF to 77ºF)."
- emergency contact instructions
- a Julian date

The Julian date indicates the day the bottle was labeled and shipped and is composed of the last two digits of the calendar year (e.g., 2008 = 08, 2009 = 09) and a day count (e.g., January 1 = 001, December 31 = 365). For example, a bottle labeled and shipped on January 1, 2008 would have a Julian date of '08001' and a bottle labeled and shipped on December 31, 2009 would have a Julian date of '09365'.

The Julian date will be used by PMB for recalls. When a lot expires, PMB will determine the last date the expired lot was shipped and will recall all bottles (i.e., both sorafenib and placebo) shipped on or before that date thus eliminating any chance of breaking the blind.

Questions about drug orders, transfers, returns, or accountability should be addressed to the PMB by calling (240) 276-6575 Monday through Friday between 8:30am and 4:30pm Eastern Time or by emailing <PMBAfterHours@mail.nih.gov> anytime.

8.1.2 Drug Orders

No blinded starter supplies will be available for this study. Blinded, patient-specific clinical supplies will be sent to the registering investigator at the time of randomization and should arrive within approximately 7 to 10 days. Patients will be randomized by the ECOG-ACRIN Operations Office – Boston in Boston, MA. The assigned patient ID number must be recorded by the registering institution at the time of randomization for proper clinical supply dispersion. Once a patient has been randomized, the ECOG-ACRIN Operations Office – Boston will electronically transmit a clinical drug request for that patient to the PMB. This request will be entered and transmitted by the ECOG-ACRIN Operations Office – Boston the day the patient is randomized and will be processed by PMB the next business day and shipped the following business day. Shipments within the United States will be sent by US Priority Mail (generally two to three day delivery) and shipments to Canada will be sent by FedEx (generally one to two day delivery). Thus, if a patient is registered on Monday, ECOG-ACRIN would enter a clinical drug request for that patient on Monday and PMB would process that request on Tuesday and ship the drug on Wednesday. United States clinical sites could expect to receive their order approximately Friday or Monday (depending on the US Mail service) and Canadian clinical sites could expect to receive their order either Thursday or Friday. Shipments to United States clinical sites can be expedited (i.e., receipt on Thursday in example above) by the provision of an express courier account name and number to the ECOG-ACRIN Operations Office – Boston at the time the patient is randomized.

The initial request will be for 2 – 140 tablet bottles (a 70 day / 2 month supply at a dose of two tablets twice daily) of Sorafenib or matching Placebo. Six (6) weeks after the initial electronic request (i.e., two plus (2+) weeks before needed), sites may reorder an additional 2 – 140 tablet bottles (a 70 day / 2 month supply at a dose of two tablets twice daily). Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can 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)

Rev. 6/14

account < https://eapps-ctep.nci.nih.gov/iam/ > and the maintenance of an "active" account status and a "current" password.

All drug orders will be shipped directly to the registering physician at the shipping address provided on their current Supplemental Investigator Data Form (IDF) on file with CTEP. The registering investigator must maintain an active investigator registration status with CTEP, DCTD through the annual submission of an FDA Form 1572 (Statement of Investigator), a Curriculum Vitae, a Supplemental Investigator Data Form (IDF), and a Financial Disclosure Form (FDF).

8.1.3 Drug Transfers

Bottles may **NOT** be transferred from one patient to another patient or from one protocol to another protocol. All other transfers (e.g., a patient moves from one participating clinical site to another participating clinical site, the principal investigator at a given clinical site changes) must be approved in advance by the PMB. To obtain an approval for transfer, investigators should complete and submit to the PMB (fax number 240-276-7893) a Transfer Investigational Agent Form available on the CTEP home page (http://ctep.cancer.gov) or by calling the PMB at 240-276-6575. The patient ID number (e.g., "44444") and the patient initials (e.g., "FL") should be entered in the "Received on NCI Protocol No." and the "Transferred to NCI Protocol No." fields in addition to the protocol number (i.e., "E1208").

8.1.4 Drug Returns

Only undispensed clinical supplies should be returned to the PMB. When it is necessary to return study drug (e.g., sealed bottles remaining when a patient permanently discontinues protocol treatment, expired bottles recalled by the PMB), investigators should return the study drug to the PMB using the NCI Return Drug List available on the CTEP home page (http://ctep.cancer.gov) or by calling the PMB at 240-276-6575. The patient ID number (e.g., "44444") and the patient initials (e.g., "FL") should be entered in the "Lot Number" field. A separate line item is required for each patient ID (e.g., "44444") being returned. **Dispensed bottles with remaining tablets should be documented in the patient-specific NCI Investigational Agent Accountability Record (i.e., logged is as "returned by patient" and logged out as "destroyed on site") and destroyed on site in accordance with institutional policy**.

8.1.5 Drug Accountability

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, disposition, and return of all drugs received from the PMB using the NCI Investigational Agent Accountability Record available on the CTEP home page (http://ctep.cancer.gov) or by calling the PMB at 240-276-6575. A separate NCI Investigational Agent Accountability Record must be maintained for each patient ID number (e.g., "44444") on this protocol. It is recommended that the combination julian date / order

number in the upper right hand corner of the patient-specific bottle label be recorded as the lot number.

8.1.6 Emergency Unblinding

Rev. 6/14

In the event of an emergency or severe adverse reaction necessitating identification of the medication for the welfare of the patient, please contact the Study Chair, **(Jeff Geschwind, MD, 410-614-6597)**, first to ensure the reason for unblinding is valid. Then call a member of the ECOG-ACRIN Operations Office – Boston drug team at (617) 632-3610 Monday through Friday between 9:00 AM and 5:00 PM Eastern Time. For unblinding outside of these hours, contact AnswerConnect at 1-866-296-8940. This service will request the reason for unblinding and then page the on-call ECOG-ACRIN staff who will return your call and provide the unblinded treatment assignment if applicable. Remember, AnswerConnect should only be contacted outside of normal business hours and only in the event of an emergency. The ECOG-ACRIN Operations Office – Boston or AnswerConnect will require the protocol number (i.e., "E1208"), the patient ID number (e.g., "44444"), and the patient initials (e.g., "FL") to unblind the patient. Please note that, if a patient is emergently unblinded, he/she is considered to be off-therapy and must discontinue protocol treatment.

8.1.7 Chemical Name

4–{4-[3-(4-chloro-3-trifluoromethyl-phenyl) ureido]-phenoxy}-pyridine-2 carboxylic acid methylamide-4-methylbenzensulfonate

8.1.8 Other Names: Nexavar®; BAY 43-9006 tosylate; BAY 54-9085 (BAY 54-9085 is the tosylate salt of BAY 43-9006)

8.1.9 Classification

Kinase inhibitor (Raf, VEGF-R, and PDGF-R)

8.1.10 Mechanism of Action:

The ras / raf signaling pathway is an important mediator of responses to growth signals and angiogenic factors. This pathway is often aberrantly activated in human tumors due to the presence of activated ras, mutant b-raf, or over expression of growth factor receptors.

Sorafenib is a potent inhibitor of c-raf and wild-type and mutant b-raf in vitro. Additionally, further characterization of sorafenib revealed that this agent inhibits several receptor tyrosine kinases (RTKs) that are involved in tumor progression (VEGF-R, PDGF-R, Flt3, and c-KIT) and p38α, a member of the MAPK family.

8.1.11 Molecular Formula

$C_{12}H_{16}ClF_3N_4O_3$ X $C_7H_8O_3S$

8.1.12 M.W.:

BAY 43-9006 tosylate: 637 Daltons; BAY 43-9006 (free base): 465 Daltons

8.1.13 Approximate Solubility

0.81 g/100 mL in ethanol and 4.9 g/100 mL in polyethylene glycol (PEG) 400

8.1.14 How Supplied

"Sorafenib" and matching "Placebo" are supplied as an immediate-release, film-coated, round, red-colored tablet for oral administration. Each tamper-evident, child-resistant, opaque, high-density polyethylene (HDPE) bottle contains 140 tablets. For "Sorafenib", each tablet contains 200mg of the free base (i.e., BAY 43-9006) with croscarmellose sodium, microcrystalline cellulose, hydroxypropylmethylcellulose, sodium lauryl sulfate, and magnesium stearate. For "Placebo", each tablet contains croscarmellose sodium, microcrystalline cellulose, hydroxypropylmethylcellulose, sodium lauryl sulfate, and magnesium stearate. For "Sorafenib" and "Placebo", the film coat consists of hydroxypropylmethyl cellulose, polyethylene glycol, titanium dioxide and red iron oxide. The film coating has no effect on the rate of release of the active sorafenib.Storage and Stability

Sorafenib is shipped at room temperature by US Priority Mail. The tablets should be stored at controlled room temperature (15ºC to 25ºC; 59ºF to 77ºF). Storage conditions should not exceed 25ºC (77ºF). The intact bottles of 200mg tablets are stable for at least 36 months when stored at controlled room temperature. Shelf-life studies of sorafenib are continuing and investigators will be notified when lots have expired.Route of Administration: Oral

8.1.15 Method of Administration:

Following oral administration, sorafenib's mean relative bioavailability is 38-49%. When given with a moderate fat meal, bioavailability was similar to that in the fasted state. With a high fat meal, sorafenib's bioavailability was reduced by 29% compared to administration in the fasted state. Thus, it is recommended that sorafenib be taken on an empty stomach (at least 1 hour before or 2 hours after eating) and with at least 250 mL of water.

8.1.16 Potential Drug Interactions

Sorafenib is neither a clinically meaningful inhibitor nor a clinically meaningful inducer of CYP2C19, CYP2D6, and CYP3A4 isoenzymes and is not expected to significantly increase or decrease the exposure of coadministered compounds metabolized by these pathways. However, concomitant administration of sorafenib and CYP3A4 inducers, such as phenytoin, carbamazepine, phenobarbital, rifampin, or St. Johns Wort, should be avoided. Co-administration with doxorubicin or docetaxel leads to a moderate increases in doxorubicin exposure and docetaxel AUC, respectively. Co-administration with irinotecan leads to a significant increase in SN-38 (i.e., the active metabolite of sorafenib, which is eliminated by UGT1A9) exposure.Compliance:

Patients will be required to return all bottles of study medication at the end of each cycle. The number of tablets remaining should be documented and recorded on the Patient Medication Calendar (**See Appendix XI**).

E1208 Shipment Schedule

Patient Randomized with ECOG-ACRIN	Initial e-Order Transmitted by ECOG-ACRIN	Initial e-Order Received and Approved by PMB	Initial Order Shipped By PMB	Initial Order Received at Site *
Monday	Monday	Tuesday	Wednesday	US Priority Mail
Tuesday	Tuesday	Wednesday	Thursday	US Priority Mail
Wednesday	Wednesday	Thursday	Monday	US Priority Mail
Thursday	Thursday	Friday	Monday	US Priority Mail
Friday	Friday	Monday	Tuesday	US Priority Mail

8.1.17 Side Effects

Please refer to Section 5.5 Comprehensive Adverse Events and Potential Risks List (CAEPR) for Sorafenib (BAY-43-9006, NSC 724772)

8.1.18 Nursing/Patient Implications

1. Monitor for jaundice.
2. Evaluate patient for GI intolerance.
3. Sorafenib should be taken on an empty stomach (at least 1 hour before or 2 hours after eating) and with at least 250 mL of water.

8.1.19 References

Investigator Drug Brochure Sorafenib. Bayer Pharmaceuticals.

8.2 Cisplatin

8.2.1 Other Names

Cis-diaminedichloroplatinum Cis-diaminedichloroplatinum (II), diaminedichloroplatinum, cis-platinum, platinum, Platinol, Platinol-AQ, DDP, CDDP, DACP, NSC 119875.

8.2.2 Classification

Alkylating agent.

8.2.3 Mode of Action

Inhibits DNA synthesis by forming inter- and intra-strand crosslinks. Other possible mechanisms include chelation of DNA and binding to cell membranes thereby stimulating immune mechanisms.

8.2.4 Storage and Stability

Intact vials of cisplatin are stored at room temperature. Solutions diluted with sodium chloride or dextrose are stable for up to 72 hours

at room temperature. Due to the risk of precipitation, cisplatin solutions should **not** be refrigerated.

Rev. 10/11

8.2.5 Dose Specifics

Cisplatin 50mg lyophilized powder for solution

8.2.6 Preparation

Please refer to Section 5.3.1 for preparation details. The chemoembolization dose should be prepared immediately prior to use.

8.2.7 Administration

Please Refer to Section 5.3.4 for administration details.

8.2.8 Incompatibilities

Amsacrine, cefepime, gallium nitrate, mesna, piperacillin, sodium bicarbonate, thiotepa. Cisplatin may react with aluminum which is found in some syringe needles or IV sets, forming a black precipitate.

8.2.9 Compatibilities

Admixture: Amphotericin-B, aztreonam, carmustine, cefazolin, cephalothin, droperidol, etoposide, floxuridine, hydroxyzine, ifosphamide, leucovorin, magnesium sulfate, mannitol, potassium chloride.

Y-site: Allopurinol, bleomycin chlorpromazine, cimetidine, cyclophosphamide, dexamethasone, diphenhydramine, doxapram, doxorubicin, famotidine, filgrastim, fludarabine, fluorouracil, furosemide, ganciclovir, heparin, hydromorphone, lorazepam, melphalan, methotrexate, methylprednisolone, metoclopramide, mitomycin, morphine, ondansetron, paclitaxel, prochlorperazine, ranitidine, sargramostim, vinblastine, vincristine, vinorelbine.

Consult your pharmacist regarding specific concentrations.

8.2.10 Availability

Rev. 12/10

NOTE: The use of lyophilized cisplatin powder will only be allowed for those patients registered prior to activation of addendum #3.

Commercially available as a mg/mL solution in 50 and 100 mg vials. Vials of lyophilized powder are no longer commercially available, but may be obtained directly from the manufacturer for chemoembolization use.

8.2.11 Side Effects

Renal: A dose-related, cumulative renal tubular injury can occur; adequate hydration and diuresis usually minimize the risk. Salt-wasting nephropathy and/or orthostatic hypotension with hyporeninemic hypoaldosteronism can occur in up to 10% of patients.

Neurologic: A dose-related ototoxicity, manifested by high-frequency hearing loss and tinnitus, occurs in about 30% of patients.

Paresthesias, decreased vibratory, position, and touch sensations are less common; particularly at cumulative doses < 400 mg/m².

Hematologic: Mild leukopenia and thrombocytopenia occur in 25-30% of patients, but are rarely dose-limiting; anemia is less common. A potentially fatal hemolytic uremic syndrome has been reported.

Gastrointestinal: Severe, dose-limiting nausea and vomiting occur in almost 100% of patients unless adequate antiemetic prophylaxis is given. Even with successful prophylaxis of acute nausea a delayed (72-96 hour) reaction, requiring additional therapy may occur. Anorexia and taste changes may also occur.

Hypersensitivity: Allergic reactions are reported in up to 20% of patients Symptoms include: rash, facial edema, wheezing, hypotension, and tachycardia. Severe anaphylaxis is rare.

Other: Electrolyte wasting (magnesium, potassium and sodium), papilledema, optic neuritis, retrobulbar neuritis, diarrhea, mouth sores, hair loss, dizziness, dehydration, nail changes, fatigue, fluid retention, chills, lowered white blood cell counts, rash, muscle aches, joint pain, headache, confusion, loss of coordination, difficulty swallowing, indigestion, blood clotting in veins, fainting, seizures, difficulty urinating.

