Protocol Update #13
11/15/2017

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

PROTOCOL UPDATE TO CALGB 80802

PHASE III RANDOMIZED STUDY OF SORAFENIB PLUS DOXORUBICIN VERSUS SORAFENIB IN PATIENTS WITH ADVANCED HEPATOCELLULAR CARCINOMA (HCC)

Investigational Agent: Sorafenib (IND# 69896, NSC# 724772) will be supplied by CTEP DCTD.

[X]	**Update:**	[ ]	**Status Change:**
[ ]	Eligibility changes	[ ]	Activation
[X]	Therapy / Dose Modifications / Study Calendar changes	[ ]	Closure
[ ]	Informed Consent changes	[ ]	Suspension / temporary closure
[ ]	Scientific / Statistical Considerations changes	[ ]	Reactivation
[X]	Data Submission / Forms changes		
[X]	Editorial / Administrative changes		
[ ]	Other:		

Expedited review is allowed. IRB approval (or disapproval) is required within 90 days. Please follow your IRB of record guidelines.

UPDATES TO THE PROTOCOL:

Cover Page

- Dr. Qian Shi has replaced Dr. Donna Niedzwiecki as the Primary Statistician, and all contact information has been updated.
- Tyler Zemla has replaced Xing (Cynthia) Ye as the Secondary Statistician, and all contact information has been updated.
- The position of "PET Faculty Statistician" has been removed, along with all contact information for Dr. Kouros Owzar, as the statistical responsibilities previously associated with this position will now be handled by the Primary Statistician.

Cover Page (pg. 2)

- A title has been added above the 1st table for clarity that reads: "**Study Resources**."
- Data submission for this study will now be performed using Medidata Rave®. Therefore, under "**Study Resources,**" the website link for Medidata Rave® has been added in the left column.

Cancer Trials Support Unit (CTSU) Address and Contact Information

All text in the 3rd column under the "**For study data submission**" heading has been replaced with updated information as data submission for this study will now be performed using Medidata Rave®.

Section 5.0 (Registration/Randomization, Stratification, and Data and Sample Submission)

- Section 5.1 (CTEP Investigator Registration Procedures) and Section 5.2 (CTEP Associate Registration Procedures / CTEP-IAM Account) have been removed and replaced with a new Section 5.1 entitled "**CTEP Registration Procedures**" which includes updated CTSU boilerplate language. Subsequent sections have been renumbered accordingly.
- All text in Section 5.2 (CTSU Registration Procedures) (formerly Section 5.3) has been completely revised to include updated CTSU boilerplate language.
- All text in Section 5.4 (Patient Registration/Randomization Procedures) (formerly Section 5.5) has been completely revised to include updated CTSU boilerplate language.

Section 5.7 (Data Submission)

- Data submission for this study will now be performed using Medidata Rave®, therefore the 1st and 2nd paragraphs have been entirely removed and replaced with four new paragraphs that outline the new data submission procedures.
- In the 3rd column of the rows below the "Sample Submission" heading in the table, the phrase "via Rave" has been added to the 1st sentence to reflect the new data submission process.
- In the 3rd column of the row below the "Follow-up (Post-treatment)" heading in the table, the phrase "submit via Rave" has been added to the 1st sentence and the phrase "via Rave" has been added to the 2nd sentence to reflect the new data submission process.
- In footnote *, the phrase "the comments field at the end of the Medidata Rave® Form" has replaced "CALGB Remarks Addenda," and the word "typing" has replaced "writing" to reflect the new data submission process.
- In footnote #, the phrase "via Medidata Rave® and to the Imaging Core Lab via fax per Section 5.8" has replaced "and the Imaging Core Lab" for clarity and to reflect the new data submission process.
- In footnote ***, the phrase "via Medidata Rave®" has been added to reflect the new data submission process.

Section 10.3 (Sorafenib [Nexavar®] [IND 69896/NSC 724772])

In the 1st paragraph under the "*STORAGE*" heading, new 2nd and 3rd sentences have been added to provide guidance on handling temperature excursions.

Section 11.1 (Supportive Care)

In the 2nd sentence of the 1st paragraph, the phrase "via Medidata Rave®" has been added to reflect the new data submission process.

Section 11.5.1 (Filgrastim [G-CSF], Sargramostim [GM-CSF], and Pegfilgrastim)

In the 2nd sentence of the 1st paragraph, the phrase "via Medidata Rave®" has been added to reflect the new data submission process.

Section 12.4 (Evaluation of Best Overall Response)

In the 1st sentence of the "Note" below the table, the phrase "via Medidata Rave®" has been added to reflect the new data submission process.

Section 13.1.2 (Disease Progression)
In the 3rd sentence of the 1st paragraph, the phrase "via Medidata Rave®" has been added to reflect the new data submission process.

Section 13.2 (Extraordinary Medical Circumstances)
In the 2nd bullet below the 1st paragraph, the phrase "via Medidata Rave®" has been added to reflect the new data submission process.

Section 15.0 (Adverse Event Reporting [AER])
In the 2nd sentence of the 4th bullet under the "**Additional Instructions or Exclusion to CTEP-AERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing an Agent Under a CTEP IND or non-CTEP IND**" heading, the phrase "via Medidata Rave®" has been added to reflect the new data submission process.

UPDATES TO THE MODEL CONSENT:

No changes have been made to the model consent document.

A replacement protocol and model consent document have been issued.
This study remains closed to new patient accrual.

ATTACH TO THE FRONT OF EVERY COPY OF THIS PROTOCOL

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

CALGB 80802

PHASE III RANDOMIZED STUDY OF SORAFENIB PLUS DOXORUBICIN VERSUS SORAFENIB IN PATIENTS WITH ADVANCED HEPATOCELLULAR CARCINOMA (HCC)

Investigational Agent: Sorafenib (IND# 69896, NSC# 724772) will be supplied by CTEP DCTD.

