



Eastern Cooperative Oncology Group

**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**

STUDY CHAIR: John Kauh, M.D.

INTERVENTIONAL RADIOLOGY CO-CHAIR: Michael Soulen, M.D.
INTERVENTIONAL RADIOLOGY CO-CHAIR: Jean-Francois H. Geschwind, 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: Yang Feng, M.P.H., M.S.
GI COMMITTEE CHAIR: Al B. Benson, III, MD
CALGB CO-CHAIR: Bert O'Neill, M.D.
SWOG CO-CHAIR: Melanie Thomas, M.D.

Version Date: June 22, 2009**Sorafenib/Placebo (NSC #724772, CTEP IND #69,896) Supplied by the NCI for This Study****STUDY PARTICIPANTS****ACTIVATION DATE**

**Lead Group – Investigators from this Group
should enroll patients through ECOG.**
ECOG

(date)

**Endorsing Group(s) – Investigators from these
Groups must enroll patients through the CTSU.**
CALGB
SWOG

**Ordering Group(s) – Investigators must have a
current affiliation with one of these Groups to
receive investigational agent and/or an
Investigator's Brochure for this protocol.**
ECOG
CTSU

STUDY CHAIR

John Kauh, M.D.
Emory University
1365-C Clifton Road, NE
Suite C2108
Atlanta, GA 30322
Office: 404-778-2407
FAX: 404-778-5676
JKauh@emory.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

INTERVENTIONAL RADIOLOGY CO-CHAIR

Jean-Francois Geschwind, M.D.
Johns Hopkins University
600 N. Wolfe Street
Blalock 545
Baltimore, MD 21287
Office: 410-614-6597
Fax: 410-955-0233
Email: jfg@jhmi.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

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

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

TRANSPLANT SURGERY CO-CHAIR

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

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

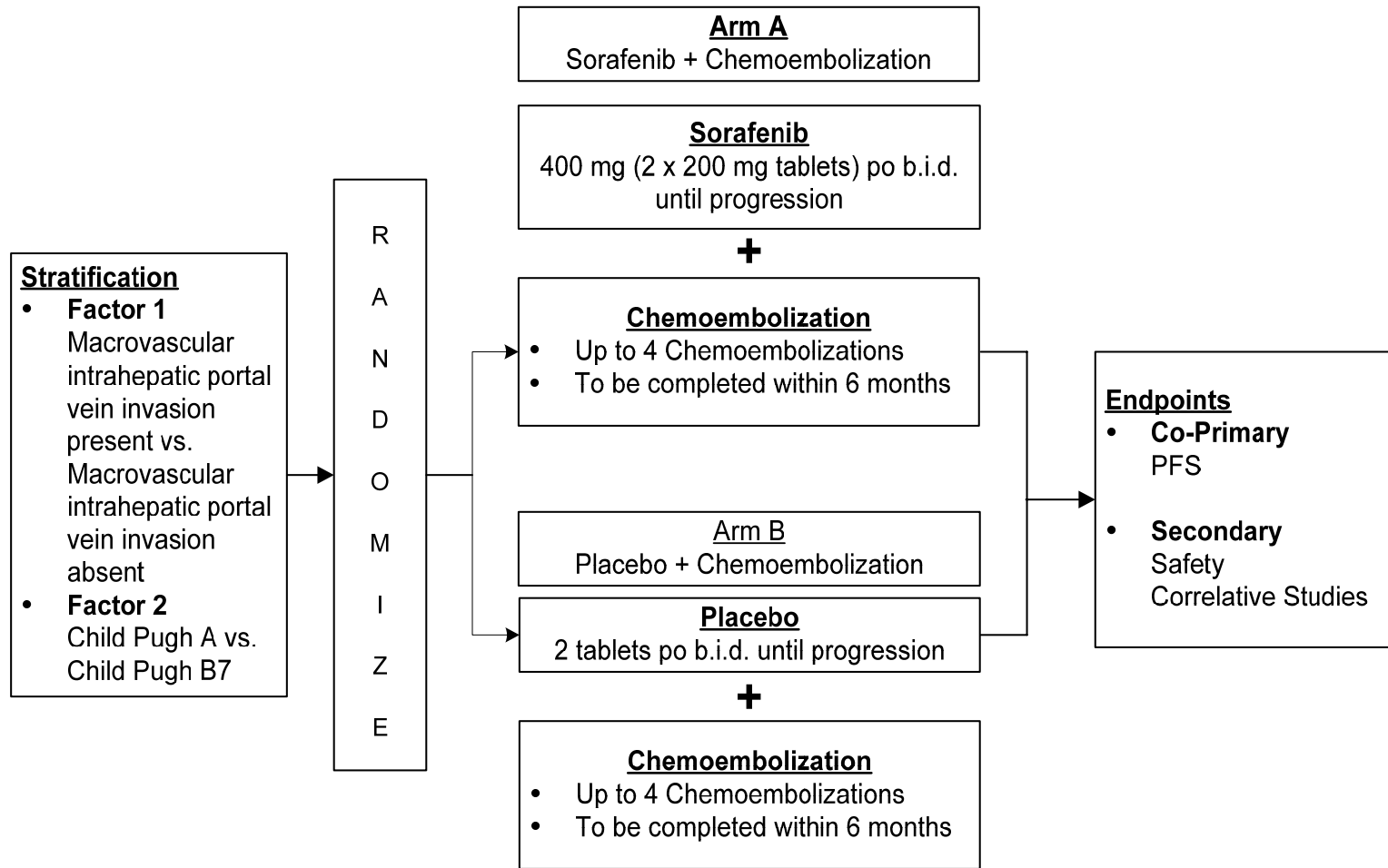
HEPATOLOGY CO-CHAIR

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

STUDY CHAIR LIAISON (SCL)

Ira Blount
Emory University
1365 Clifton Road
Suite C3012
Atlanta, GA 30322
Phone: 404-778-4449
Fax: 404-778-4389
Email: lblount@emory.edu

Schema



Accrual goal = 400 patients

1. Introduction

1.1 Rationale

There are pre-clinical and clinical data suggesting hepatic artery embolization leads to increase VEGF expression and neo-angiogenesis. 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 . Sorafenib is currently FDA approved for the treatment of hepatocellularcarcinoma based upon the results of the "Sorafenib HCC Assessment Randomized Protocol Trial" (SHARP).

Given the 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

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.

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.

3. Eligibility Criteria

- 3.1 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
 - 3.2 Patients must have HCC limited to the liver. There must be no clinical or radiographic evidence of extrahepatic HCC.
 - 3.3 Portal Lymphadenopathy IS permitted for patients with HBV or HCV – as lymphadenopathy is commonly associated with hepatitis unrelated to malignancy.
 - 3.4 Patients must have measurable disease
 - 3.5 Patients must not be candidates for curative resection, orthotopic liver transplantation, or radiofrequency ablation (RFA).
 - 3.6 Patients may have been treated with RFA in the past, but no sooner than 4 weeks before study registration.
 - 3.7 Patients may have undergone previously attempted curative liver resection.
 - 3.8 Patients may NOT have been previously treated with brachytherapy such as Yttrium-90 microsphere.
 - 3.9 Patients may **NOT** have been previously treated with sorafenib, chemoembolization, or systemic chemotherapy including cytotoxic agents or molecularly targeted agents.
 - 3.10 Branch portal vein invasion by tumor is permitted but patients with main portal vein invasion by tumor are not eligible.
 - 3.11 Patients must have Child-Pugh score of A or B7.
 - 3.12 Patients must have an ECOG performance status of 0 or 1.
-

4. Tumor Assessment:

4.1 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.