8.2.12 Nursing Implications

Prior to administration, assess:

- Labs: CBC, platelet count, BUN, creatinine.
- Urine output: 100-150 mL/hr for at least 4-6 hours.
- Signs of ototoxicity or neurotoxicity.

Administer supportive medications:

- Antiemetics: $5HT_3$ antagonists and dexamethasone combinations can usually be given once daily.
- Hydration
- Diuretics - may be ordered.

Observe for signs of allergic reaction.

8.2.13 References

Alberts DS. Carboplatin versus cisplatin in ovarian cancer. Semin Oncol 1995;22 (5 Suppl 12):88-90.

Bonomi P. Platinum/etoposide therapy in non-small cell lung cancer. Oncology 1992;49 (Suppl 1):43-50.

Dabholkar M, Reed E. Cisplatin. Cancer Chemother Biol Response Modifiers 1993;14:86-97.

Fram RJ. Cisplatin and platinum analogues: recent advances. Curr Opin Oncol 1992;4:1073-9.

Garrow GC, Johnson, DH. Treatment of "good risk" metastatic testicular cancer. Semin Oncol 1992;19:159-65.

Markman M. Current status of intraperitoneal therapy for ovarian cancer. Curr Opinion Obstet Gynecol 1993;5:99-104.

Ozols RF, *et al.* Advanced ovarian cancer. Dose intensity. Ann Oncol 1993; (4 Suppl 4):49-56.

Saxman S. Salvage therapy in recurrent testicular cancer. Semin Oncol 1992;19:143-7.

Wheeler RH, Spencer S. Cisplatin plus radiation therapy. J Infusional Chemother 1995;5:61-6.

8.3 Doxorubicin

8.3.1 Other Names

Adriamycin, Rubex, Adriamycin RDF, Adriamycin PFS, hydroxydaunorubicin, ADR

8.3.2 Classification

Anthracycline antibiotic

8.3.3 Mode of Action

Intercalation between adjoining nucleotide pairs in the DNA helix causes inhibition of DNA and DNA-dependent RNA synthesis. Free radical generation is responsible for cardiac toxicity. Doxorubicin also inhibits topoisomerase II.

8.3.4 Storage and Stability

Rubex or Adriamycin RDF intact vials are stable protected from light at room temperature. Adriamycin PFS vials must be refrigerated. Reconstituted solutions are stable for 24 hours at room temperature and 48 hours under refrigeration. The Adriamycin RDF 150 mg multidose vial is stable after reconstitution for 7 days at room temperature or 15 days if refrigerated and protected from sunlight.

Rev. 12/10

8.3.5 Dose Specifics

50 mg when administered in combination with cisplatin and mitomycin

When used as single agent with conventional chemoembolization, dose per body surface area (m^2) based upon serum bilirubin.

- If serum bilirubin < 1.5 mg/m^2 then doxorubicin dose 75mg/m^2
- If serum bilirubin 1.5 to 2.0 mg/m^2 then doxorubicin dose 50mg/m^2

8.3.6 Preparation

Please refer to Section 5.3.1 for preparation details. The chemoembolization dose should be prepared immediately prior to use.

8.3.7 Administration

Please refer to Section 5.3.4 for information regarding drug administration procedures.

8.3.8 Incompatibilities

Physically incompatible with heparin, fluorouracil, aminophylline, cephalothin, dexamethasone, diazepam, hydrocortisone, and furosemide.

8.3.9 Availability

Commercially available as powder for injection in 10, 20, 50, 100, 150 mg vials, and as 2 mg/ml solution for injection in 10, 20, 50, and 200 mg vials.

8.3.10 Side Effects

Hematologic: Leukopenia (dose-limiting), also thrombocytopenia and anemia. Nadir 10-14 days, recovery in 21 days.

Dermatologic: Alopecia, usually complete; hyperpigmentation of nailbeds and dermal creases; radiation recall.

Gastrointestinal: Nausea and vomiting, sometimes severe; anorexia, diarrhea; mucositis.

Cardiovascular: Arrhythmias, ECG changes; rarely sudden death. Congestive heart failure due to cardiomyopathy related to total cumulative dose; risk is greater with doses greater than 550 mg/m², mediastinal irradiation, pre-existing cardiac disease, advanced age; risk is reduced with weekly or continuous infusion regimens.

Other: Red discoloration of urine; fever; anaphylactoid reaction; may enhance cyclophosphamide cystitis or mercaptopurine hepatotoxicity; secondary AML/MDS (risk is uncommon, but may be increased when given in combination with an alkylating agent, especially if one or both are given at a higher than standard doses).

Local effects: Vesicant if extravasated; flush along vein, facial flush.

8.3.11 Nursing/Patient Implications

- Monitor CBC, platelet counts.
- Advise patient of alopecia. Instruct on how to obtain wig, hairpiece, etc. Hair loss generally occurs 2-4 weeks after injection and is usually complete.
- Advise patient of red discoloration of urine for 24 hours after administration of the drug.
- Administer antiemetics as indicated.
- Assess for stomatitis and treat symptomatically. Generally occurs 7-10 days after injection.

8.3.12 References

Speth PA. Clinical pharmacokinetics of doxorubicin. Clin Pharmacokinetics 1988; 15:51-31.

Von Hoff DD, *et al.* Risk factors for doxorubicin-induced congestive heart failure. Ann Intern Med 1979; 91:710-717.

Lum BL, *et al.* Doxorubicin: Alteration of dose scheduling as a means of reducing cardiotoxicity. Drug Intell Clin Pharm 1985; 19:259-264.

8.4 Mitomycin

8.4.1 Other Names

Mutamycin, mitomycin C.

8.4.2 Classification

Antitumor antibiotic.

8.4.3 Mode of Action

Mitomycin is cell cycle non-specific. It appears to be most active in late G1 and early S phase of the cell cycle. The mechanism of action is similar to alkylating agents, causing cross-linking of DNA and possible inhibition of RNA and protein synthesis.

8.4.4 Storage and Stability

Unreconstituted vials are stored at room temperature. At a concentration of 0.5 mg/ml the drug is chemically stable for at least 7 days at room temperature and 14 days when refrigerated and protected from light.

8.4.5 Dose Specifics

Rev. 10/11

Mitomycin 5mg powder for injection.

8.4.6 Preparation

Please refer to Section 5.3.1 for preparation details. The chemoembolization dose should be prepared immediately prior to use.

8.4.7 Administration

Please refer to Section 5.3.4 for information regarding drug administration procedures.

8.4.8 Incompatibilities

Undergoes rapid decomposition at acidic and basic pH.

8.4.9 Compatibilities

Dilute solutions (20-40 mg/ml) are chemically stable at room temperature in normal saline for 12 hours, in 5% dextrose for 3 hours and in sodium lactate 1/6 M for 24 hours. Mitomycin 5-15 mg is

compatible with heparin (1000-10,000 units) in 30 ml normal saline for 48 hours at room temperature. The pH of maximal stability is 6-10.

Rev. 12/10

8.4.10 Availability

NOTE: The use of mitomycin will only be allowed for patients registered prior to the activation of addendum #3.

Commercially available in 5, 20 and 40 mg vials.

8.4.11 Side Effects

Hematologic: Leukopenia, thrombocytopenia: late, cumulative and dose-limiting; anemia; hemolytic uremic syndrome (renal failure, profound thrombocytopenia, pulmonary edema, and hypotension) rarely.

Dermatologic: Stomatitis, alopecia, dermatitis, pruritus; tissue necrosis, ulceration, and cellulitis if extravasation occurs; skin erythema and ulceration weeks to months after administration and distant from the site of injection.

Gastrointestinal: Nausea, vomiting, anorexia.

Hepatic: Veno-occlusive disease of the liver, manifested as abdominal pain, hepatomegaly and liver failure, in patients receiving mitomycin and autologous bone marrow transplantation.

Neurologic: Paresthesias.

Pulmonary: Interstitial pneumonitis (infrequent but severe); acute bronchospasm.

Renal: Nephrotoxicity, increasing in frequency when doses exceed 50 mg/m², manifested as increased serum creatinine and BUN.

Other: Fatigue, pain on injection, phlebitis, fever, lethargy, weakness, blurred vision; secondary AML/MDS (risk is uncommon, but may be increased when given in combination with an anthracycline, especially if one or both drugs are given at higher than standard doses); secondary tumors (rare).

8.4.12 Nursing Implications

1. Administer antiemetics as needed.
2. Monitor CBC, platelet count.
3. Observe for GI toxicity of stomatitis, diarrhea, and treat symptomatically.
4. Observe and monitor for interstitial pneumonitis and pulmonary fibrosis - may respond to corticosteroid therapy.
5. Pt. may experience malaise - educate pt. to incorporate periods of rest in daily routine.
6. Monitor serum creatinine. 2% of patients have been found to have a rise in creatinine.

8.4.13 References

Grem JL, Merritt JA, Carbone PP. Treatment of mitomycin-associated microangiopathic hemolytic anemia with vincristine. Arch Intern Med 1986; 146: 566-568.

Chang AY-C, *et al.* Pulmonary toxicity induced by mitomycin C is highly responsive to glucocorticoids. Cancer 1986; 57: 2285-2290.

Zein TA, Friedberg N, Kim H. Bone marrow suppression after intravesical mitomycin C treatment. J Urol 1986; 136: 459-460.

Doll DC, Weiss RB, Issell BF. Mitomycin: Ten years after approval for marketing. J Clin Oncol 1985; 3: 276-286.

Sheldon R, Slaughter D. A syndrome of microangiopathic hemolytic anemia, renal impairment, and pulmonary edema in chemotherapy-treated patients with adenocarcinoma. Cancer 1986; 58: 1428-1436.

Rev. 12/10, 5/11

8.5 LC bead

8.5.1 LC bead Description

LC bead comprise a range of hydrogel microspheres that are biocompatible, hydrophilic, non resorbable, precisely calibrated and capable of loading doxorubicin. LC bead is produced from polyvinyl alcohol and are available in the following size ranges:

Rev. 10/11

Nominal Bead Size	Label Colour	
100 – 300 µm	Yellow	***Upon loading with doxorubicin, LC Bead undergo a slight decrease in size, up to 20% when loading at 25mg/ml***
300 – 500 µm	Blue	
500 – 700 µm	Red	
700 – 900 µm	Green	

Rev. 12/10

8.5.2 Availability

LC beads are commercially available for this study.

8.5.3 How Supplied

i. 10 ml glass vial
ii. Each vial contains approximately 2 m of LC bead in non-pyrogenic, sterile physiological buffered saline. Total volume of saline and LC bead is approximately 8ml.
iii. The vial is stopper sealed by an aluminium cap equipped with a colour-coded lid.
iv. Each vial is intended for single patient use only. Do not resterilise. Discard any unused material.

8.5.4 Contraindications:

i. Patients intolerant to vascular occlusion procedures.
ii. Vascular anatomy that precludes catheter placement or emboli injection
iii. Presence or likely onset of vasospasm.
iv. Presence or likely onset of hemorrhage.

v. Presence of severe atheromatous disease.
vi. Presence of feeding arteries smaller than distal branches from which they emerge.
vii. Presence of patent extra-to-intracranial anastomoses or shunts.
viii. Presence of collateral vessel pathways potentially endangering normal territories during embolisation.
ix. Presence of end arteries leading directly to cranial nerves.
x. Presence of arteries supplying the lesion not large enough to accept LC bead.
xi. Vascular resistance peripheral to the feeding arteries precluding passage of LC bead into the lesion.
xii. Do not use LC bead for embolization of large diameter arteriovenous shunts (ie. Where the blood does not pass through the arterial/capillary/venous transition but directly from artery to vein).
xiii. Do not use LC bead for embolization in any vasculature where LC bead Embolic Agent could pass directly into the internal carotid artery or other non-target territories

8.5.5 Preparation

Please refer to Section 5.3.1.3 for preparation details.

8.5.6 Administration

Please refer to Section 5.3.1.4 for information regarding drug administration procedures.

8.5.7 References

LC bead Package Label.
http://www.biocompatiblesoncology.com/docLib/d5a1dc7a14cd9646aba7808b6c03c525

Rev. 5/11

9. Statistical Considerations

9.1 Primary Endpoint

Rev. 3/10

The primary endpoint of this study is progression free survival (PFS) of HCC patients with or without vascular invasion. PFS is defined to be the time from randomization to progression or death without evidence of progression. For cases without documentation of progression, follow-up will be censored at the date of last disease assessment without progression, unless death occurs within 4 months following the date last known progression-free, in which case the death will be counted as an event. Overall Survival (OS) is an important secondary endpoint. OS is defined as the time from randomization to death from any cause, or censored at last known date of survival. It is expected that the overall control median PFS is 8-10 months for all patients. This study will target a 44% improvement in median PFS with approximately 85% power while maintaining a significance level of 2.5% in a one-sided test assuming exponential PFS. Table 1 below shows the range of detectable differences and approximate power for several possible control median PFS values.

Table 1: PFS Designs with 44% Improvement in Median PFS, HR of 1.44, Significance Level of One-Sided 2.5%

Median PFS (H0)	Median PFS (Ha)	Approximate Power
8	11.5	85%
8.6	12.4	85%
10	14.4	85%

Rev. 9/10

Rev. 12/10

Rev. 3/10

This study will require 400 patients. Assuming an approximately 1:2 ratio of patients with vascular invasion vs. non-vascular invasion, approximately 134 patients will be in the vascular invasion group; approximately 326 patients will be in the non-vascular invasion group. In each stratum, the study will randomize patients using a 1:1 design such that half of the patients will be randomized to Sorafenib + chemoembolization (LC bead chemoembolization or conventional chemoembolization at the discretion of the treating institution); half of the patients will be randomized to Placebo + chemoembolization (LC bead chemoembolization or conventional chemoembolization at the discretion of the treating institution). All patients will be stratified in the randomization on vascular invasion (Yes vs. No), Child-Pugh Score (A vs. B7), and institutional choice of chemoembolization method (LC bead vs conventional).

Assuming an accrual rate of 10 patients per month and exponential failure for PFS, the study will require approximately 40 months for enrollment and a follow up period of at most 13 months (if overall control median PFS is 10 months for all patients) after closure to accrual to reach full information.

The study design incorporates six interim analyses and one final analysis for PFS. Each interim analysis will be performed every 6 months to correspond with the scheduled Data Monitoring Committee (DMC) meetings once the trial reaches 25% information, projected to be 18 months after start of accrual. All PFS analyses will use the multi-time point (for the vascular invasion at 4, 8 and

12 months, and the non-vascular invasion group at 8, 12 and 16 months) Cochran-Mantel-Haenszel (CMH) test of Freidlin, et al. (29) with an overall one-sided 0.025 type I error. Patients will be stratified using the same factors as the randomization (vascular invasion, Child-Pugh Score). Full information will occur when 326 events have occurred. Critical values at interim analyses will be determined using a truncated Lan-DeMets version of the O'Brien-Fleming error rate spending function. Boundary values at a nominal significance less than 0.0005 will be truncated at 0.0005, with the boundary adjusted at the next non-boundary time point to preserve the overall one-sided type I error of 0.025.