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Study Resources

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Alliance Biorepository at Ohio State University
The Ohio State University
Innovation Centre
2001 Polaris Parkway
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Fax: 614-293-7967
path.calgb@osumc.edu

IROC Ohio (Alliance Imaging Core Lab)
The Ohio State University
Wright Center of Innovation
395 W. 12th Ave., RM #414
Columbus, OH 43240
Tel: 614-293-9151
Fax: 614-293-9275

Medidata RAVE® iMedidata Portal
https://login.imedidata.com

Alliance Statistics and Data Center
Mayo Clinic
200 First Street SW, Harwick, 8th Floor
Rochester, MN 55905
Tel: 507-284-5380
Fax: 507-284-1902

Alliance Patient Registration
Tel: 507-284-4130
Fax: 507-284-0885

Adverse Event Reporting
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm

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The pharmacogenomic component of this study is conducted as part of the NIH Pharmacogenomics Research Network, which is funded through a separate U01 mechanism (see http://www.nigms.nih.gov/pharmacogenomics/research_net.html) for details

Document History	**Effective Date:**		
Activation	02/15/2010	Update 7	04/15/2013
Update 1	06/15/2010	Update 8	03/10/2014
Update 2	09/15/2010	Update 9	08/01/2014
Update 3	04/15/2011	Update 10	09/15/2014
Update 4	10/15/2011	Update 11	03/07/2016
Update 5	06/15/2012	Update 12	06/15/2017
Update 6	07/15/2012	Update 13	11/15/2017

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

CONTACT INFORMATION		
For regulatory requirements:	**For patient enrollments:**	**For study data submission:**
Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal. Regulatory Submission Portal: (Sign in at www.ctsu.org, and select the Regulatory Submission sub-tab under the Regulatory tab.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-2878 for regulatory assistance.	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.	Data collection for this study will be done exclusively through Medidata Rave. Please see the data submission section of the protocol for further instruction.
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. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU RSS.		
For clinical questions (i.e. patient eligibility or treatment-related) Contact the Study Chair, Protocol Coordinator, and (where applicable) Data Manager. Contact information can be found on cover page of protocol		
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.		
The CTSU Website is located at https://www.ctsu.org		

PHASE III RANDOMIZED STUDY OF SORAFENIB PLUS DOXORUBICIN VERSUS SORAFENIB IN PATIENTS WITH ADVANCED HEPATOCELLULAR CARCINOMA (HCC)

Eligibility Criteria

Pathologically or cytologically proven hepatocellular carcinoma.
No known mixed histology or fibrolamellar variant (Sec 4.1.1).
Locally advanced or metastatic disease (Sec 4.1.2).
Patients must have measurable disease (Sec 4.2).
No prior adjuvant therapy with sorafenib or other Raf/VEGFR inhibitors. Other prior adjuvant tx is allowed if completed >6 months prior to registration with documented recurrence of HCC.
Prior locoregional therapies allowed provided that patient either has a target lesion that has not been subjected to local therapy and/or the target lesion(s) within field of local therapy has shown ≥ 20% increase in size since last treatment. Such therapy must be completed ≥4 weeks prior to registration (Sec 4.3.2).

Initial Required Laboratory Values	
Granulocytes	≥1,500/µL
Hemoglobin	≥8.5 g/dL (see Sec 4.7)
Platelets	≥75,000/µL
Creatinine	≤1.5 x ULN (or CrCL ≥60 cc/min)
Child-Pugh Score	A (see App I)
Bilirubin	≤3 mg/dL
ALT/AST	≤5 x ULN
PT-INR	≤1.7* (see Sec 4.7)

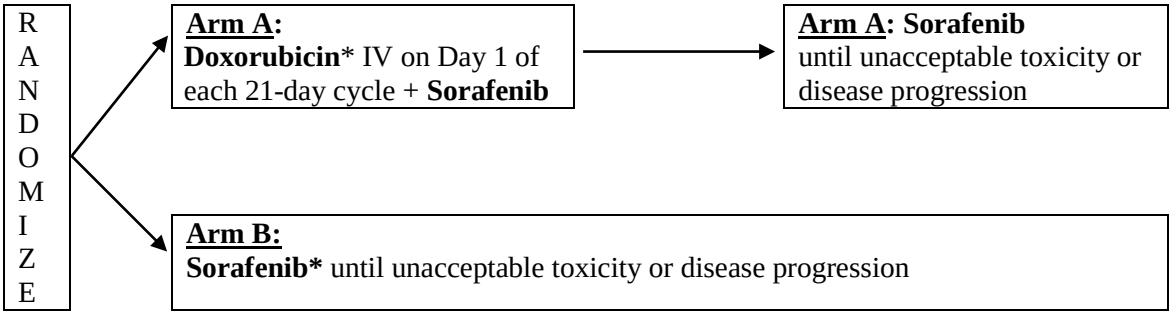
*Not required for patients on anticoagulation agents

No prior systemic tx for metastatic disease.
No prior exposure to systemic intravenously given doxorubicin.
Antiviral tx is allowed, but interferon therapy must be stopped ≥4 weeks prior to registration (Sec 4.3.6).
Allografts are not allowed, including but not limited to liver and bone marrow transplants.
No known CNS tumors including brain metastases.
No significant GI bleeding events requiring intervention, transfusion, or admission to hospital within 30 days prior to registration.
≥ 4 weeks since major surgery.
No rifampin or St. John's Wort (Sec 4.3.9).
Hypertension must be well controlled (<140/90 mm Hg) (Sec 4.4.3).
No known history of congestive heart failure > NYHA II
No myocardial infarction within 6 months prior to registration.
No known history of serious myocardial dysfunction, defined as scintigraphically (MUGA, myocardial scintigram) determined absolute LVEF below 45% or an LVEF on ECHO below the normal limit of normal at the individual institution (Sec 4.4.4).
No known history of bleeding diathesis.
Patients receiving combination anti-retroviral therapy for HIV are excluded (Sec 4.4.6).
Age ≥18 years.
ECOG Performance Status: 0 or 1.
Non-pregnant and non-nursing (Sec 4.6).

Schema

1 Cycle = 21 Days

At randomization, patients will be stratified by extent of disease (locally advanced; metastatic).



*Dose of doxorubicin and sorafenib is based on bilirubin. See Section 7.0 for doses.

TABLE OF CONTENTS

1.0 INTRODUCTION

1.1 Hepatocellular Carcinoma (HCC)

Hepatocellular carcinoma is the fifth most common cancer worldwide and the third leading cause of cancer death (1). While the current incidence of HCC in the United States is relatively low (2), it has risen in the U.S. over the past two decades (3).

Chronic HBV infection is the predominant risk factor in Asia and sub-Saharan Africa, whereas chronic HCV infection is the leading risk factor for HCC in Western countries and Japan (4, 5). Recently, a minimum of a 2-fold increase in the age-adjusted rates for HCC, up to 7 per 100,000 patients observed in the United States (3), is explained by the increasing incidence of hepatitis C infection during the previous two decades.

Other causes of HCC include alcohol-induced cirrhosis, which contributes to about one-third of the cases of HCC in the United States (6). Another newly recognized contributing factor to the continued rise in the incidence of HCC is the increased prevalence of non-alcoholic-steatohepatitis (NASH) among diabetic and morbidly obese patients (body mass index [BMI] $\geq$ 35) (7, 8).

The current distribution of patients seen for HCC by most medical oncologists mirrors the distribution of HCC attributable to hepatitis C, hepatitis B, alcoholic liver disease, and NASH, in addition to the less commonly reported metabolic diseases with hemochromatosis (9), possibly the most recognized.

Currently, the only curative therapies for HCC are surgery and liver transplantation (10); thus, an urgent need exists for effective therapies that will improve survival in advanced HCC.

1.2 Sorafenib

Sorafenib, an oral multi-kinase inhibitor, blocks tumor cell proliferation by targeting Raf/MEK/ERK signaling at the level of Raf kinase, and exerts an anti-angiogenic effect by targeting the vascular endothelial growth factor receptor (VEGFR) -1/-2/-3 and the platelet derived growth factor receptor-beta (PDGFR-beta) tyrosine kinases (11). Sorafenib has been studied in a double blind placebo-controlled randomized phase III study, SHARP (Sorafenib HCC Assessment Randomized Protocol), evaluating overall survival in patients with advanced hepatocellular carcinoma and Child-Pugh A cirrhosis (12). A planned interim analysis after 603 patients were randomized and 321 deaths had occurred revealed a 2.8-month statistically significant ($p \leq 0.001$) improvement in overall survival for patients treated with sorafenib (10.7 months) versus placebo (7.9 months). Based on these data, sorafenib has been approved by the FDA for treatment of patients with advanced HCC.

1.3 Sorafenib plus Doxorubicin Preclinical Data

Preclinical data suggest that combining sorafenib with a variety of chemotherapeutic agents results in additive anti-tumor activity (13). Doxorubicin in combination with sorafenib results in tumor growth delay when 5×10^6 cells are injected into the flank of NCr Nu/Nu female mice. The combination of doxorubicin plus sorafenib at the maximum tolerated dose level, caused a tumor growth delay (expressed in days relative to control tumors) of 12.4 days compared to single agent sorafenib (6.6 days) and single agent doxorubicin (6.1 days). In addition, the percent weight change of tumors at day 13 was 11.9% for the combination versus 4.6% for sorafenib and 3.8% for doxorubicin.

1.4 Phase I Study of Sorafenib plus Doxorubicin

A phase I study evaluated sorafenib in combination with doxorubicin 60 mg/m^2 every 3 weeks for a maximum of six cycles (14). Doses of sorafenib were escalated through four cohorts up to

400 mg po bid: cohort 1, 100 mg (50 mg tablets) bid; cohort 2, 200 mg (50 mg tablets) bid; and cohort 3, 400 mg bid. To improve patients' compliance, a 200 mg tablet was introduced, and in order to compare the pharmacokinetics of both tablets, the 400 mg bid dose level was analyzed separately using 50 mg tablets (cohort 3A) and 200 mg tablets (cohort 3B). Of 54 patients, all four patients with HCC on the study achieved prolonged stability of disease and stayed on therapy for more than one year. The maximum tolerated dose of the combination treatment of sorafenib with doxorubicin was not reached at the highest dose level administered in this study, i.e. a continuous regimen of 400 mg sorafenib bid together with 60 mg/m^2 doxorubicin on Day 1 of the 3-week cycles. The safety profile of the combination treatment was dominated by the well-known myelotoxicity of doxorubicin and the dermatological toxicities of sorafenib. The myelotoxicity related to doxorubicin was virtually the same in non-HCC patients and HCC patients. Cardiotoxic effects in association with doxorubicin treatment were assessed by MUGA scans in 14 evaluable patients. Ten patients had a left ventricular ejection fraction (LVEF) relative decrease ranging between 5-35%. Of those patients, five were from cohort 3A (200 mg in 50 mg tablets bid). Only one patient from cohort 3A had a relative decrease in LVEF of 27.6%, resulting in cardiac dysfunction, which resolved after discontinuation of doxorubicin but continuation of sorafenib. In cohort 3B, there were no detectable LVEF changes.

Pharmacokinetic parameters were assessed in 23 patients. Comparison of C_{max} and $AUC_{(0–8)}$ values from Day 21 of Cycle 1 (sorafenib in the absence of doxorubicin), and Day 1 of Cycle 2 (sorafenib plus doxorubicin) showed that doxorubicin administration contributes to increased either C_{max} or $AUC_{(0–8)}$ compared with sorafenib alone, but had no relevant effect on steady-state sorafenib pharmacokinetics. When 400 mg bid sorafenib was co-administered in cohort 3A (200 mg in 50 mg tablets bid), mean C_{max} of doxorubicin was increased by 103%, and mean AUC by 47%. In contrast to this finding, a slight reduction in mean C_{max} and no effect on mean AUC was observed following co-administration of 400 mg bid sorafenib in cohort 3B. The last dose level is the one used in the phase II study described below and in the current study.