Rev. 9/10

Rev. 3/10

At each interim analysis the null hypothesis of equal PFS on the two arms will be tested against the one-sided alternative of increased PFS on the Sorafenib +chemoembolization arm. The p-value from the one-sided multi-time point CMH test will be compared to the truncated O'Brien-Fleming boundary. If the Sorafenib+chemoembolization arm is found to be statistically significantly superior in PFS to the Placebo+chemoembolization arm at an interim analysis, the ECOG-ACRIN DMC may consider closing the study for efficacy as described below. Conversely, if the repeated confidence interval (calculated using Jennison-Turnbull repeated confidence interval methodology) of the PFS hazard ratio computed from the corresponding proportional hazards regression model at a given information fraction does not contain the target alterative hazard ratio of 1.44, DMC may consider closing the study for futility.

Rev. 3/10

The trial will maintain a one-sided 0.025 overall significance level and the testing between PFS and OS will be hierarchical with PFS as the primary outcome and OS as the secondary outcome. The monitoring plan for interim analyses will focus on PFS. We will maintain testing for efficacy and futility and the following rules will be applied.

- If the repeated confidence interval on the PFS hazard ratio computed from the corresponding proportional hazards regression model at given information fraction does not contain the target alterative hazard ratio of 1.44, the recommendation to the ECOG-ACRIN DMC will be to stop the trial and declare no benefit of Sorafenib.
- If PFS crosses the efficacy boundary, we will analyze OS and if OS also crosses the efficacy boundary, the recommendation to the ECOG-ACRIN DMC will be to stop the trial and declare a benefit of Sorafenib.
- If PFS crosses the efficacy boundary, we will analyze OS and if OS does not cross the efficacy boundary, the recommendation to the ECOG-ACRIN DMC will be to continue the trial (accrual or follow-up or both) to ensure adequate power for OS.
- If PFS does not cross any boundary at an interim analysis, OS will not be evaluated at that analysis.

Progressions identified between evaluation times will be moved forward to the next scheduled evaluation time for the multi-time point CMH test and PFS events occurring after the last evaluation time will not be included in the primary PFS analysis.

We will evaluate PFS at points post randomization corresponding to scheduled imaging evaluations as described in Section 7 for both the vascular invasion (4, 8 and 12 months) and the non-vascular invasion group (8, 12 and 16 months).

Assuming that Sorafenib + chemoembolization is more effective than Placebo + chemoembolization, there is approximately 85% overall power to detect a 44% improvement in median PFS by a multi-time point procedure (as described by Freidlin, et al (2007)), while maintaining a significance level of 2.5% in a one-sided test assuming exponential PFS based on simulations conducted by the ECOG-ACRIN Statistical Center.

Rev. 12/10

As of amendment #3 the study design has been modified to allow institution choice for method of chemoembolization (LC bead or conventional chemoembolization). A recent paper (Lammer et al Cardiovasc Intervent radiol (2010) 33:41-52)) compared LC bead versus conventional chemoembolization, however that paper provided no data showing any difference in PFS (or OS) rates between the two methods. Furthermore, the proportion of institutions (and therefore total numbers of patients) choosing LC beads over conventional chemoembolization is also unknown at this time. For these reasons it will be assumed that the overall PFS rate will be unaffected by choice of chemoembolization method. The study will be closely monitored as follow-up progresses for compliance with the overall PFS event rates assumed above. Reports on overall event rates will be provided to the ECOG-ACRIN DMC for discussion and potential study/sample size modification should the actual event rates deviate substantial from those assumed here. Additionally, the study is not designed nor is it powered to detect any interaction between method of chemoembolization and sorafenib with regard to any of the primary or secondary endpoints.

Rev. 9/15

9.1.1 Revised Statistical Analysis Plan

This trial closed to accrual on November 19, 2014 with 235 registrations, 59% of the intended full accrual of 400 patients. As the study will not reach the intended full information of 326 PFS events, this amendment proposed to revise the analysis plans of the trial to use a 5% one-sided significance level for the primary treatment comparison rather than the originally intended 2.5% one-sided significance level, in order to maintain power for the primary PFS comparison. Results from simulations conducted at the ECOG-ACRIN statistical center using the actual accrual information, patient follow-up, and distribution of patients with vascular versus non-vascular invasion indicate that with 201 total PFS events the study will have at least 80% power for the original target hazard ratio of 0.69 (a 44% improvement in median PFS) using the originally proposed stratified CMH test. Assuming complete data submission from registering sites, full information for PFS is expected to be achieved at one year post closure, or around November 2015. It is also being proposed that the interim monitoring plan be modified to include one additional interim analysis at 80% information time for PFS, corresponding to 161 PFS events, expected to occur around late summer 2015. The original truncated O'Brien-Fleming boundary function would continue to be used for the interim monitoring as would the plan to report the trial early as negative if the target hazard ratio is not included in the associated repeated confidence interval on the hazard ratio.

Hierarchical testing of PFS followed by OS as described above would also continue to be followed with testing at the 0.05 one-sided level via a stratified log rank test for OS should the PFS efficacy boundary be crossed. With the actual accrual and stratification (vascular versus non-vascular invasion) patterns of the trial and with two years of follow-up post closure (to November 2016) the study will have 80% power for a one-sided stratified 0.05 level log rank test for overall survival under the alternative of a 44% improvement in median OS (the original target improvement) and 87% power for a 50% improvement in median OS. With two years of follow-up for overall survival full information would now occur at 187 deaths.

9.2 Secondary Endpoints

Overall Survival is a secondary endpoint. It is expected that the median OS is 9 months for patients with vascular invasion and 18 months without vascular invasion. This study will target a 44% improvement in median OS (9 months median OS vs. 13 months median OS between the Placebo + chemoembolization arm and the Sorafenib + chemoembolization arm for the patients with vascular invasion; 18 months median OS vs. 26 months median OS between the arms for the patients without vascular invasion). Assuming that Sorafenib +chemoembolization is more effective than placebo + chemoembolization, there is 85% power to detect a 44% improvement in median OS while maintaining a significance level of 2.5% in a one-sided - log-rank test stratified on vascular invasion (Yes vs. No) and Child-Pugh Score (A vs. B7)for the primary comparison assuming exponential survival. The study design incorporates an expected three interim analyses and one final analysis for OS. The number of OS interim analyses is expected to be 3, and could be as many as 6. For example, if PFS crosses the efficacy boundary at 36 months, the three interim analyses for OS will occur at roughly 63%, 79% and 92% information times and one final analysis at 100% information. These information times should correspond to approximately 36, 42, 48 and 53 months after the start of accrual. Analyses will use a one-sided logrank test stratified on vascular invasion (Yes vs. No) and Child-Pugh Score (A vs. B7), using a one-sided overall type I error of 0.025. Full information will occur at 280 deaths. Critical values at interim analyses will be determined using a truncated version of the Lan-Demets error spending rate function corresponding to the O'Brien-Fleming boundary. At each interim analysis the null hypothesis will be tested. The p-value from the one-sided log-rank test will be compared to the truncated O'Brien-Fleming boundary. If the Sorafenib+TACE arm is found to be statistically superior in OS to the TACE arm at an interim analysis, the DMC may consider closing the study.

Rev. 3/10

Rev. 3/10

Rev. 3/10

Toxicity is another secondary endpoint. In addition to the usual continuous adverse event monitoring via ECOG-ACRIN's real time AE mechanism (CTEP-AERS), toxicity reporting through CRFs and semi-annual interim toxicity reporting that occurs on all ECOG-ACRIN studies, this trial will include a detailed toxicity review after 50 patients have accrued to each treatment arm to evaluate the rates of all toxicities. Results of this analysis will be reported to the ECOG-ACRIN Data Monitoring Committee. With 50 patients per arm, the 90% confidence interval around any given toxicity rate will be no wider than 25%. Additionally, there is 0.64 probability of observing a rare toxicity (rate of at least 2%) with a

maximum 90% confidence interval width of 20%, after 50 patients have been enrolled in each arm.

With a full accrual of 200 patients per arm, the study will be able to detect at least a13% absolute difference for adverse events in the range of roughly 20% (for example, 20% versus 33%) of grade 3 or higher toxicity with a one-sided type I error rate of 2.5% and 80% power. The 90% confidence interval around any given toxicity rate will be no wider than 12%. Also, there is 0.87 probability of observing a rare toxicity with a true rate of 1%, with a maximum 90% confidence interval width of 7%, with 200 patients in each arm.

Rev. 3/10

The analysis population for efficacy will be intention-to-treat including all randomized patients. The analysis population for safety will be all treated patients.

Rev. 9/10

9.3 Gender and Ethnicity

This study is open to both men and women and to all racial/ethnic groups. According to the most recent ECOG-ACRIN experience, there is no evidence for outcome to be affected differentially by race ethnicity or gender. Thus, the study will not have separate accrual targets for different subgroups.

Based on previous data from E1203, E4298 and E6202 the anticipated accrual in subgroups defined by gender and race is:

Ethnic Category	**Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	3	13	16
Not Hispanic or Latino	68	316	384
Ethnic Category: Total of all subjects	71	329	400
Racial Category			
American Indian or Alaskan Native	0	0	0
Asian	8	16	24
Black or African American	39	56	95
Native Hawaiian or other Pacific Islander	0	0	0
White	24	257	281
Racial Category: Total of all subjects	71	329	400

9.4 Study Monitoring

This study will be monitored by the ECOG-ACRIN Data Monitoring Committee (DMC). The DMC meets twice each year. For each meeting, all monitored studies are reviewed for safety and progress toward completion. When appropriate, the DMC will also review interim analyses of outcome data. Copies of the toxicity reports prepared for the DMC meetings are included in the study reports prepared for the ECOG-ACRIN group meeting (except that for double blind studies, the DMC may review unblinded toxicity data, while only pooled or blinded data will be made public). These group meeting reports are made available to the local investigators, who may provide them to their IRBs. Only the

study statistician and the DMC members will have access to interim analyses of outcome data. Prior to completion of this study, any use of outcome data will require approval of the DMC. Any DMC recommendations for changes to this study will be circulated to the local investigators in the form of addenda to this protocol document. A complete copy of the ECOG-ACRIN DMC Policy can be obtained from the ECOG-ACRIN Operations Office – Boston.

10. Correlative Studies

Specimens requested for "Pharmacogenetic/Pharmacokinetic" ancillary (Appendix IV), or banking for future research are to be submitted only from patients who have given written consent for the use of their specimens for these purposes.

All specimens must be labeled with the ECOG-ACRIN protocol number, the patient's initials and ECOG-ACRIN sequence number, the collection date, and the type of sample.

Kits for the collection and shipment of blood specimens: To order the kits complete the E1208 Collection and Shipping Kit Order Form (Appendix VI) and Fax to Zemotak-International at (800) 815-4675.

Summary of sample submission timelines:

Rev. 12/10

	Baseline	Day 1 or S/P 1 hour post –S/P	Day 8[2] of S/P treatment	Day 15[2] of S/P treatment	3-5 days prior to TACE #2[2]	3-5 days prior to TACE #3[2]
Tissue Block	Biopsy or resection					
Plasma, two (2) 7mL heparin tubes	X	X[1]	X[1,2]	X[1,2]	X	X
Peripheral blood, PAXgene DNA	Sample may be drawn any time, although baseline (prior to treatment) preferred					

1 If this blood draw is not taken on day one, 1-hour post day 8 or day 15 sorafenib/placebo dose is requested. NOTE, however, that the pre- sorafenib/placebo blood draw on days 8 and 15 are more important than the 1 hour post- sorafenib/placebo draw.

Rev. 12/10 2 All draws are to be taken during the times the patient is taking S/P. Request patient bring the sorafenib/placebo to take AFTER the research and clinical blood draws. However, if patient has already taken the medication, draw the blood and note time of sorafenib/placebo administration and time of blood draw in STS. If blood draws cannot be drawn on a specified day, draw as close to the designated day as possible. If patient is not available for the pre-TACE draws, the draws may be taken 10-14 days after S/P has been reinitiated, after any TACE treatment.

10.1 Sample Preparations

10.1.1 Tissue Submissions:

Rev. 12/10

Submit from patients who have answered "Yes" to "*I agree to participate in the research laboratory tests that are being done as part of this study*" or banking for future research (my specimens may be kept for use in future research to learn about, prevent, treat, or cure cancer).

Tissue block of the most recent diagnostic biopsy or resection

Rev. 12/14

NOTE: If no blocks are available from metastatic sites of disease, submit blocks from primary disease sites. If no blocks are available for submission, contact the ECOG-ACRIN CBPF to obtain alternative submission requirements.

The following forms MUST be submitted with all tissue submissions:

- STS generated shipping manifest
- Copy of the surgical pathology report and surgical procedure report.
- Immunologic studies reports, if performed

10.1.2 Blood Submissions

NOTE: Institutions outside North America are not required to submit fresh specimens (blood) from consented patients due to the problems and costs of international shipping. If sites wish to participate in these studies, contact the ECOG-ACRIN CBPF to obtain alternative shipping guidelines.

Rev. 12/14

A. Peripheral Blood

Rev. 12/10

Submit from patients who answer "Yes" to *"I agree to participate in the protein and DNA studies that are being done as part of this treatment trial"* or banking for future research (my specimens may be kept for use in future research to learn about, prevent, treat, or cure cancer)..

- Draw peripheral blood into one **PAXgene DNA** vacutainer, then gently invert tube 8-10 times.
- NOTE: If PAXgene DNA vacutainer is not available, an EDTA vacutainer may be substituted.
- May be shipped at ambient or frozen and shipped with plasma.

Collection prior to start of any study treatment is preferred, but sample collection may occur at any time patient is on study. Draw the PAXgene DNA blood tube AFTER all other draws, including any clinical blood draws.

B. Plasma (Limited Institution)

Rev. 12/10

Institutions must have the resource to process the specimens (dry ice required).

Submit from patients who answer "Yes" to "*I agree to participate in the blood drug levels study that is being done as part of this treatment trial*."

- At each time point specified, draw two (2) 7mL heparinized vacutainers
- Separate by centrifugation at approximately 1200g x 20 minutes
- Aliquote into four cryovials and store at -70°C.

NOTE: If a -70°C freezer is unavailable, store at -20°C and ship on dry ice within 24 hours (or next business day if drawn on Friday).

10.2 Shipping Procedures

Tissue specimens are to be submitted at ambient within one month of patient registration.

It is requested that blood specimens be batched and shipped frozen on dry ice on a quarterly basis. If -70°C freezer is not available, plasma specimens are to be stored at -20°C and shipped on dry ice within 24 hours of collection. Blood specimens are to be shipped SUNDAY THROUGH THURSDAY only via overnight courier. Do not ship specimens the day before a holiday.

Ship to:

Rev. 12/14

ECOG-ACRIN Central Biorepository and Pathology Facility
MD Anderson Cancer Center
Department of Pathology, Unit 085
Tissue Qualification Laboratory for ECOG-ACRIN, Room G1.3586
1515 Holcombe Blvd
Houston, TX 77030
Phone: Toll Free 1-844-744-2420 (713-745-4440 Local or International Sites)
Fax: 713-563-6506
Email: eacbpf@mdanderson.org

Shipping manifest generated from the ECOG-ACRIN STS system must accompany the specimens.