1.5 Randomized Phase II Study of Doxorubicin plus Sorafenib versus Placebo

Based on the preclinical and phase I study data, sorafenib was next evaluated in combination with doxorubicin as part of a multi-center randomized, double-blinded phase II study of doxorubicin plus or minus sorafenib or placebo in chemotherapy-naïve HCC patients (15). It is important to note that the design of this study was developed before the start of the SHARP trial. The study included patients with measurable, histologically proven, inoperable HCC and no prior systemic treatments for HCC. Patients were required to have an ECOG performance status of 0-2; Child–Pugh (CP) score A; life expectancy ≥12 weeks; and adequate hematologic, hepatic, renal, and cardiac function. While prior local therapies were allowed as long as the patient showed progression of disease at time of enrollment, patients with prior chemoembolization were excluded.

Patients received doxorubicin 60 mg/m^2 intravenously every 21 days, for a maximum of 360 mg/m^2, plus either sorafenib 400 mg orally twice daily or placebo. In certain instances when continued benefit and lack of toxicity were observed, patients were allowed to continue doxorubicin up to a cumulative dose of 450 mg/m^2, pending the approval of the study chair. After doxorubicin was discontinued, treatment with sorafenib or placebo was continued as a single agent. Treatment continued until disease progression or unacceptable treatment-related toxicities. Patients underwent a MUGA test or echocardiography to assess for left ventricular ejection fraction (LVEF) at baseline, at two weeks, every six weeks thereafter, and at completion of therapy.

The primary population for efficacy analysis was the intent-to-treat (ITT) population. The doxorubicin plus placebo arm was compared to historical control using a 1-sample test with significance level 0.1. The primary endpoint was TTP, defined as the time from randomization

to the first documented radiologic disease progression. Secondary efficacy variables included overall survival (OS) and progression-free survival (PFS), both measured from the date of randomization. Overall response rate was assessed according to the RECIST criteria by independent radiologic review.

A data monitoring committee (DMC) was instituted for the study. On the basis of the reported interim results of a large phase III trial of sorafenib versus placebo which showed a significant increase in median overall survival in favor of sorafenib (10.7 months versus 7.9 months) (12), the DMC performed an unplanned interim analysis in February 2007. The DMC stated that the results of the interim analysis of the phase II study, although immature, indicated that the patients randomized to receive doxorubicin/placebo may be at a considerable disadvantage, and thus advised the sponsor to discontinue this phase II trial. The study was therefore discontinued, and treatment assignments were unblinded.

Ninety-six patients were enrolled, of whom 47 patients were randomized to the doxorubicin plus sorafenib arm, and 49 to the doxorubicin plus placebo arm. There were no statistical differences in any of the demographics between the two cohorts. Mean age was 65 years and 85% of patients had ECOG PS 0-1. Patients' risk factors for HCC were similar to the SHARP trial (2): the majority of patients had extrahepatic disease (51.1% for doxorubicin plus sorafenib and 79.6 % for doxorubicin plus placebo) or macroscopic vascular invasion (27.8 versus 32.4%).

The median total dose of doxorubicin administered was 165 mg/m^2 given over a median of 4 cycles (range 1 to 7 cycles) in the doxorubicin plus sorafenib arm; and 120 mg/m^2 given over a median of 2 cycles (range 1 to 9 cycles) in the doxorubicin plus placebo arm. The median duration of treatment with study medication (sorafenib or placebo) was 5.7 cycles (range 0-21 cycles) in the doxorubicin plus sorafenib arm, and 2.7 cycles (range 1-18.4 cycles) in the doxorubicin plus placebo arm.

The median TTP, which was the primary endpoint, was 6.4 months (95% CI, 4.8-9.2) for the doxorubicin plus sorafenib arm and 2.8 months (95% CI, 1.6-5) for the doxorubicin plus placebo arm. An exploratory comparison of overall survival between the two arms showed a significant difference of 13.7 months (95% CI, 8.9-not reached) in favor of doxorubicin plus sorafenib versus 6.5 months (95% CI, 4.5-9.9) for doxorubicin plus placebo ($p = 0.006$, HR = 0.49). Median PFS based on independent radiological review was 6 months (95% CI, 4.6-8.6) for patients who received doxorubicin plus sorafenib, and 2.7 months (95% CI, 1.4-2.8) for patients who received doxorubicin plus placebo. Based on independent radiological assessment, there was one complete response (2%) in the doxorubicin plus placebo arm and two partial responses (4%) in the doxorubicin plus sorafenib arm. An analysis was performed on patients with evaluable scans to determine the magnitude of reduction in the size of target lesions. Waterfall plots showed that a substantially greater proportion of patients treated with doxorubicin plus sorafenib (62% of those with a post baseline scan) had some degree of tumor shrinkage compared with patients treated with doxorubicin plus placebo (29%).

The toxicity profile was similar between the two arms of the study, and patients exhibited toxicities commonly seen with single agent doxorubicin and sorafenib. Grade 3 and 4 toxicities, including fatigue, were reported in 6% of patients on each arm and hand-foot skin reactions were reported in the doxorubicin plus sorafenib arm only (6.4 %). Diarrhea (10.6% and 6.3%), and neutropenia (38% and 31.1%) were reported in the doxorubicin plus sorafenib and the doxorubicin plus placebo arms, respectively.

Left ventricular systolic dysfunction (LVSD) developed on therapy at a higher rate with doxorubicin/sorafenib compared with doxorubicin/placebo (19% versus 2%) and all but one patient had CTC grade 1 or 2. Hypertension and bleeding, which are adverse events frequently attributed to anti-VEGF therapy and are thought to represent class effects, were also noted. All grade treatment-emergent hypertension was reported in eight subjects (17%) receiving

doxorubicin/sorafenib and in none receiving doxorubicin/placebo. These events were limited to grade 1 (2 events) and grade 2 (6 events). Only one subject received antihypertensive medication at any time during the study, and no dose limiting hypertension was seen. Grade 3 and 4 treatment related bleeding events occurred in two patients in the doxorubicin plus sorafenib arm, both of which were related to gastrointestinal bleeds. Death within 30 days of starting study medication occurred in five patients (11%) randomized to the doxorubicin plus sorafenib arm and ten patients (21%) in the doxorubicin plus placebo arm. Of these fifteen patients, the cause of death was reported as progression of HCC in two patients on the doxorubicin plus sorafenib and in seven patients on the doxorubicin plus placebo arm. For the three other patients who received doxorubicin plus sorafenib, serious adverse events leading to death were liver dysfunction in one subject, and cardiac ischemia/infarction in two patients. As for the three other patients who received doxorubicin plus placebo, two patients had serious adverse events leading to death: febrile neutropenia and thrombosis/thrombus/embolism. For the third patient, there were no treatment-emergent adverse events leading to death.

1.6 Explanation and Rationale for a possible Synergistic Effect between Sorafenib and Doxorubicin

The results of the SHARP trial support the growing body of evidence of the activity of sorafenib in HCC. However, its design does not allow us to evaluate the potential favorable interaction that may exist between sorafenib and doxorubicin. An additive or synergistic interaction between sorafenib and anthracyclines (e.g. doxorubicin) has been reported in the literature. Inhibition of the Ras/Raf/MEK/ERK pathway may help prevent activation of the mdr resistance pathway which may underlie doxorubicin resistance in many tumors (16). In addition, A Raf-1–dependent but MEK1/2- and ERK1/2-independent bFGF-mediated protection of endothelial cells against stress-mediated apoptosis has been reported (17). Raf inhibition by sorafenib and possible subsequent inhibition of FGF receptor signaling may enhance the cellular susceptibility to doxorubicin (18, 19). Lastly, anthracyclines are thought to be modulators of angiogenesis (20). Thus, this phase III trial will allow patients with advanced HCC to receive sorafenib, the new standard of care for advanced HCC, while evaluating any additive or synergistic effects of doxorubicin by randomizing patients to doxorubicin versus no added therapy. This is also important considering the lack of any survival advantage for single agent doxorubicin in HCC (21, 22).

1.7 The Importance of the Study

The NCI GI Steering Committee created a Task Force in Hepatobiliary Cancer in 2007. Shortly thereafter, sorafenib was shown to improve survival in selected patients with HCC. Subsequent research has focused on combination therapies, some with sorafenib and some without sorafenib. Meanwhile, a randomized phase II trial has been conducted that suggests that the combination of sorafenib and doxorubicin could further improve outcomes for this population of patients. This trial is therefore important in several ways. It is a first effort for the CALGB and Hepatobiliary Task Force. It is the first Phase III trial in HCC in the cooperative groups. So far, it represents the only therapy that suggests an improvement in survival beyond the one year based on randomized phase II study (15). This is critically important as we continue to combat the increasingly prevalent and deadly HCC.

1.8 Inclusion of Women and Minorities

HCC's etiology implies that various ethnicities are prone to develop the cancer, which will ensure the inclusion of minorities in the study. The cancer, however, is more common among men than women due to gender differences of androgen receptor CAG repeats (23), and we do expect accrual to be influenced by this natural fact of the disease. Nonetheless, every effort will

be made to include women and minorities with the help of various U.S. and Canadian cooperative groups. The potential impact of gender and ethnicity on outcome will be explored at the time of final analysis.

Accrual Targets					
Ethnic Category	**Sex/Gender**				
	Females		**Males**		**Total**
Hispanic or Latino	9	+	20	=	29
Not Hispanic or Latino	135	+	316	=	451
Ethnic Category: Total of all subjects	144	+	336	=	480
Racial Category					
American Indian or Alaskan Native	2	+	3	=	5
Asian	14	+	34	=	48
Black or African American	14	+	34	=	48
Native Hawaiian or other Pacific Islander	2	+	3	=	5
White	112	+	262	=	374
Racial Category: Total of all subjects	144	+	336	=	480

1.9 Rationale for Performance Status Criterion Change (in Update #8)

On November 8, 2013, the Alliance DSMB placed accrual on hold for CALGB 80802. This was due to an imbalance in treatment related deaths in the combination arm compared to the sorafenib alone arm, as determined and attributed by the investigators at the sites. While placed on hold, the study team reviewed and collected additional data concerning these events and other deaths of patients on study. This data was presented to and analyzed with the Alliance DSMB on November 21, 2013. After thorough review, the committee voted unanimously to allow the protocol to re-open to accrual

Noted during the review was that there was a limited number of subjects enrolled on both arms who were not appropriate study candidates for different reasons that indirectly correlate with poor performance status. Therefore, the DSMB requested the implementation of only enrolling patients with an ECOG Performance Status of 0 or 1, thereby excluding patients with an ECOG Performance Status of 2 going forward. This change is reflected in Update #8 of the protocol.

2.0 OBJECTIVES

2.1 Primary Objective

Compare overall survival (OS) of patients treated with sorafenib and doxorubicin to that of those treated with sorafenib.

2.2 Secondary Objectives

2.2.1 Compare time to progression (TTP) of patients treated with sorafenib and doxorubicin to that of those treated with sorafenib.

2.2.2 Compare progression-free-survival (PFS) of patients treated with sorafenib and doxorubicin to that of those treated with sorafenib.

2.2.3 Compare tumor response using RECIST criteria of patients treated with sorafenib and doxorubicin to that of those treated with sorafenib.

[See Sections 9.1.2, 9.2.3, and 9.3.3 for correlative science and pharmacogenomic substudy objectives.]

3.0 ON-STUDY GUIDELINES

This clinical trial can fulfill its objectives only if patients appropriate for this trial are enrolled. All relevant medical and other considerations should be taken into account when deciding whether this protocol is appropriate for a particular patient. Physicians should consider the risks and benefits of any therapy, and therefore only enroll patients for whom this treatment is appropriate. Although they will not be considered formal eligibility (exclusion) criteria, physicians should recognize that the following may seriously increase the risk to the patient entering this protocol:

- Substance abuse, medical, psychological or social condition, and psychiatric illness which would prevent the patient from giving informed consent.
- Medical conditions such as uncontrolled infection, uncontrolled diabetes mellitus or hypertension which, in the opinion of the treating physician, would make this protocol unreasonably hazardous for the patient.
- Patients with a previous malignancy except for cervical carcinoma in situ, adequately treated basal cell carcinoma, or superficial bladder tumors [Ta, Tis and T1], or other malignancies that may influence patient outcome as determined by the study chair.
- Inability to take oral medications.
- Life expectancy of ≤ 12 weeks.
- Women of childbearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control) prior to the initiation of protocol treatment, for the duration of the study participation, and for at least 30 days after completing study treatment. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

4.0 ELIGIBILITY CRITERIA

All questions regarding eligibility criteria should be directed to the CALGB study chair. Please note that the study chair cannot grant waivers to eligibility requirements.