10.3 ECOG-ACRIN Sample Tracking System

It is **required** that all specimens submitted on this trial be entered and tracked using the ECOG-ACRIN Sample Tracking System (STS). The software will allow the use of either 1) an ECOG-ACRIN user-name and password previously assigned (for those already using STS), or 2) a CTSU username and password.

When you are ready to log the collection and/or shipment of the specimens required for this study, please access the Sample Tracking System software by clicking https://webapps.ecog.org/Tst.

Important: Any case reimbursements associated with specimen submissions may not be captured if specimens are not logged into STS. Additionally, please note that the STS software creates pop-up windows, so you will need to enable pop-ups within your web browser while using the software. A user manual and interactive demo are available by clicking this link: http://www.ecog.org/general/stsinfo.html. Please take a moment to familiarize yourself with the software prior to using the system.

An STS generated shipping manifest should be shipped with all specimen submissions.

Please direct your questions or comments pertaining to the STS to ecog.tst@jimmy.harvard.edu.

Rev. 12/14

10.3.1 Study Specific Notes

ECOG-ACRIN Generic Specimen Submission Form (#2981) and Shipment Notification Form (Appendix V) (faxed to the receiving laboratory) will be required only if STS is unavailable at time of

sample submission. Indicate the appropriate Lab ID# on the submission form:

- ECOG-ACRIN CBPF

Retroactively enter all specimen collection and shipping information when STS is available.

10.4 Banking

Residual material from the specimens submitted will be retained at the ECOG-ACRIN Central Repository for possible use in future ECOG-ACRIN approved studies. Any residual blocks will be available for purposes of individual patient management on specific written request. If future use is denied or withdrawn by the patient, the specimens will be removed from consideration for use in any future study.

Rev. 9/10

10.5 Imaging Correlative Science-Centralized Reader Study

Centralized submission of required baseline and follow-up imaging to ACRIN will be made for determination of:

- Central evaluation of PFS (in comparison to site reported progression)
- Evaluation of inter-reader concordance of EASL criteria for tumor response following chemoembolization +/- Sorafenib at 4 months and 8 months following initial chemoembolization
- Central evaluation for non-RECIST (e.g. EASL) response rates at 4 months and 8 months following initial chemoembolization therapy
- Value of EASL response at four months and eight months post chemoembolization as a predictive marker of PFS and overall survival
- Evaluation of effects of intra-hepatic vs. extra-hepatic tumor progression on overall survival

Rev. 12/10

Submission Requirements are outlined in Section 5.3.4 and Appendix X.

Justification

For patients with locally advanced hepatocellular carcinoma (HCC), therapeutic options include chemoembolization (30) or systemic therapy with the multikinase inhibitor sorafenib (31, 32). However, these therapies often do not elicit dramatic tumor shrinkage. As such, traditional response assessment methods, such as RECIST (33), fail to identify early responders(34). Assessment of therapeutic response requires longer observation times until disease progression is observed. Improved early-response assessment would facilitate triaging patients for additional therapy.

The European Association for the Study of the Liver (EASL) recommended an alternative to RECIST for grading therapeutic response of HCC (35, 36). The EASL criteria uses the longest dimension of enhancing tumor as the primary metric for gauging tumor response. However, the ability of radiologists to reproducibly assess viable tumor with a single linear measure has not been examined. In a retrospective single-institution study (37), we demonstrated that the EASL criteria demonstrated poor inter-observer concordance, and could not successfully predict long-term clinical outcomes. Conversely, semi-quantitative volumetric assays were more reproducible, and demonstrated greater predictive value for overall survival (OS).

Furthermore, there remains debate in the oncology, hepatology, and interventional radiology communities on the advisability of localized treatment of intra-hepatic disease (in order to decrease morbidity—and possibly mortality—from hepatic failure) in the setting of more disseminated tumor burden. While this study will not specifically address this question, the centralized reader analysis in this study will indirectly evaluate the contribution of hepatic vs. extrahepatic tumor progression as a contributor to mortality.

Central image study analysis plan

The ACRIN core lab will provide the central reader study. Two expert readers will evaluate each case independently, with a third reader performing adjudication of disagreements in time-point specific RR or PFS. Detailed plans for the reader study and the proposed analysis are as follows:

For the secondary objective of determination of central versus local site determination of progression free survival, all imaging studies will be read independently by both readers for standard RECIST analysis of time to tumor progression. For each patient time-point where progression status is not agreed upon by the two readers, a third expert reader will evaluate the case to determine whether a progression event has occurred, thus providing a single centrally determined time to progression. The centralized TTP and PFS will be compared to that result obtained through site evaluation.

For the secondary objective of determination of the inter-reader concordance for response characterization at four and eight months by the European Association for the Study of Liver (EASL) criteria, the Pearson correlation coefficient will be computed to examine the linear relationship between responses from two readers. Then, the Kappa statistics will be applied to assess agreement between readers.

For the secondary objective of determination of the value of objective tumor response at four and eight months by the EASL criteria to predict PFS (by RECIST) and OS, we will fit the Cox proportional hazard models to examine the effect of objective tumor response (responder or non-responder groups) to predict PFS (by RECIST) and OS, at each of 4 and 8 months. In addition, we will repeat similar analyses with 2D-EASL, % necrosis, and estimated viable tumor volume to predict PFS and OS.

For the secondary objective of evaluation of the effects of intra-hepatic vs. extra-hepatic progression on OS, the compartmental assessment will be made for each patient once, at the time that individual patient reaches any type of progression. This single progression type (intra-hepatic or extra-hepatic) per patient will be taken into account in our analysis. We will use the Cox proportional hazard models adjusted by progression type, the actual time that the progression type is evaluated, and treatment type. Other potential covariates include the stratification by venous involvement at baseline and the degree of liver disease at baseline by Childs-Pugh Score.

Necrosis adjusted response assessment

In addition, ACRIN readers will perform a necrosis adjusted assessment of tumor status in an attempt to obtain a more robust measure of tumor responsiveness early after therapy. For this analysis, the primary metric of interest will be the proposed EASL guidelines, namely, the largest enhancing diameter of tumor (rather than the whole tumor—including necrotic areas). This metric will be

assessed at baseline, and at 4 months and 8 months post initialization of chemoembolization. Patients who do not receive contrast enhanced imaging at all three time points, or who received different imaging modalities (CT vs. MRI) during this time frame, will be eliminated from this sub-study. Objective response rate (CR + PR) by the EASL criteria (sum of the longest diameters of enhancing tumors) will be assessed. Additional metrics of interest will include:

- Two-dimensional EASL
  - sum of the products of the longest and shortest diameters of enhancing tumors
- Estimated tumor necrosis
  - 0% to 100%
- Estimated residual viable tumor volume
  - three-dimensional product of whole tumor diameters multiplied by the estimated necrosis

For each metric above (EASL, 2D-EASL, % necrosis, and estimated viable tumor volume), the objective tumor response at either four or eight months will be evaluated as a potential predictor of PFS (by central RECIST analysis) and OS. Analyses will be performed over the entire cohort, as well as over the two baseline stratification schemes (vascular-invasive vs. non-vascular invasive; Child-Pugh A vs. Child-Pugh B7). The ability of early response assessment to predict PFS and OS as a function of treatment group (chemoembolization and placebo vs. chemoembolization and sorafenib) will also be assessed. In addition, sub-analyses may be performed for those patients receiving MRI vs. those receiving CT for liver assessment in this period in order to assess whether modality of imaging has an effect on fidelity of response assessment.

Qualitative and compartmental analysis of tumor response/progression

In addition to the above described image response/progression metrics, readers will evaluate the qualitative status of disease in four distinct anatomic compartments: liver parenchyma, hepatic vasculature, lymph nodes, and distant metastases. Readers will determine whether the hepatic tumor burden (and hepatic vascular tumor burden for patients with vascular invasion at baseline) has qualitatively decreased, increased, or shown stability at all time points. Progression in individual compartments will also be identified if new disease is seen at any time point.

For all patients, time to qualitative progression (TTQP) will be graded for 1) liver compartment only, 2) liver and/or venous compartment, and 3) any compartment. For each compartment-specific progression assessment, the relationship between TTQP and OS will be assessed. Analyses will be undertaken for the entire cohort, as well as for the individual patient strata, treatment group, and imaging modality (CT or MRI).

We seek to determine whether the patterns of tumor progression (intra- vs. extra-hepatic) are influenced by either treatment arm of vascular invasion at enrollment. This information should provide data to help guide future trial design to better determine whether intra-hepatic tumor control alone through locally targeted therapies such as chemoembolization might improve clinical outcomes even in the face of pre-existing or progressing extra-hepatic tumor.

11. Records to Be Kept

Please refer to the E1208 Forms Packet for the forms submission schedule and copies of all forms. The E1208 Forms Packet may be downloaded by accessing the ECOG World Wide Web Home Page (http://www.ecog.org). Forms must be submitted to the ECOG-ACRIN Operations Office – Boston, FSTRF, 900 Commonwealth Avenue, Boston, MA 02215 (ATTN: DATA).

This study will be monitored by the CTEP Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly from the ECOG-ACRIN Operations Office – Boston to CTEP by electronic means.

11.1 Records Retention

FDA regulations (21 CFR 312.62) require clinical investigators to retain all trial-related documentation, including source documents, long enough to allow the sponsor to use the data to support marketing applications.

This study will be used in support of a US marketing application (New Drug Application), all records pertaining to the trial (including source documents) must be maintained for:

- two years after the FDA approves the marketing application, or
- two years after the FDA disapproves the application for the indication being studied, or
- two years after the FDA is notified by the sponsor of the discontinuation of trials and that an application will not be submitted.

Please contact the ECOG-ACRIN Operations Office – Boston prior to destroying any source documents.

12. Patient Consent and Peer Judgment

Current FDA, NCI, state, federal and institutional regulations concerning informed consent will be followed.

13. References

1. Bosch FX, Ribes J, Diaz M, et al: Primary liver cancer: worldwide incidence and trends. Gastroenterology 127:S5-S16, 2004
2. El-Serag HB, Mason AC: Rising incidence of hepatocellular carcinoma in the United States. N Engl J Med 340:745-50, 1999
3. Abou-Alfa GK, Schwartz L, Ricci S, et al: Phase II Study of Sorafenib in Patients With Advanced Hepatocellular Carcinoma. J Clin Oncol, 2006
4. Bismuth H, Majno PE, Adam R: Liver transplantation for hepatocellular carcinoma. Semin Liver Dis 19:311-22, 1999
5. Llovet JM, Bruix J, Fuster J, et al: Liver transplantation for small hepatocellular carcinoma: the tumor-node-metastasis classification does not have prognostic power. Hepatology 27:1572-7, 1998

6. Mazzaferro V, Regalia E, Doci R, et al: Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 334:693-9, 1996
7. Harnois DM, Steers J, Andrews JC, et al: Preoperative hepatic artery chemoembolization followed by orthotopic liver transplantation for hepatocellular carcinoma. Liver Transpl Surg 5:192-9, 1999
8. NCCN Clinic Practice Guidelines in Oncology - Hepatobiliary Cancers, National Comprehensive Cancer Network, 2008
9. Lam VW, Ng KK, Chok KS, et al: Risk factors and prognostic factors of local recurrence after radiofrequency ablation of hepatocellular carcinoma. J Am Coll Surg 207:20-9, 2008
10. Shiina S, Teratani T, Obi S, et al: A randomized controlled trial of radiofrequency ablation with ethanol injection for small hepatocellular carcinoma. Gastroenterology 129:122-30, 2005
11. Lu DS, Yu NC, Raman SS, et al: Radiofrequency ablation of hepatocellular carcinoma: treatment success as defined by histologic examination of the explanted liver. Radiology 234:954-60, 2005
12. Lin SM, Lin CJ, Lin CC, et al: Radiofrequency ablation improves prognosis compared with ethanol injection for hepatocellular carcinoma < or =4 cm. Gastroenterology 127:1714-23, 2004
13. Breedis C, Young G: The blood supply of neoplasms in the liver. Am J Pathol 30:969-77, 1954
14. Kan Z, Ivancev K, Lunderquist A, et al: In vivo microscopy of hepatic tumors in animal models: a dynamic investigation of blood supply to hepatic metastases. Radiology 187:621-6, 1993
15. Brown DB, Geschwind JF, Soulen MC, et al: Society of Interventional Radiology position statement on chemoembolization of hepatic malignancies. J Vasc Interv Radiol 17:217-23, 2006
16. Llovet JM, Real MI, Montana X, et al: Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. Lancet 359:1734-9, 2002
17. Madden MV, Krige JE, Bailey S, et al: Randomised trial of targeted chemotherapy with lipiodol and 5-epidoxorubicin compared with symptomatic treatment for hepatoma. Gut 34:1598-600, 1993
18. Pelletier G, Ducreux M, Gay F, et al: Treatment of unresectable hepatocellular carcinoma with lipiodol chemoembolization: a multicenter randomized trial. Groupe CHC. J Hepatol 29:129-34, 1998
19. Pelletier G, Roche A, Ink O, et al: A randomized trial of hepatic arterial chemoembolization in patients with unresectable hepatocellular carcinoma. J Hepatol 11:181-4, 1990
20. Lo CM, Ngan H, Tso WK, et al: Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. Hepatology 35:1164-71, 2002
21. Bruix J, Sherman M: Management of hepatocellular carcinoma. Hepatology 42:1208-36, 2005

22. Llovet JM, Burroughs A, Bruix J: Hepatocellular carcinoma. Lancet 362:1907-17, 2003
23. Gupta S, Kobayashi S, Phongkitkarun S, et al: Effect of transcatheter hepatic arterial embolization on angiogenesis in an animal model. Invest Radiol 41:516-21, 2006
24. Sergio A, Cristofori C, Cardin R, et al: Transcatheter arterial chemoembolization (TACE) in hepatocellular carcinoma (HCC): the role of angiogenesis and invasiveness. Am J Gastroenterol 103:914-21, 2008
25. Huynh H, Nguyen TT, Chow KH, et al: Over-expression of the mitogen-activated protein kinase (MAPK) kinase (MEK)-MAPK in hepatocellular carcinoma: its role in tumor progression and apoptosis. BMC Gastroenterol 3:19, 2003
26. Yoshiji H, Kuriyama S, Yoshii J, et al: Halting the interaction between vascular endothelial growth factor and its receptors attenuates liver carcinogenesis in mice. Hepatology 39:1517-24, 2004
27. Llovet JM, Ricci S, Mazzaferro V, et al: Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 359:378-90, 2008
28. K. Abou-Alfa PJ, J. Knox, I. Davidenko, J. Lacava, T. Leung, A. Mori, M. Le Berre, D. Voliotis, L. Saltz: Final results from a phase II (PhII), randomized, double-blind study of sorafenib plus doxorubicin (S+D) versus placebo plus doxorubicin (P+D) in patients (pts) with advanced hepatocellular carcinoma (AHCC), ASCO Gastrointestinal Symposium. Orlando, FL, 2008, pp 128
29. Freidlin B, Korn, EL, Hunsberger S, Gray R, Saxman S, and Zujewski A (2007). *Journal of Clinical Oncology, Vol 25, (May), 2007: 2122.* Proposal for the Use of Progression-Free Survival in Unblinded Randomized Trials

Rev. 9/10

30. Ruutiainen AT, Soulen M. Transarterial chemoembolization in the management of primary and secondary liver tumors. In: Interventional Radiological Treatment of Liver Tumors. Eds: Adam A, Mueller P. Cambridge: 2009. 74-91.
31. Abou-Alfa, G.K., et al., *Phase II study of sorafenib in patients with advanced hepatocellular carcinoma.* J Clin Oncol, 2006. 24(26): p. 4293-300.
32. Llovet et al. Sorafenib in Advanced Hepatocellular Carcinoma. N Engl J Med, 2008. 359(4): 378-90.
33. Therasse, P., et al., *New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada.* J Natl Cancer Inst, 2000. 92(3): p. 205-16.
34. Forner A, Ayuso C, Varela M, Rimola J, Hessheimer AJ, de Lope CR, Reig M, Bianchi L, Llovet JM, Bruix J. Evaluation of tumor response after locoregional therapies in hepatocellular carcinoma: are response evaluation criteria in solid tumors reliable? Cancer 2009. 115(3): 616-23.
35. Bruix, J. and M. Sherman, *Management of hepatocellular carcinoma.* Hepatology, 2005. 42(5): p. 1208-36.
36. Llovet, J.M., et al., *Design and endpoints of clinical trials in hepatocellular carcinoma.* J Natl Cancer Inst, 2008. 100(10): p. 698-711.
37. Ruutinien et al. MRI Evaluation of Tumor Response in Patients with Advanced HCC Undergoing Chemoembolization: Effect of Response Model on Predictive Model and Reader Variability. RSNA Annual meeting, 2008.

A Phase III Randomized Trial of Chemoembolization with or without Sorafenib in Unresectable Hepatocellular Carcinoma (HCC) in Patients with and without Vascular Invasion

Version Date: March 28, 2014

Appendix I

Informed Consent Template for Cancer Treatment Trials (English Language)
[Deleted in Addendum #6]

INFORMED CONSENT INTENTIONALLY REMOVED FROM PROTOCOL DOCUMENT

Appendix I was removed from the protocol document in Addendum #6 and is posted as a separate document on the ECOG website. This was removed from the protocol to comply with NCI formatting guidelines.

A Phase III Randomized Trial of Chemoembolization with or without Sorafenib in Unresectable Hepatocellular Carcinoma (HCC) in Patients with and without Vascular Invasion

Appendix II

Pathology Submission Guidelines

The following items are included in Appendix II:

1. Guidelines for Submission of Pathology Materials (instructional sheet for Clinical Research Associates [CRAs])
2. Instructional memo to submitting pathologists
3. List of Required Materials for E1208

Rev. 12/14

4. ECOG-ACRIN Generic Specimen Submission Form (#2981

Rev. 12/14

Guidelines for Submission of Pathology Materials

The following items should always be included when submitting pathology materials to the ECOG-ACRIN Central Biorepository and Pathology Facility:

- Institutional Surgical Pathology Report
- Pathology materials (see attached List of Required Material)

Instructions:

1. Place the Patient ID label provided by the ECOG-ACRIN Operations Office – Boston in Part A of the Pathology Material Submission Form. If a label is not available, **TYPE or PRINT** the following information in **Part A** of the form:

   Patient's name (last, first)

   Protocol number

   Protocol case number (the patient's ECOG-ACRIN sequence number; for intergroup studies, include both the ECOG-ACRIN and other group's sequence numbers)

   Patient's hospital number

   Institution

   Affiliate (if appropriate)
2. Complete blank areas of the pathologist's instructional memo and forward it, along with the List of Required Material and the Pathology Material Submission Form, to the appropriate pathologist.
3. The pathologist should return the required pathology samples and surgical pathology reports. If any other reports are required, they should be obtained from the appropriate department at this time.
4. Keep a copy of the submission forms for your records.
5. Double-check that ALL required forms, reports and pathology samples are included in the package to the Central Biorepository and Pathology Facility. (See appropriate List of Required Material.)
   Pathology specimens submitted WILL NOT be processed by the Central Biorepository and Pathology Facility until all necessary items are received.
6. Mail pathology materials to:

   ECOG-ACRIN Central Biorepository and Pathology Facility
   MD Anderson Cancer Center
   Department of Pathology, Unit 085
   Tissue Qualification Laboratory for ECOG-ACRIN, Room G1.3586
   1515 Holcombe Blvd
   Houston, TX 77030
   Phone: Toll Free 1-844-744-2420 (713-745-4440 Local or International Sites)
   Fax: 713-563-6506
   Email: eacbpf@mdanderson.org

If you have any questions concerning the above instructions or if you anticipate any problems in meeting the pathology material submission deadline of one month, contact the Pathology Coordinator at the ECOG-ACRIN Central Biorepository and Pathology Facility.

List of Required Material

E1208: A Phase III Randomized Trial of Chemoembolization with or without Sorafenib in Unresectable Hepatocellular Carcinoma (HCC) in Patients with and without Vascular Invasion

Pre-Treatment

Rev. 12/14

1. Institutional pathology report ***(must be included with EVERY pathology submission).***
2. Reports of immunological studies, if performed
3. **Required path materials: Paraffin-embedded tumor tissue block.**

   NOTE: Since blocks are being used for laboratory studies, in some cases the material may be depleted and, therefore, the block may not be returned.

ECOG-ACRIN
cancer research group
Reshaping the future of patient care

Robert L. Comis, MD, and Mitchell D. Schnall, MD, PhD
Group Co-Chairs

MEMORANDUM

TO: _____
(Submitting Pathologist)

FROM: Stanley Hamilton, M.D., Chair
ECOG-ACRIN Laboratory Science and Pathology Committee

DATE: _____

SUBJECT: *Submission of Pathology Materials for* E1208: *A Phase III Randomized Trial of Chemoembolization with or without Sorafenib in Unresectable Hepatocellular Carcinoma (HCC) in Patients with and without Vascular Invasion*

Rev. 12/14

The patient named on the attached request has been entered onto an ECOG-ACRIN protocol by _____ (ECOG-ACRIN Investigator). This protocol requires the submission of pathology materials for laboratory studies or banking.

Please complete PART B of the Submission Form. Keep a copy for your own records, and return the completed Submission Form, the surgical pathology report(s), the slides and/or blocks, and any other required material (see attached List of Required Material) to the Clinical Research Associate (CRA). The CRA will forward all required pathology material to the ECOG-ACRIN Central Biorepository and Pathology Facility.

Blocks and slides submitted for this study will be retained at the ECOG-ACRIN Central Repository for future studies. Paraffin blocks will be returned upon written request for purposes of patient management.

Please note: Since blocks are being used for laboratory studies, in some cases the material may be depleted, and, therefore, the block may not be returned.

If you have any questions regarding this request, please feel free to contact the Central Biorepository and Pathology Facility at 1-844-744-2420 (713-745-4440 Local or International Sites) or email: eacbpf@mdanderson.org.

The ECOG-ACRIN CRA at your institution is:

Name:_____

Address:_____

Phone: _____

Thank you.

ECOG-ACRIN Generic Specimen Submission Form

Form No. 2981v3

Institution Instructions: This form is to be completed and submitted with **all specimens** ONLY if the Sample Tracking System (STS) is not available. **Use one form per patient, per time- point.** All specimens shipped to the laboratory must be listed on this form. Enter all dates as MM/DD/YY. Keep a copy for your files. Retroactively log all specimens into STS once the system is available. **Contact the receiving lab to inform them of shipments that will be sent with this form.**

Protocol Number _____ **Patient ID** _____ **Patient Initials** Last _____ First _____

Date Shipped _____ **Courier** _____ **Courier Tracking Number** _____

Shipped To (Laboratory Name) _____ **Date CRA will log into STS** _____

FORMS AND REPORTS: Include all forms and reports as directed per protocol, e.g., pathology, cytogenetics, flow cytometry, patient consult, etc.

Required fields for all samples				**Additional fields for tissue submissions**				**Completed by Receiving Lab**
Protocol Specified Timepoint:								
Sample Type (fluid or fresh tissue, include collection tube type)	**Quantity**	**Collection Date and Time 24 HR**		**Surgical or Sample ID**	**Anatomic Site**	**Disease Status** (e.g., primary, mets, normal)	**Stain or Fixative**	**Lab ID**

Fields to be completed if requested per protocol. Refer to the protocol-specific sample submissions for additional fields that may be required.					
Leukemia/Myeloma Studies:	**Diagnosis**	**Intended Treatment Trial**	**Peripheral WBC Count (x1000)**	**Peripheral Blasts %**	**Lymphocytes %**
Study Drug Information:	**Therapy Drug Name**	**Date Drug Administered**	**Start Time 24 HR**	**Stop Time 24HR**	
Caloric Intake:	**Date of Last Caloric Intake**		**Time of Last Caloric Intake 24HR**		

CRA Name _____ **CRA Phone** _____ **CRA Email** _____

Comments

9/12/14

A Phase III Randomized Trial of Chemoembolization with or without Sorafenib in Unresectable Hepatocellular Carcinoma (HCC) in Patients with and without Vascular Invasion

Appendix III

Patient Thank You Letter

We ask that the physician use the template contained in this appendix to prepare a letter thanking the patient for enrolling in this trial. The template is intended as a guide and can be downloaded from the ECOG web site at http://www.ecog.org. As this is a personal letter, physicians may elect to further tailor the text to their situation.

This small gesture is a part of a broader program being undertaken by ECOG-ACRIN and the NCI to increase awareness of the importance of clinical trials and improve accrual and follow-through. We appreciate your help in this effort.

[PATIENT NAME] [DATE]

[PATIENT ADDRESS]

Dear [PATIENT SALUTATION],

Thank you for agreeing to take part in this important research study. Many questions remain unanswered in cancer. With the help of people like you who participate in clinical trials, we will achieve our goal of effectively treating and ultimately curing cancer.

We believe you will receive high quality, complete care. I and my research staff will maintain very close contact with you. This will allow me to provide you with the best care while learning as much as possible to help you and other patients.

On behalf of ***[INSTITUTION]*** and the ECOG-ACRIN Cancer Research Group, we thank you again and look forward to helping you.

Sincerely,

[PHYSICIAN NAME]

A Phase III Randomized Trial of Chemoembolization with or without Sorafenib in Unresectable Hepatocellular Carcinoma (HCC) in Patients with and without Vascular Invasion

Appendix IV

Ancillary For Pharmacogenetic and Genomic Studies: Pharmacogenetic/Pharmacodynamic Study of Sorafenib and Sorafenib Associated Pharmacokinetic Laboratory Studies

Study Co-Chair: Jill Kolesar, Pharm.D.

Patients registered to E1208, E1404, E1804, E2501, E2804, E2603, E5203, or E2805 are eligibile to participate in this ancillary study.

NOTE: E1208, E2805, and E2603 are blinded treatment trials. All patients on these trials are eligible to participate in these ancillary studies.

IV.1 Ancillary for Pharmacogenetic and Genomic Studies

The Ancillary for Pharmacogenetic and Genomic Studies is a series of ancillary laboratory studies that seek to address questions about treatment response and toxicity that may span several studies and/or diseases. Thus, these correlatives may fall within the purview of a single disease committee, or span several. Each pharmacogenomic ancillary to be conducted in ECOG-ACRIN will be embedded into the parent protocols, with participation in the ancillary obtained via responses to questions embedded in the parent consent form. The general objectives of the pharmacogenetic/pharmacokinetic ancillary are not specific to any one parent protocol: however, specific correlative objectives may be driven by the parent or related parent protocols.

The development of novel targeted agents for the treatment of cancer has altered the process of the investigation of new treatments through the various stages of clinical research. Simultaneously, advances in biology have brought new questions regarding the mode of action, the toxicity, and the efficacy of treatments into the Phase II and III arena, historically the purview of the cooperative group. Some of the questions raised must be addressed in each tumor separately; others are independent of the tumor type and are properly asked across studies. The major questions may be summarized:

a. What tumor characteristics are responsible for some patients responding and others not?
b. What are the characteristics of normal tissues that cause some patients to have side-effects and others not?
c. When a treatment is administered at a particular dose, does it achieve the desired effect at the level of its target, in tumor and/or in normal tissue?
d. Can this variation in tumor and normal tissue make-up, and in biological responses to treatment be related to the outcome of such treatment in such a way as to refine that treatment for future patients?

The answers to these questions are in the tumors and tissues of patients treated on therapeutic trials. The analyses that accompany these studies are therefore of major importance to understanding both the successes and the failures of the trials. .

The primary focus of the ancillary is in the acquisition of materials to permit pharmacogenetic and pharmacogenomic analyses to be performed. The overall

purpose of these analyses is to explain and predict variability in drug responses among patients. The central **hypothesis** of the studies under this ancillary is that ***safe and effective drug use depends on an understanding of variability in both normal and tumor cells in individual patients***.

IV.2 Pharmacogenetic/Pharmacodynamic study of Sorafenib

Study Co-Chair: Jill Kolesar, Pharm.D.

Specimens for this study are outlined in Section 10 and will be submitted from patients answering "yes" to "I agree to participate in the protein and DNA studies that are being done as part of this clinical trial"

IV.2.1 Objectives

- To identify SNP profiles corresponding to response and/or toxicity (single agent studies).
- To measure polymorphisms in the promoter and coding regions of raf, VEGFR-2, PDGF, and other genes as may emerge as critical to the activity of sorafenib in the clinic, with particular reference to genes signaling to and mediating apoptosis.
- To profile polymorphisms in drug metabolizing enzymes.

IV.2.2 Identifying a SNP Profile

NOTE: This study will be performed on samples submitted from patients on single agent sorafenib only.

The GeneChip® Mapping Assay by Affymetrix genotypes greater than 10,000 human single nucleotide polymorphisms (SNPs) on a single array, including most of the known CYP polymorphisms using a single polymerase chain reaction (PCR) primer. As its name implies, it is a mapping tool designed to identify regions of the genome that are linked to, or associated with, a particular trait or phenotype (Kaller, 2007). In addition, it is also useful for determination of allele frequencies in various populations and for mapping regions with loss of heterozygosity during cancer progression. Briefly, the assay involves collection of DNA samples, purification, PCR amplification and hybridization, and will be done at the UW Biotechnology Gene Expression Center.

Patients enrolled in E1404 and E1804 will provide two DNA Paxgene tubes and Affymetrix will be used as a mapping method to identify polymorphism profiles that predict response and toxicity. Subjects with a complete response and those with a progressive disease will be compared to identify a SNP profile predictive of response. Individuals with grade III-IV nausea, diarrhea or pancreatitis, the expected toxicities of sorafenib, will be compared to individuals without grade III-IV toxicity to identify a SNP profile predictive of toxicity. SNP profiles identified in E1404 and 1804 will be validated across the other ECOG-ACRIN studies that include sorafenib.

IV.2.3 Frequency and Correlation of B-Raf Mutations in Tumor Tissue

NOTE: Laser capture microdissection will be performed on tumor blocks submitted from participating patients.

Rationale:

Sorafenib is a potent c-raf and B-Raf kinase inhibitor with IC50's of 2-6nM and 25nM, respectively. In addition, sorafenib is an inhibitor of the V599E mutant B-Raf, with an IC50 of 38nM. In addition to the V599E mutation, more than 30 different mutations in the B-Raf gene, primarily in the kinase region, have been identified in human cancers. In an evaluation of 22 of the identified mutations, Wan and colleagues showed that 18 mutations were associated with elevated kinase activities, while three had reduced B-Raf kinase, but actually activated c-raf. V599E is a highly activating mutation, with significant sensitivity to sorafenib, therefore we hypothesize that activating mutation in B-Raf will predict sensitivity to sorafenib (Wan, 2004).