4.1 Documentation of Disease:

4.1.1 Histologic Documentation: Patients must have pathologically or cytologically proven hepatocellular carcinoma. Known mixed histology (e.g. hepatocellular carcinoma plus cholangiocarcinoma) or fibrolamellar variant is not allowed.

4.1.2 Stage: Patients must have locally advanced or metastatic disease. Locally advanced disease is defined as disease deemed to be unresectable or non-eligible for transplant without distant metastases.

4.2 Patients must have Measurable Disease

Lesions must be accurately measurable in at least one dimension (longest diameter to be recorded) as ≥ 2 cm with conventional techniques or as ≥ 1 cm with spiral CT scan.

4.3 Prior Treatment

4.3.1 No prior adjuvant sorafenib or other Raf/VEGF inhibitors. Other prior adjuvant therapy is allowed if completed > 6 months prior to registration with documented recurrence of HCC.

4.3.2 Patients may have been treated with loco regional therapies provided that they either have:

- A target lesion that has not been subjected to local therapy, or

- The target lesion(s) within the field of the local therapy has shown an increase of ≥ 20% in the size since last treatment.

Such therapy must be completed at least 4 weeks prior to registration. Patients that have received palliative radiation therapy to the bone need not wait 4 weeks to begin protocol therapy.

4.3.3 Prior therapies allowed include the following:

A. Bland embolization, radiation, radioactive microspheres, etc.

B. Chemoembolization using any chemotherapy (except, see "D", below)

C. Chemoembolization drug-eluting beads using doxorubicin

D. Prior therapy with chemoembolization using doxorubicin in the non-drug eluting beads form is NOT allowed.

4.3.4 No prior systemic therapy for metastatic disease.

4.3.5 No prior exposure to systemic doxorubicin administered intravenously.

4.3.6 Antiviral treatment is allowed, however interferon therapy must be stopped at least 4 weeks prior to registration.

4.3.7 Allografts are not allowed: No prior history of any allograft, including but not limited to liver and bone marrow transplants.

4.3.8 Patients must have completed any major surgery ≥ 4 weeks from registration.

4.3.9 Concomitant treatment with Rifampin or St John's Wort is not allowed. Patients should discontinue these drugs at least 4 weeks prior to registration.

4.4 Patient History

4.4.1 No known CNS tumors including brain metastases.

4.4.2 No clinically significant gastrointestinal bleeding events requiring intervention, transfusion, or admission to hospital within 30 days prior to registration.

4.4.3 Patients with a history of hypertension should be well controlled (< 140/90 mmHg) on a regimen of anti-hypertensive therapy.

4.4.4 Significant history of cardiac disease is not allowed:

- Congestive heart failure > Class II New York Heart Association (NYHA)
- Myocardial infarction within 6 months prior to registration
- Serious myocardial dysfunction, defined as scintigraphically (MUGA, myocardial scintigram) determined absolute left ventricular ejection fraction (LVEF) below 45% or an LVEF on ECHO below the normal limit of normal at the individual institution.

4.4.5 No history of bleeding diathesis.

4.4.6 Patients receiving combination anti-retroviral therapy for human immunodeficiency virus (HIV) are excluded from the study because of possible pharmacokinetic interactions with sorafenib.

4.5 Age and Performance Status

4.5.1 Age: ≥ 18 years of age

4.5.2 ECOG Performance Status: 0 or 1

4.6 Pregnancy/Nursing Status:

The effects of sorafenib on the developing fetus at the recommended therapeutic dose are unknown and may be teratogenic. Thus, women who are pregnant should not go on study. Women should not breastfeed while participating in this study.

4.7 Required Initial Laboratory Values

Granulocytes	≥ 1,500/µL
Hemoglobin	≥ 8.5 g/dL*
Platelets	≥ 75,000/µL
Creatinine	≤ 1.5 x ULN (or Creatinine Clearance calculated ≥60 cc/minute)
Child-Pugh score	A (Appendix I)**
Bilirubin	≤ 3 mg/dL
ALT and AST	≤ 5 x ULN
PT-INR	≤ 1.7***

* Patients with recent or ongoing gastrointestinal bleed may not be transfused to reach the entry hemoglobin of 8.5 g/dL. Physicians should ensure patients requiring transfusion prior to registration do not have an occult or clinically apparent gastrointestinal bleed.

**Patients must have a Child-Pugh score of A and meet all laboratory value requirements.

*** Not required for patients on anticoagulation agents. Patients who are being therapeutically anticoagulated with an agent such as coumadin or heparin will be allowed to participate provided that no prior evidence of underlying abnormality in these parameters exists.

5.0 REGISTRATION/RANDOMIZATION, STRATIFICATION, AND DATA AND SAMPLE SUBMISSION

5.1 CTEP Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to OPEN, RAVE, or TRIAD or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) (https://ctepcore.nci.nih.gov/rcr). Documentation requirements per registration type are outlined in the table below.

Documentation Required	IVR	NPIVR	AP	A
FDA Form 1572	✔	✔		
Financial Disclosure Form	✔	✔	✔	
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔	
HSP/GCP training	✔	✔	✔	

Documentation Required	IVR	NPIVR	AP	A
Agent Shipment Form (if applicable)	✔			
CV (optional)	✔	✔	✔	

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and IRBs covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Added to a site roster
- Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol PI on the IRB approval

Additional information can be found on the CTEP website at < TBD >. For questions, please contact the RCR Help Desk by email at < RCRHelpDesk@nih.gov >.

5.2 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. Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to the following:

- An active Federal Wide Assurance (FWA) number
- An active roster affiliation with the Lead Network or a participating organization
- A valid IRB approval
- Compliance with all protocol specific requirements.