Mutational Analysis:

Mutations in the kinase domain of B-Raf will be analyzed by direct sequencing. Briefly, PCR primers encompassing the kinase domain will be synthesized and the B-Raf gene will be amplified by PCR. After exo-sap clean-up samples will be sequenced in both the 5' and 3' direction and samples will be reported as wild-type or mutant at each known position.

IV.2.4 Polymorphisms in Drug Metabolizing Enzymes- Polymorphisms in CYP3A4/5, CYP2C9, MDR

NOTE: Studies on DNA isolated from peripheral blood (PAXgene DNA vacutainer).

Rationale and Preliminary Data:

CYP3A4, CYP3A5, CYP2C9 are monooxygenases that metabolize numerous drugs, including the anti-cancer agents sorafenib. Each has functional polymorphisms that may increase or decrease expression, in turn contributing to the pharmacokinetic variability seen with sorafenib. Although each of the CYP polymorphisms is rare, when taken together, approximately 10% of the Caucasian population may have one of these polymorphisms.

Functional consequences of a polymorphism in the *CYP3A4* promoter region (A290G) (i.e., *CYP3A4*1B*) have been studied as a possible cause of variability in CYP3A4 expression, showing consistent, moderate (1.5-2 fold) increases in transcription with the variant promoter in both cancer cell lines and in primary cultured hepatocytes (Kuehl, 2001). CYP3A4*1B frequency varies by ethnicity, with only 0.2% of Caucasian controls having the CYP3A4*1B/*1B genotype, but up to 37% of African American reference populations (Ma, 2002).

The CYP3A5*1 allele is necessary for CYP3A5 to be expressed in the liver (Hustert, 2001). Two alleles for CYP3A5, the CYP3A5*3 and the CYP3A5*6 polymorphisms result in alternative splicing, protein truncation and an absence of CYP3A5 activity, thus those with the CYP3A5*1 are high expressers, while, those with the *3 and *6 polymorphisms have no activity (Lee, 2003). The *6 polymorphism is rare, with the *6/*6 genotype frequency of 0%, and an allele frequency of 0.001 in a Dutch Caucasian population of 500 individuals (Lamba, 2002). Additionally, the CYP3A5*1 allele is rare in Caucasian populations, with the *1/*1 genotype reported as less than 1%, but up to 37% of African Americans, and is associated with a decreased risk of non small cell lung cancer (NSCLC). Conversely, despite being described as the variant, the CYP3A5*3

allele is quite common, with a homozygous frequency of 83%-85% reported for Caucasians, but only 13-16% for African Americans without cancer (Quaranta, 2006).

A recent evaluation of NSCLC cancer by the Kolesar laboratory demonstrates that of the 171 tumors, 146 (85.4%) were designated as wild type, 20 (11.7%) heterozygous, and 5 (2.9%) homozygous variant for the CYP3A4*1B allele. Similarly, for the CYP3A5*3(3B) allele, 104 (78.2%) were wild type, 22 (16.5%) heterozygous, and 7 (5.3%) homozygous variant, showing that CYP3A4 and CYP3A5 polymorphisms are more frequent in NSCLC than in normal volunteers.

CYP2C9 has two functional polymorphisms, the *2, and the *3, with approximately 2% of Caucasians having the *2/*2 genotype and 1% of Caucasian with the *3/*3 genotypes. Both are inactivating polymorphisms, with individuals with the *2/*2 genotype having a 30-50% reduction in metabolism and those with the *3/*3 having an almost 90% reduction. Individuals with the CYP2C9*2/*2 or CYP2C9*3/*3 are expected to have decreased metabolism of sorafenib, increased concentrations and increased toxicity (Kirchheiner, 2005).

MDR is the gene that codes for P glycoprotein (PgP), a transmembrane pump important in drug efflux (Choudhuri, 2006). While sorafenib has not specifically been shown to be an MDR substrate, recent evidence shows that MDR upregulation by cytotoxics is mediated by the Raf-kinase pathway, and suggesting that agents such as sorafenib that target Raf kinase may also influence MDR. Additionally, a recent evaluation by Sparreboom and colleagues showed that the homozygous T -allele of MDR*8 (1236C > T) was associated with a trend for a higher area under the curve of tipifarnib as compared to patients with only one or no variant alleles [mean (+/-SD), 5,303 +/- 1,620 ng.h/mL vs. 3,619 +/- 1,275 ng.h/mL; P = 0.047) (Sparreboom, 2004). Therefore, we will evaluate both MDR C3435T and MDR*8 (C1236T), two common (allele frequency 48% in Caucasians) polymorphisms in MDR.

Genotyping:

PCR primers are synthesized by the UW-Madison biotechnology center for the following alleles; CYP3A4*1B, CYP3A5*6, *3(3B), *3(4B), AND *1B/*1C, ABCB1(MDR), CYP2C9*2, *3 and bioinylated the 5' end of every forward primer except CYP3A4*1B, CYP3A5*3(3B), and CYP3A5*1B/*1C (reverse primer biotinylated). PCR is carried out using Amplitaq Gold PCR master mix (ABI, Foster City, CA, USA), 10 pmole of each primer, and 10ng DNA, using an annealing temperature of 53°C for 55 cycles on a MJ Research Tetrad thermal cycler. Pyrosequencing is carried out as previously described using a PSQ96 instrument and software (Pyrosequencing AB, Uppsala, Sweden). Genotype was called variant if it differed from the Refseq consensus sequence for the SNP position.

IV.2.5. Polymorphism analysis with a focus on angiogenesis and apoptosis

NOTE: Studies on DNA isolated from peripheral blood (PAXgene DNA vacutainer).

Rationale

Single nucleotide polymorphisms, and increasingly haplotypes, have been shown to determine the risk of diseases, and response to treatment. For kinase-

targeted drugs, mutations in the targets have proven to be associated with sensitivity or resistance. Toxicity (hypertension, rash, fatigue) and response (tumor shrinkage, PFS, DCE-MRI) to sorafenib are quite variable at standard doses (usually 400 mg bid). This variability may be at a pharmacokinetic, pharmacodynamic, or pharmacogenetic level. Other studies are addressing the PK and PD variability: in a broad trial in ECOG-ACRIN, encompassing several Phase II and Phase III studies, we propose to investigate a possible pharmacogenetic contribution. We have shown further that responses to antiangiogenic therapies may depend especially on the ability of the tumor cell to engage the pathways leading to apoptosis, and have identified several genes the expression of which may confer sensitivity or resistance to these processes. After additional confirmatory studies, we envisage an analysis of variation in such genes as determinants of therapeutic response and toxicity.

Research Plan

Defined SNP's will be assayed either by heteroduplex capillary or gel electrophoresis methods, and exploratory studies will be conducted as needed using microarray-based platforms, the technology for which is rapidly developing. The technology to be used will be state of the art at the time of the analysis.

IV.2.6 Statistical Analysis

The pharmacogenetic/pharmacodynamic studies of sorafenib are open to patients on the following ECOG studies with anticipated enrollment of eligible patients as follows: E1404: 37; E1804: 39; E2501: 165; E2805: 444; E2603: 380; E5203: 36; and E2804: 165; E1208 : 100, for a total of 1366 eligible patients. Throughout, it is assumed that 80% of eligible patients will participate and have adequate samples submitted, so that samples will be available for analysis for 1096 patients. The first 4 studies listed above are single-agent sorafenib studies in recurrent aggressive non-Hodgkin's lymphoma, advanced urothelial cancer, advanced non-small cell lunch cancer, and resected renal cell carcinoma, respectively, with 548 anticipated samples. The last 3 studies above involve combination sorafenib and chemotherapy or other biologics in unresectable locally advanced or stage IV melanoma, metastatic or advanced unresectable GEJ adenocarcinoma, and advanced renal cell carcinoma, respectively, with 465 anticipated samples. For all studies, sorafenib is given 400 mg PO twice daily, however, cycle length and number of cycles vary across studies; the type of chemotherapy or other biologics differ across the combination studies.

Due to differences in disease site and stage, sorafenib schedule, and treatment regimen, the effects of genotypes on outcomes may be different across studies. Analyses will be conducted within individual studies, by pooling within single-agent sorafenib studies, and by pooling across all studies as appropriate. Initial univariate analyses will not adjust for disease and treatment regimen differences. Additional analyses correlating genotypes associated with sorafenib activity with outcome will attempt to control for disease and treatment differences and their potential interactions with genotype on outcome using stratified analyses or adjusting for these factors in multivariate regression models.

SNP Profile Studies

Approximately 60 eligible patients from E1404 and E1804 will have samples available for an analysis of SNP arrays using the Affymetrix GeneChip. Dchip

software (Ching, 2003) will be used to analyze the SNP arrays. Groups defined by objective response (complete and partial response vs. stable disease and progression) and sorafenib toxicity (grade III-IV nausea, diarrhea, or pancreatitis vs. no such toxicity) will be compared in separate analyses to identify polymorphisms predictive of response and sorafenib toxicity. Loss of heterozygosity will also be tested between the groups using methods proposed by Lin et al. (2004). A resampling based approach (as in Westfall and Young, 1992) will be used to adjust p-values in order to control the overall type I error rate and the false discovery rate (FDR). Exploratory analyses of expression patterns among multiple SNPs will be conducted using recursive partitioning, principal components analysis, and other exploratory techniques. Along with the CYP and MDR polymorphisms, other newly identified polymorphisms from the SNP profile studies based on these 60 patients will be studied further among all patients participating in the sorafenib pharmacogenetic studies.

Polymorphisms in Drug Metabolizing Enzymes

One of the primary hypotheses is that inactivating CYP polymorphisms are expected to have increased toxicity. Toxicity among all homozygous variant inactivating polymorphisms in CYP genes will be compared to the heterozygotes and homozygous wild-types; analyses will be conducted separately within single-agent sorafenib and combination therapy studies. Differences in toxicity that can be detected with 80% power are presented in the following table for varying prevalence of the group with higher toxicity and for varying true underlying toxicity rates, based on 548 anticipated patients in single-agent sorafenib studies and using a two-sided Fisher's exact test with 5% type I error.

Table IV.1 Toxicity Rate Differences within Single-Agent Sorafenib Studies (n=548)

	Prevalence of PG Group with Higher Toxicity						
True Toxicity Rate	**5%**	**7%**	**15%**	**25%**	**50%**	**85%**	**95%**
10%	---------	.268 vs .087	.201 vs .082	.170 vs .077	.137 vs .063	.113 vs .024	--------
25%	.513 vs .236	.465 vs .234	.385 vs .226	.346 vs .218	.303 vs .197	.271 vs .130	.260 vs .049
50%	.768 vs .486	.725 vs .483	.647 vs .474	.606 vs .465	.561 vs .439	.526 vs .353	.514 vs .232

Data Analysis Plan

Prevalence will be estimated for each polymorphism in CYP3A4, CYP3A5, CYP2C9, and MDR genes, as well as newly identified polymorphisms from the SNP array studies. Univariate analyses will be conducted to test associations within subgroups (e.g. single-agent sorafenib studies) between each polymorphism and outcome of interest, including toxicity, response, and progression-free survival. The overall type I error rate of 0.05 will be controlled within each group and for each outcome by adjusting the alpha level within each set of univariate tests of polymorphisms using a resampling based approach.

The joint association of combinations of polymorphisms on outcome will be explored using logistic regression (toxicity and response endpoints) and Cox proportional hazards regression (survival endpoints). These multivariate analyses will also control for other important predictors of outcome and will examine interactions between polymorphisms, disease, and treatment.

Recursive partitioning and other exploratory regression techniques will be used to explore SNP-SNP interactions and gene interactions in order to identify combinations of polymorphisms that can be used to predict high and low risk groups.

B-Raf Mutations in Tumor Tissue

B-Raf mutations are expected to vary by malignancy (Davies, 2002). Therefore, the prevalence and correlation of B-Raf mutations with clinical outcomes including response, toxicity, and progression-free survival, will be examined separately by ECOG-ACRIN parent study. Common activating mutations will be examined across studies. As in the analysis of polymorphisms in drug metabolizing enzymes above, the general data analysis plan will first examine univariate associations between B-Raf mutations and clinical outcome, and will control for overall type I error by adjusting p-values using a resampling-based approach. Fisher's Exact and Chi-square tests will be used to compare categorical outcomes between groups, and Wilcoxon rank-sum and Kruskall-Wallis tests will be used for continuous outcomes. Multivariable regression analyses will then be used to explore the relationship of multiple mutations, treatment, and patients characteristics with clinical outcome. Finally, recursive partitioning and other exploratory clustering techniques will be used to examine interactions between B-Raf mutations.

Additional genes and exploratory analyses

Additional genes found to be important to sorafenib resistance or sensitivity through anti-angiogenesis or apoptosis pathways will be explored in a similar manner as above. Exploratory pathway analysis methods, including multi-dimensional scaling (Cox and Cox, 2001) will also be used.

An analysis of indirectly-measured haplotypes and their associations with phenotypes, possibly adjusting for other covariates and their interactions, will be conducted using haplo.stats software available on-line, and associations will be tested based on the family of score tests proposed by Schaid et al (2002), which assume ambiguous haplotypes due to unknown linkage phase of the genetic markers. The score test handles both continuous and categorical phenotypes.

IV.3 Sorafenib Associated Pharmacokinetic Laboratory Studies

Study Co-Chair: Jill Kolesar, Pharm D.

NOTE: This aspect of the Pharmacogenetic/Pharmacokinetic ancillary is limited to institutions with the resources to process the samples (centrifuging and -70°C required) and patients who answer "yes" to "I agree to participate in the blood drug levels study that is being done as part of this clinical trial."

The plasma samples will be collected at baseline, 1-hour post-sorafenib initial treatment, cycle 1 days 8 and 15, cycle 2 day 1 and cycle 3 day 1. At each time point, plasma from **two (2) 7mL green top (heparinized) vacutainers,** will be collected (Section 10.1.2). It is requested that the patient bring the sorafenib/placebo to take AFTER the research and clinical blood draws. However, if patient has already taken the medication, the blood will be drawn and time of sorafenib/placebo administration will be noted.

Rationale and Preliminary Data

Initial phase I studies have identified the pharmacokinetics of sorafenib to exhibit significant interpatient variability, with terminal half-lives ranging from 16-53 hours. As

sorafenib is metabolized by CYP3A4/5 and CYP2C9 polymorphisms in these enzymes may alter the observed plasma pharmacokinetics, and evaluation of sorafenib pharmacokinetics in subjects with variant genotypes is warranted.

Assay Methodology and Pharmacokinetic Analysis:

Pharmacokinetics will be evaluated as previously described by Strumberg for sorafenib.

Standard pharmacokinetic parameters for sorafenib will be assessed including area under the concentration-time curve (AUC), clearance, half-life, volume of distribution and Cmax in plasma and whole blood.

Statistics

Approximately 10% of the 1013 eligible patients enrolled in the pharmacogenetic studies of sorafenib are expected to participate in the pharmacokinetic studies. Therefore, we expect pharmacokinetic samples to be available from approximately 102 patients, 55 from single-agent sorafenib trials and 47 from combination sorafenib and chemotherapy trials.

Serial steady-state trough concentrations will be collected as described in Table IX.1. Sorafenib pharmacokinetic parameter estimates and associated interindividual variability will be estimated with population pharmacokinetic models using non-linear mixed effects modeling in the software package R. Standard pharmacokinetic parameters, such as clearance, volume, area under the curve (AUC), and Cmax will be estimated. Pharmacokinetic data will be analyzed separately for patients on single-agent sorafenib studies and combination sorafenib and chemotherapy trials, and parameter estimates will be compared, with any significant difference in these estimates indicating a possible drug interaction.

Pharmacokinetic parameters will be correlated with polymorphisms in drug metabolizing enzymes, including CYP3A4, CYP3A5, CYP2C9, and MDR. Two main objectives are to compare patients with primary functional MDR polymorphisms to those without such polymorphisms, and for the CYP genes all inactivating homozygote variants will be compared to the heterozygotes and homozygous wild-types.

The Wilcoxon rank-sum test will be used to compare pharmacokinetic parameters, such as AUC, between these groups. Initial univariate analyses will be conducted separately for single-agent and combination sorafenib studies, and subsequently may be pooled if results do not appear to differ by study type. For each of the primary comparisons of MDR and CYP genes, an alpha of 0.025 within each pharmacokinetic parameter correlation will be used to control the overall type I error rate at 0.05. The following table illustrates the power to detect varying differences in AUC from 82 mg*h/l assuming a common standard deviation of 14.8 (Strumberg et al, 2005) comparing those with and without homozygous variant polymorphisms for varying prevalences. The calculations are based on 55 anticipated patients in single-agent sorafenib studies and use a two-sided Wilcoxon rank-sum test with 0.025 alpha, assuming normal underlying distributions. As can be seen in the table, with the prevalence of all inactivating homozygous variant CYP polymorphisms and functional MDR polymorphisms expected to be greater than 5%, there should be sufficient power to detect a decrease in AUC of 30% or more among those receiving single-agent sorafenib.

Table IX.2

Prevalence of homozygous variant polymorphism (total n=55)	50% change in AUC	40% change in AUC	30% change in AUC
0.02	0.66	0.46	0.27
0.05	0.99	0.92	0.70
0.10	0.99	0.99	0.94
0.25	0.99	0.99	0.99
0.50	0.99	0.99	0.99

It should be noted that the computed power is conditional on the number of variant cases, and even if the expected prevalence is correct, there would be substantial chance of getting no variant cases for the rare polymorphisms. For instance, there is a 33% chance of having no variant cases out of 55 patients if the true prevalence for the variant polymorphism is 0.02.

Additional analyses will examine correlations between specific CYP, MDR, and other identified polymorphisms with pharmacokinetic parameters, and the overall alpha level will be controlled by adjusting p-values using resampling-based techniques. Correlation of sorafenib toxicity (grade III-IV nausea, diarrhea, or pancreatitis vs. no such toxicity) with pharmacokinetic parameters will also be examined using two-sided Wilcoxon rank-sum tests with alpha of 0.05.

Multivariate regression analysis of pharmacokinetic endpoints will be conducted among all 102 available subjects with sorafenib pharmacokinetic data using non-linear mixed effects models and including pharmacogenetic markers and clinical covariates, including race, sex, performance status, treatment, dose, among others. Multivariable logistic regression analysis will be used to explore the effect on toxicity of multiple pharmacogenetic markers, pharmacokinetic parameters, clinical characteristics, and their interaction.

IV.4 References

Alizadeh AA, Eisen MB, Davis RE, et al. Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling. Nature 403: 503–511, 2000.

Bruno R, Vivier N, Vergniol JC, De Phillips SL, Montay G, Sheiner LB. A population pharmacokinetic model for docetaxel (Taxotere): model building and validation. J Pharmacokinet Biopharm 24:153-72, 1996.

Calvert AH, Newell DR, Gumbrell LA, et al. Carboplatin dosage: prospective evaluation of a simple formula based on renal function. J Clin Oncol 7:1748-1756, 1989.

Cheng Li and Wing Hung Wong (2003). DNA-Chip Analyzer (dChip). In The analysis of gene expression data: methods and software. Edited by G Parmigiani, ES Garrett, R Irizarry and SL Zeger. Springer.

Choudhuri S, Klaassen CD. Structure, function, expression, genomic organization, and single nucleotide polymorphisms of human ABCB1 (MDR1), ABCC (MRP), and ABCG2 (BCRP) efflux transporters. Int J Toxicol. 2006 Jul-Aug;25(4):231-59.

Cox TF and Cox MAA. Multidimensional Scaling. United Kingdom, CRC press, 2001.

Dchip software is available on-line at www.dchip.org.

Dresser GK, Spence JD, Bailey DG. Pharmacokinetic-pharmacodynamic consequences and clinical relevance of cytochrome P450 3A4 inhibition. Clin Pharmacokinet 38:41-57, 2000

Egorin MJ, Van Echo DA, Olman EA, Whitacre MY, Forrest A, Aisner J. Prospective validation of a pharmacologically based dosing scheme for the cis-diamminedichloroplatinum(II) analogue diamminecyclobutanedicarboxylatoplatinum. Cancer Res 45:6502-6, 1985.

Evans WE, McLeod HL. Pharmacogenomics--drug disposition, drug targets, and side effects. N Engl J Med 348:538-49, 2003.

haplo.stats software on-line at:
http://mayoresearch.mayo.edu/mayo/research/biostat/schaid.cfm

Horie N, Aiba H, Oguro K, Hojo H, Takeishi K. Functional analysis and DNA polymorphism of the tandemly repeated sequences in the 5'-terminal regulatory region of the human gene for thymidylate synthase. Cell Struct Funct 20:191-7, 1995.

Hustert E. Haberl M. Burk O. Wolbold R. He YQ. Klein K. Nuessler AC. Neuhaus P. Klattig J. Eiselt R. Koch I. Zibat A. Brockmoller J. Halpert JR. Zanger UM. Wojnowski L. The genetic determinants of the CYP3A5 polymorphism. Pharmacogenetics. 11(9):773-9, 2001 Dec.

Iyer L, King CD, Whitington PF, et al. Genetic predisposition to the metabolism of irinotecan (CPT-11). Role of uridine diphosphate glucuronosyltransferase isoform 1A1 in the glucuronidation of its active metabolite (SN-38) in human liver microsomes. J Clin Invest 101:847-54, 1998.

Kaller M, Lundeberg J, Ahmadian A. Arrayed identification of DNA signatures. Expert Rev Mol Diagn. 2007 Jan;7(1):65-76.

Kirchheiner J, Brockmoller J. Clinical consequences of cytochrome P450 2C9 polymorphisms. Clin Pharmacol Ther. 2005 Jan;77(1):1-16

Kuehl P. Zhang J. Lin Y. Lamba J. Assem M. Schuetz J. Watkins PB. Daly A. Wrighton SA. Hall SD. Maurel P. Relling M. Brimer C. Yasuda K. Venkataramanan R. Strom S. Thummel K. Boguski MS. Schuetz E. Sequence diversity in CYP3A promoters and characterization of the genetic basis of polymorphic CYP3A5 expression. Nature Genetics. 27(4):383-91, 2001 Apr.

Lamba JK, Lin YS, Schuetz EG, Thummel KE. Genetic contribution to variable human CYP3A-mediated metabolism. Adv Drug Deliv Rev 54:1271-94, 2002.

Lee SJ, Usmani KA, Chanas B, Ghanayem B, Xi T, Hodgson E, Mohrenweiser HW, Goldstein JA. Genetic findings and functional studies of human CYP3A5 single nucleotide polymorphisms in different ethnic groups. Pharmacogenetics. 2003 Aug;13(8):461-72.

Liu W, Innocenti F, Chen P, Das S, Cook EH Jr, Ratain MJ. Interethnic difference in the allelic distribution of human epidermal growth factor receptor intron 1 polymorphism. Clin Cancer Res 9:1009-12, 2003.

Ma MK. Woo MH. McLeod HL. Genetic basis of drug metabolism. American Journal of Health-System Pharmacy. 59(21):2061-9, 2002

McLeod HL, Krynetski EY, Relling MV, Evans WE. Genetic polymorphism of thiopurine methyltransferase and its clinical relevance for childhood acute lymphoblastic leukemia. Leukemia 14:567-72, 2000.

Metzger R, Leichman CG, Danenberg KD, Danenberg PV, Lenz HJ, Hayashi K, Groshen S, Salonga D, Cohen H, Laine L, Crookes P, Silberman H, Baranda J, Konda B, Leichman L. ERCC1 mRNA levels complement thymidylate synthase mRNA levels in predicting response and survival for gastric cancer patients receiving combination cisplatin and fluorouracil chemotherapy. J Clin Oncol. 16:309-16, 1998.

Miners JO, McKinnon RA, Mackenzie PI. Genetic polymorphisms of UDP-glucuronosyltransferases and their functional significance. Toxicology 181-182:453-6, 2002.

Ming Lin, Lee-Jen Wei, William R. Sellers, Marshall Lieberfarb, Wing Hung Wong, and Cheng Li (2004). dChipSNP: Significance Curve and Clustering of SNP-Array-Based Loss-of-Heterozygosity Data. Bioinformatics 20: 1233-1240.

Quaranta S, Chevalier D, Allorge D, Lo-Guidice JM, Migot-Nabias F, Kenani A, Imbenotte M, Broly F, Lacarelle B, Lhermitte M. Ethnic differences in the distribution of CYP3A5 gene polymorphisms. Xenobiotica. 2006 Dec;36(12):1191-200

Relling MV, Dervieux T. Pharmacogenetics and cancer therapy, Nat Rev Cancer 1: 99-108, 2001.

Rosenwald A, Wright G, Chan WC, et al. The use of molecular profiling to predict survival after chemotherapy for diffuse large-B-cell lymphoma. N Engl J Med 346: 1937–1947, 2002.

Salonga D, Danenberg KD, Johnson M, et al. Colorectal tumors responding to 5-fluorouracil have low gene expression levels of dihydropyrimidine dehydrogenase, thymidylate synthase, and thymidine phosphorylase. Clin Cancer Res 6:1322-7, 2000

Schaid D, Rowland C, Tines D, Jacobson R, Poland G (2002) Score tests for association between traits and haplotypes when linkage phase is ambiguous. Am J Hum Genet 70:425–434.

Shipp MA, Ross KN, Tamayo P, Weng AP, Kutok JL, Aguiar RCT, Gaasenbeek M, Angelo M, Reich M, Pinkus GS, Ray TS, Koval MA, Last KW, Norton A, Lister TA, Mesirov J, Neuberg DS, Lander ES, Aster JC, Golub TR. Diffuse large B-cell lymphoma outcome prediction by gene-expression profiling and supervised machine learning. Nat Med 8: 68–74, 2002.

Shirota Y, Stoehlmacher J, Brabender J, et al. ERCC1 and thymidylate synthase mRNA levels predict survival for colorectal cancer patients receiving combination oxaliplatin and fluorouracil chemotherapy. J Clin Oncol 19:4298-304, 2001.

Sparreboom A, Marsh S, Mathijssen RH, Verweij J, McLeod HL. Pharmacogenetics of tipifarnib (R115777) transport and metabolism in cancer patients. Invest New Drugs. 2004 Aug;22(3):285-9.

Strumberg D, Richly H, Hilger RA, et al. Phase I clinical and pharmacokinetic study of the Novel Raf kinase and vascular endothelial growth factor receptor inhibitor SORAFENIB in patients with advanced refractory solid tumors. J Clin Oncol. 2005 Feb 10;23(5):965-72.

van't-Veer LJ, Dai H, Vijver MJvd, He YD, Hart AAM, Mao M, Peterse HL, Kooy KVD, Marton JM, Witteveen AT, Schreiber GJ, Kerkhoven RM, Roberts C, Linsley PS,

Bernards R, Friend SH. Gene expression profiling predicts clinical outcome of breast cancer. Nature 415: 530–536, 2002.

Wan PT, Garnett MJ, Roe SM, Lee S, Niculescu-Duvaz D, Good VM, Jones CM, Marshall CJ, Springer CJ, Barford D, Marais R; Cancer Genome Project. Mechanism of activation of the RAF-ERK signaling pathway by oncogenic mutations of B-RAF.Cell. 2004 Mar 19;116(6):855-67.

Westfall and Young. Resampling-based multiple testing. Wiley, 1992.

Yeh KT, Chen JC, Chen CM, Wang YF, Lee TP, Chang JG.CYP3A5*1 is an inhibitory factor for lung cancer in Taiwanese. Kaohsiung J Med Sci. 2003 May;19(5):201-7.

A Phase III Randomized Trial of Chemoembolization with or without Sorafenib in Unresectable Hepatocellular Carcinoma (HCC) in Patients with and without Vascular Invasion

Appendix V

E1208 Shipment Notification Form

Rev. 12/14

ONLY IN THE EVENT ECOG-ACRIN STS IS NOT AVAILABLE

ECOG-ACRIN Generic Specimen Submission Form (#2981) and Shipment Notification Form (Appendix V) (faxed to the receiving laboratory) will be required only if STS is unavailable at time of sample submission. Indicate the appropriate Lab on the submission form:

- ECOG-ACRIN CBPF

Retroactively enter all specimen collection and shipping information when STS is available.

A Phase III Randomized Trial of Chemoembolization with or without Sorafenib in Unresectable Hepatocellular Carcinoma (HCC) in Patients with and without Vascular Invasion

Appendix VI

E1208 Collection and Shipping Kit Order Form

Starter kits are not available. It is preferred that the patient has registered to the trial. At a minimum, there must be a signed consent to participate in the optional studies or banking.
FAX Completed form to Zemotak-International at (800) 815-4675

Date: _____

To obtain the proper kit, provide the following information:

E1208 patient case number: _____

Kit Requested (Indicate samples to be submitted):

☐ Pharmacogenomic (PAXgene DNA)

☐ Pharmacokinetic (Plasma, heparin)

NOTE: Kits include collection and shipping supplies. However, batch quarterly shipment of plasma on dry ice from multiple patients preferred. PAXgene DNA sample may be stored and shipped with the plasma samples.

Kit is to be shipped to:

Institution Contact: _____

Phone number for contact: _____

Institution Address:

_____

_____

_____

NOTE: Questions are to be directed to the ECOG-ACRIN CBPF, Attn: Adekunle Raji
1-844-744-2420
(713-745-4440 Local)
Email: eacbpf@mdanderson.org

Rev. 12/14

Comments: _____

_____

_____

A Phase III Randomized Trial of Chemoembolization with or without Sorafenib in Unresectable Hepatocellular Carcinoma (HCC) in Patients with and without Vascular Invasion

Appendix VII

Cooperative Research and Development Agreement (CRADA)

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as Collaborator(s) and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the Intellectual Property Option to Collaborator (http://ctep.cancer.gov/industry/collaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing investigational Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.
2. For a clinical protocol where there is an investigational Agent used in combination with (an)other investigational Agent(s), each the subject of different collaborative agreements , the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data):
    a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NIH, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.
    b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own investigational Agent.
    c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own investigational Agent.
3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available exclusively to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order.-Additionally, all Clinical Data and Results and Raw Data will be collected , used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.
5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.
6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

    Regulatory Affairs Branch, CTEP, DCTD, NCI
    Executive Plaza North, Suite 7111
    Bethesda, Maryland 20892
    FAX 301-402-1584
    Email: anshers@mail.nih.gov

The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborators confidential/proprietary information.