In addition, the site-protocol Principal Investigator (PI) must meet the following criteria:

- Active registration status
- The IRB number of the site IRB of record listed on their Form FDA 1572
- An active status on a participating roster at the registering site

Sites participating on the NCI CIRB initiative that are approved by the CIRB for this study are not required to submit IRB approval documentation to the CTSU Regulatory Office. For sites using the CIRB, IRB approval information is received from the CIRB and applied to the RSS in an automated process. Signatory Institutions must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB via IRB Manager to indicate their intent to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office. In order for the SSW approval to be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study.

5.2.1 Downloading Site Registration Documents:

Site registration forms may be downloaded from the CALGB 80802 protocol page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU RSS.

- 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
- Either enter the protocol # in the search field at the top of the protocol tree, or
- Click on the By Lead Organization folder to expand
- Click on the Alliance link to expand, then select trial protocol #CALGB 80802
- Click on LPO Documents, select the Site Registration documents link, and download and complete the forms provided.

5.2.2 Requirements for CALGB 80802 Site Registration:

- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)

5.2.3 Submitting Regulatory Documents:

Submit required forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal, where they will be entered and tracked in the CTSU RSS.

Regulatory Submission Portal: www.ctsu.org (members' area) → Regulatory Tab → Regulatory Submission

When applicable, original documents should be mailed to:

CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

5.2.4 Checking Your Site's Registration Status:

You can verify your site registration status on the members' section of the CTSU website.

- 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
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

Note: The status given only reflects compliance with IRB documentation and institutional compliance with protocol-specific requirements outlined by the Lead Network. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

5.3 Registration Requirements

Informed Consent: The patient must be aware of the neoplastic nature of his/her disease and willingly consent after being informed of the procedures to be followed, the experimental nature of the therapy, alternatives, potential benefits, side effects, risks, and discomforts. Human protection committee approval of this protocol and a consent form is required.

5.4 Patient Registration/Randomization Procedures

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://ctepcore.nci.nih.gov/iam >) and a 'Registrar' role on either the LPO or participating organization roster. Registrars must hold a minimum of an AP registration type.

All site staff 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. To assign an IVR or NPIVR as the treating, crediting, consenting, drug shipment (IVR only), or investigator receiving a transfer in OPEN, the IVR or NPIVR must list on their Form FDA 1572 in RCR the IRB number used on the site's IRB approval.

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.

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.

5.5 Registration to Companion Studies

The substudies included within CALGB 80802 are:

- CALGB 580901: The Evaluation of Tumor Necrotic Areas using a New Volumetric Method of Assessing Non-viable Tumor as a Correlate for Response (Section 9.1)
- CALGB 150902: Correlative Science Studies in CALGB 80802 (Section 9.2)
- CALGB 60901: Pharmacogenomic Studies in CALGB 80802 (Section 9.3)

CALGB 580901 should only be offered to patients at sites that can perform standard tri-phasic CT scans of the liver and meet the minimal scan requirements in Section 9.1.4.

CALGB 150902 and CALGB 60901 must be offered to all patients enrolled on CALGB 80802 (although patients may opt not to participate).

5.5.1 Imaging Study: CALGB 580901

If a patient answers "yes" to Model Consent Question #1, "I agree to take part in the CT imaging study described above", s/he has consented to participate in CALGB 580901. This CT imaging study does not require separate IRB approval. The patient should be registered to CALGB 580901 at the same time s/he is registered to the treatment trial CALGB 80802 and scans should be submitted per Section 5.8.

This substudy should only be offered to patients at sites that can meet the minimal CT scan requirements in Section 9.1.4.

5.5.2 Correlative Study: CALGB 150902

If a patient answered "yes" to "I agree that my specimen may be used for the research studies described above", (Question #2) in the Model Consent, the patient should be registered to CALGB 150902 at the same time that s/he is registered to the treatment trial (80802) and samples submitted per Section 5.9.

5.5.3 Pharmacogenomic Studies: CALGB 60901

If a patient answers "yes" to "I agree that my blood specimen may be used for the genetic research studies described above," (Question #3) in the Model Consent, s/he has consented to participate in the pharmacogenomic studies described in Section 9.2. The patient should be registered to CALGB 60901 at the same time s/he is registered to the treatment trial CALGB 80802 and samples should be submitted per Section 5.9.

5.6 Stratification Factors

Extent of disease:

a) Locally Advanced, b) Metastatic

5.7 Data Submission

As of Update #13 to the protocol, this study will use Medidata Rave® for remote data capture (RDC) of all future data collection.

The Rave system can be accessed through the iMedidata portal at https://login.imedidata.com. For additional information regarding account setup or training, please visit the training section of the Alliance website. Forms should be submitted in compliance with the table below, and a copy of the All Forms Packet can be downloaded from the Alliance and CTSU websites.

Site personnel with Rave roles assigned on the appropriate roster may receive a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the "accept" link in the upper right corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen. Personnel who did not receive an invitation should contact the Alliance Service Center.

Users who have not previously activated their iMedidata/Rave account at the time of an initial site registration approval for a study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website's Rave tab under the Rave Resource Materials heading (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website under the Rave tab at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

Form*		Submission Schedule
Baseline		
C-1911	80802 On-Study Form	Within one month of registration
C-2000	Solid Tumor Evaluation Form	
Report	Baseline CT/MRI report	
Report	Pathology report to confirm HCC diagnosis	
C-1922	CALGB 80802 Imaging Form#	
Sample Submission		
C-1442	Pharmacogenomic Submission and Quality Assurance Form	Submit form to Alliance Biorepository at OSU with samples and to the Alliance Statistics and Data Center via Rave.
C-1928	80802 Sample Submission Form	
Treatment		
C-1912	80802 Treatment Form**	Each cycle (q 3 weeks) during protocol treatment.
C-1913	80802 Adverse Event Form***	
C-1914	80802 Follow-up and Response Form	Every 2 cycles (q 6 weeks) during protocol treatment.
C-2000	Solid Tumor Evaluation Form	
C-1922 Report	CALGB 80802 Imaging Form# CT/MRI reports	
Follow-up (Post-treatment)		
C-1914 C-2000 C-1922 Report	Follow-up and Response Form Solid Tumor Evaluation Form CALGB 80802 Imaging Form# CT/MRI reports	If treatment ended for reasons other than disease progression submit via Rave: Every 3 months for 1 year, then every 6 months until 3 years after registration. After progression, submit only C-1914 via Rave every 6 months until 3 years after registration to report survival data.