A Phase III Randomized Trial of Chemoembolization with or without Sorafenib in Unresectable Hepatocellular Carcinoma (HCC) in Patients with and without Vascular Invasion

Appendix VIII

Inducers of CYP3A4 Activity

- Phenobarbital
- Carbamazepine
- St. Johns Wort
- Efavirenz
- Nevirapine
- Etravirine
- Phenytoin
- Rifampicin
- Modafinil
- Dexamethasone
- Felbamate
- Griseofulvin
- Pioglitazone
- Primidone
- Topiramate
- Troglitazone
- Rifabutin

A Phase III Randomized Trial of Chemoembolization with or without Sorafenib in Unresectable Hepatocellular Carcinoma (HCC) in Patients with and without Vascular Invasion

Appendix IX

Child Pugh Classification

Chemical and Biochemical Parameters	Score (Points) for Increasing Abnormality		
	1	2	3
Encephalopathy	None	1 - 2	3 - 4
Ascites	None	Slight	Moderate
Albumin (g/dL)	> 3.5	2.8 - 3.5	< 2.8
Prothrombin Time Prolonged (sec)*	< 4	4 - 6	> 6
Bilirubin (mg/dL)	< 2	2 - 3	> 3

Rev. 6/14

Rev. 6/14

*Alternatively, INR may be used - if value is < 1.7, assign 1 point; if value is 1.7-2.2, assign 2 points; if value is > 2.2, assign 3 points.

Class A = 5 – 6 points
Class B = 7 – 9 points
Class C = 10 – 15 points

Stages of Hepatic Encephalopathy	
Stage 1	Euphoria or depression, mild confusion, slurred speed, disordered sleep
Stage 2	Lethargy, moderate confusion
Stage 3	Marked confusion, incoherent speech, sleeping but arousable
Stage 4	Coma, Initially responsive to noxious stimuli, but later unresponsive

Reference: Trey C, Burns DG, Saunders SJ. Treatment of hepatic coma exchange blood transfusion. N Engl J Med 1966; 274 (9): 473 – 481

A Phase III Randomized Trial of Chemoembolization with or without Sorafenib in Unresectable Hepatocellular Carcinoma (HCC) in Patients with and without Vascular Invasion

Appendix X

Tumor Imaging and Submission to ACRIN Guidelines

1. Image Acquisition

All study participants will undergo:

- Baseline (chest CT, Abdomen/pelvis CT or MRI) performed within 4 weeks prior to registration.
- 4 months after first chemoembolization (chest CT, Abdomen/pelvis CT or MRI)
- 8 months after first chemoembolization (chest CT, Abdomen/pelvis CT or MRI)
- Every 2 months beginning at 10 months post baseline

It is recognized that there is regional variability for the follow up care of chemoembolization that may result in additional tumor imaging outside of the required imaging scans. Please follow the recommended guidelines for scan interpretation to assist in determining disease progression. For questions regarding scan interpretation in relation to disease progression, investigators are urged to contact the study chair.

1.1 CT Imaging

General CT imaging parameters are outlined below. Additional scanning guidelines, per anatomic location, are detailed in the subsequent sections.

- Helical CT scanning is required; axial scanning cannot be used.
- Multi-detector scanning is preferred whenever possible, but single detector helical scanning can be used.
    - Single detector scanners: Pitch should be 1-1.5; images should be reconstructed at ≤ 5mm intervals in the axial plane.
    - Multi-detector scanners: Pitch should be based on institutional routines. Reconstruction should be performed at ≤ 5mm intervals.
- Each anatomic area (chest, abdomen, pelvis), scanner settings (kV, mAs) should be per institutional routine procedures.
- Choice of contrast agent should be according to local institutional routine. Non-contrast chest CT for purpose of lung lesion assessment is acceptable if per institutional standard. However, contrast enhanced imaging for abdomen and pelvis assessment in mandatory.
- Contrast dose should be 100-150 mL.
- Injection rates should be 2 mL/sec minimum for chest imaging (if contrast imaging is performed in the chest). Injection rate for triple phase CT of the abdomen must be 3-5 mL/sec.
- 18G IV is preferred for bolus rates of injection, especially for abdominal imaging.

- Central lines should not be used unless absolutely required due to lack of acceptable peripheral IV access. Central lines should not be used with power injector unless specifically approved for that indication.

1.1.1 Abdominal CT

Abdominal imaging should be tailored for multi-phase liver imaging techniques. Pre-contrast, arterial-phase, and portal phase contrast imaging provides optimal evaluation of liver disease for depiction of HCC; In cases when there is a contraindication to IV contrast, MRI is the preferred imaging modality for liver disease.

Recommended scanning protocol: Helical non-contrast imaging through the liver prior to contrast-enhanced imaging, followed by dual-phase (arterial and portal) contrast enhanced imaging is recommended. Arterial phase scan delay time 20-30 seconds (or via bolus timing techniques per institutional routine). Portal venous scan delay time approximately 60-75 seconds. Each vascular phase scan of the liver must be obtained in a single helical acquisition. See contrast injection protocol above

1.1.2 Pelvic CT

Pelvic imaging is should be performed in combination with abdominal imaging in all cases. The abdominal (liver) protocol should be used with the pelvic imaging to follow, preferably during the late portal phase (approximately 80-90 seconds after injection) as to preserve the multi-phase abdominal (liver) imaging protocol.

1.1.3 Chest CT

Chest imaging is required. Scanning with IV contrast is preferred, but not required. If IV contrast is used, pre-contrast imaging is not required. Chest CT scanning should be performed per institutional standards, as long as slice resolution requirements are met (< 5mm). For contrast-enhanced imaging, a scan delay of approximately 20-30 seconds is recommended. If chest imaging is combined with abdominal (and pelvic) imaging, chest imaging should either be performed prior to abdominal imaging (non-contrast chest) or after abdominal (and pelvic) imaging

1.2 MRI Imaging

General MRI imaging parameters are outlined below. Additional scanning guidelines, per anatomic location, are detailed in the subsequent sections.

- Field strength of 1 tesla or greater.
- Imaging must be performed with a specialized torso array coil or other local coil combinations appropriate for body imaging. Body coil for signal reception is not acceptable.
- Image slice thickness should be ≤10 mm.

  For contrast enhanced scanning, standard gadolinium chelates should be used at a dose of 0.1 mmol/kg to a maximum of 20mL.
- Injection rate should be 2cc/sec, and all injections must be followed by a saline flush of at least 20cc. Peripheral 22-20G IV preferred.

1.2.1 Abdominal MRI

Contrast enhanced imaging with a standard gadolinium chelate is required for MRI. Scanning protocol should be per institutional standards, but should include at a minimum pre contrast T2 and a multiphase dynamic pre- and post-contrast T1 weighted images in the axial plane. The inclusion of other imaging techniques/planes of imaging is per institutional/imaging center's standard.

For axial T2W and pre-post-gadolinium T1W series, image FOV should be per body habitus. Imaging matrix should be no less than 256 (frequency) x 128 (phase). For axial imaging, phase encoding should be anterior-posterior. Axial T2 weighted images can be performed per institutional standards, including fast/turbo spine echo (FSE/TSE), "fast-recovery" or "driven equilibrium" FSE techniques (e.g. FR-FSE), or "single shot" techniques ("SS-FSE" or "HASTE"). Fat saturation for T2W imaging is optional. Short tau inversion recovery (STIR) imaging cannot be substituted for FSE-based T2W imaging.

The multi-phase contrast enhanced T1W images can be performed as per local standards as long as the imaging plane, matrix, and slice thickness requirements are met. Multi-phase imaging will generally require the use of spoiled gradient echo techniques. Three-dimensional volumetric imaging is preferred, but multi-planar two-dimension imaging is acceptable. Fat saturation for T1W imaging is encouraged, but not required. All T1W images should be acquired using breath-held technique. Use of contrast agent and its dose should be according to institutional standards. For standard gadolinium chelates, a dose of 0.1 mmol/kg, injected at a rate of 2 cc/sec, is recommended. Saline flush (minimum 20cc) is required for MRI.

Pre-gadolinium T1W imaging is required for all MRI exams. Post gadolinium imaging should be performed using the exact imaging parameters as the pre-gadolinium study. The pre- and post-gadolinium images must be performed as a group. Post-gadolinium images must immediately follow the pre-gadolinium imaging to ensure standardization of imaging technique and gain settings. Pre-scan tuning should be performed once for the pre-gadolinium imaging and no further pre-scan tuning may be performed during the post-gadolinium imaging group.

Post-gadolinium imaging must include, at a minimum, a portal phase image (approximately 60-70 seconds after contrast injection). The additional arterial-phase imaging (approximately 20-30 seconds after contrast injection) and interstitial/delayed phase imaging (approximately 2-3 minutes after contrast injection) is strongly recommended.

1.2.2 Pelvic MRI

Pelvic imaging, if required, can be employed as part of total abdominal and pelvic imaging. Contrast-enhanced imaging is preferred. Pelvic MRI should include pre-gadolinium T1 and T2 weighted imaging in the axial plane. Specific sequences should be per institutional standards. Breath-held and free breathing imaging is acceptable. Contrast-enhanced

imaging is encouraged and should be obtained approximately 1-2 minutes after contrast injection.

1.2.3 Chest MRI

As chest MRI may not be sensitive for small lung lesions, chest MRI is not allowed for thoracic evaluation.

1.3 Patients for whom contrast enhanced imaging is not feasible.

All patients must have adequate renal function for trial entry. As such, contraindications to contrast enhanced imaging at trial outset should manifest only in the case of known severe allergy to contrast (e.g. iodine contrast allergy).

1.3.1 In patients with known contrast allergy, the following imaging modalities should be used:

- Patients with known iodine contrast allergy out outset of trial
  - Chest imaging: non-contrast chest CT
  - Abdomen-pelvis imaging: contrast enhanced MRI
- Patients with known gadolinium contrast allergy at outset of trial
  - Chest imaging: non-contrast or contrast-enhanced CT (per institutional routine)
  - Abdomen imaging: contrast enhanced CT
  - Patients with known iodine and gadolinium contrast allergies:
  - Chest imaging: non-contrast CT
  - Abdomen-pelvis imaging: non-contrast MRI

1.3.2 In patients in whom a contrast allergy is identified during participation in the study, the imaging modalities should revert to the guidelines above. If this results in a change in imaging modality in the abdomen-pelvis imaging, the study chair should be notified of the protocol deviation with documentation of the allergy discovery.

1.3.3 Patients who develop severe renal insufficiency (defined by a GFR <30 per Crockoff-Gault formula (GFR = (140-age) * (Wt in kg) * (0.85 if female) / (72 * Cr), during the course of the study may become unable to receive iodine- or gadolinium-contrast by IV. In such a case, the following modalities should be used for subsequent tumor imaging:

- Chest imaging: non-contrast CT
- Abdomen-pelvis imaging: non-contrast MRI

If this results in a change in imaging modality in the abdomen-pelvis imaging, the study chair should be notified of the protocol deviation with documentation of the allergy discovery.

1. CT/MRI Image Submission

All CT and MRI study exams must be submitted to ACRIN Image Management Center (IMC), after each timepoint/visit, for image archival and review related to secondary imaging aims to be identified in the protocol.

A completed, signed Image Transmittal Worksheet (ITW) **MUST** accompany all imaging exams submitted to ACRIN IMC for each time-point. For exams submitted via the internet, complete this worksheet and fax to (215) 923-1737. For exams submitted via

media, complete this worksheet and include with the media shipment. Please affix a label to the jacket of the media to include: Study Name, Case Number, Date of Exam, Site Name, Timepoint, and type of imaging.

*For further information or questions, email imagearchive@phila.acr.org <mailto:imagearchive@phila.acr.org>.

1.1. Electronic Transfer of CT/MRI Images

ACRIN can provide software (TRIAD, see **www.triad.acr.org**) for installation on a PC at your site that collects and submits image sets from your CT/ MRI computer or from your PACS. The images are "DICOM pushed" either from the CT/ MRI computer or from the PACS to the PC on which the software is installed. This software anonymizes, encrypts and non-destructively compresses the images as they are transferred by FTP to the ACRIN database in Philadelphia.

Image Submission software PC requirements:

1. Network capability to transmit data from a MR and PET scanner to a linked workstation or PC?
2. Do you have a PC available to transmit data (patient data, MR and PET image data) to ACRIN?
   a. Operating System Windows XP Pro
   b. Access to the Internet: Internet Explorer
   c. Minimum of 50 GB available hard drive
   d. At least 1 GB RAM
   e. Ability to view PDF documents
3. Software utilities required to run image transmission software:
   a. Windows Installer 3.1
   b. Microsoft .NET framework 2.0
   c. MDAC Type 2.8
   d. MS SQL 2005 Express

Please contact ACRIN to arrange the installation of the TRIAD software prior to first accrual.

Contact the TRIAD help desk (Triad-Support@phila.acr.org <mailto:Triad-Support@phila.acr.org>) or 215-940-8820.

1.2. CD/DVD Transfer

In the event that scrubbed image data cannot be electronically transferred, images may also be sent on media such as DVD or CD to the ACRIN IMC for transfer to the image archive; patient identifiers will be scrubbed appropriately at that time.compatibility **For Imaging Core lab image submission questions contact the lead technologist for this trial at: (imagearchive@phila.acr.org <mailto:imagearchive@phila.acr.org>)**

Images on CD or DVD should be addressed and sent to:

ACRIN Image Archive
American College of Radiology
1818 Market Street, Suite 1600
Philadelphia, PA 19103
Attn: ECOG-ACRIN 1208 Imaging Specialist

1.3. Missing and Delinquent Image Submission

ACRIN will provide the ECOG-ACRIN Statistical Center with a report indicating the image sets received and those still due for submission. Sites experiencing difficulty with image submission due to technical factors should contact **the lead technologist for this trial at: (imagearchive@phila.acr.org <mailto:imagearchive@phila.acr.org>)** for assistance in resolving these issues.

1.4. Image Quality Control

A review of the images submitted will be performed in order to ascertain the quality of image processing at the contributing institutions for adequate image quality. Sites will be notified of image quality issues and the Imaging staff will assist the local sites in correcting/resolving quality-related issues.

A Phase III Randomized Trial of Chemoembolization with or without Sorafenib in Unresectable Hepatocellular Carcinoma (HCC) in Patients with and without Vascular Invasion

Rev. 6/14

Appendix XI

E1208 Patient Medication Calendar

You will be given a bottle of tablets containing either sorafenib or placebo. For each cycle day, please record the day of the week (i.e., Monday, Tuesday, etc…), the date (i.e., July 1, July 2, etc…), and the number of sorafenib tablets you take in the morning and in the evening.

Be sure to bring the completed Patient Medication Calendar and your bottles with any remaining tablets with you to each clinic visit.

Patient Signature _____ **Date** _____

Patient ID: __ __ __ __ __			**Cycle #** _____	
Cycle Day	**Day of Week**	**Date**	**SORAFENIB**	**(200mg tablets)**
			Morning Tablets	Evening Tablets
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				
16				
17				
18				
19				
20				
21				
22				
23				
24				
25				
26				
27				
28				