* Use the comments field at the end of the Medidata Rave® Form if additional comments are necessary or additional typing space is needed. If patient never starts treatment, submit Baseline data, a C-1912 80802 Treatment Form to report reason for ending treatment, and Follow-up (Post-treatment) data.

\# Submit C-1922 80802 Imaging Form to the Alliance Statistics and Data Center via Medidata Rave® and to the Imaging Core Lab via fax per Section 5.8.

** S-096 80802 Sorafenib Medication Calendar has been provided for use by the patient and institutional staff. This form does *not* need to be submitted to the Alliance Statistics and Data Center.

*** Submit AE form via Medidata Rave® until all protocol treatment related events have resolved or until non-protocol treatment begins.

This study will use NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 for routine toxicity reporting on study forms.

5.8 Submission Procedures for Imaging Companion Study (CALGB 580901)

Patients must provide their consent to participate in CALGB 580901 (model consent question #1). Patients who cannot have triphasic CT scans will be excluded from this correlative study, but can still join the clinical trial.

CT scans must be performed at baseline and at time of restaging (q 2 cycles, i.e. q 6 weeks).

The complete CT scans must be submitted to the Alliance Imaging Core Laboratory (ICL) in digital DICOM format. BMP files, JPG files or hard copies (films) are unacceptable. The raw data of the entire image acquisition should be saved until the scan is accepted by the ICL. De-identify the patient data using institutional procedures to remove patient name and medical record number while preserving the CALGB ID number and protocol number. The de-identified digital images may be burned to a CD or transferred to a PC-based system.

The imaging data must be submitted to the ICL within **3 business days** of the scan being performed at the site. The CALGB 80802 CT Data Form (C-1922) must be faxed to the ICL (614-293-9275) within 24 hours of submitting the scans. The ICL will acknowledge receipt of the submission by e-mail within 24 hours of receipt of the materials and will send the quality check report within 3 business days.

CT data may be transferred by:

1) Web Transfer
2) FTP Transfer
3) Mail/Shipment Transfer

5.8.1 Web Transfer

Any PCs with internet access and web browser (e.g., Internet Explorer, Mozilla Firefox) can be used to web transfer DICOM images and other required files to the ICL. Upon request, the participating site can obtain standard Web Transfer information via the specific trial e-mail CALGB80802@ImagingCoreLab.com before their first data submission.

5.8.2 FTP Transfer

Any FTP software can be used to initiate access to the secure FTP Server of the ICL. Upon request, the participating site can obtain standard FTP access information via the specific trial e-mail CALGB80802@ImagingCoreLab.com before their first data submission.

5.8.3 Shipment/Mail Transfer:

If FTP data transfers cannot be completed at sites, the de-identified digital images in a DICOM format can be burned to CDs, labeled with CALGB 80802 patient ID, date of study, study period (i.e., specify baseline or follow-up) and data type (CT), and mailed to the Alliance Imaging Core Lab at:

IROC Ohio (Alliance Imaging Core Lab)
Attn: CALGB 80802
The Ohio State University
Wright Center of Innovation
395 W. 12th Ave., RM #414
Columbus, Ohio, 43240
Direct: (614) 293-2630
Office: (614) 293-2788
Fax: (614) 293-9275

For any questions regarding data transfer to the ICL, call the Corelab IT group at 614-293-2630 or 614-366-4932.

5.8.4 WebEx Conferences and Training

The Alliance Imaging Core Lab enables internet-based Visual & Virtual conferences that allow the simultaneous display of images (desktop presentations/desktop applications such as PowerPoint) and mutual communication between participating sites and the Corelab in a secure manner (SSL-encoded). The Alliance Imaging Core Lab will set up WebEx meetings for problem shooting, site training and other important issues when necessary.

5.9 Specimen Submission for Correlative and Pharmacogenomic Substudies

All participating institutions must ask patients for their consent to participate in the components of the correlative (CALGB 150902) and pharmacogenomic (CALGB 60901) substudies planned for CALGB 80802, although patient participation is optional. Rationale and methods for the scientific components of these studies are described in Section 9.2 and Section 9.3.

Type of specimen	Pre-treatment	Every cycle for the first 6 cycles, then every 2 cycles until progression	At Progression
Plasma (lavender top)*	1 x 10 mL	1 x 10 mL	1 x 10 mL
Serum (red top)*	1 x 10 mL	1 x 10 mL	1 x10 mL
Whole (venous) Blood** (lavender top)	1 x 10 mL		
[Total blood volume]	[30 mL]	[20 mL]	[20 mL]

* For patients who answer "yes" to consent question #2.

** For patients who answer "yes" to consent question #3.

5.9.1 Plasma Collection Procedures

For patients who consent to consent question #2, plasma samples will be used for the studies described in Section 9.2.

1. Collect blood in 10 mL lavender top tube. After collection, gently mix the blood by inverting the tube 8 to 10 times. Store vacutainer tubes upright at 4°C until centrifugation. Blood samples should be centrifuged within four hours of blood collection.

2. Centrifuge blood samples in a horizontal rotor (swing-out head) for 10 to 20 minutes at 1100-1300 g at room temperature. Warning: Excessive centrifuge speed (over 2000 g) may cause tube breakage and exposure to blood and possible injury. If needed, relative centrifugal force (RCF) for a centrifuge can be calculated. For an on-line calculator tool, please refer to: http://www.changbioscience.com/cell/rcf.html.

3. After centrifugation, plasma layer will be at the top of the tube. Mononuclear cells and platelets will be in a whitish layer, called the "buffy coat", just under the plasma and above the red blood cells.

4. Carefully collect the plasma layer with an appropriate transfer pipette without disturbing the buffy coat layer. Pipette the plasma into the labeled cryovials (recommended cryovials are described in Section 5.9.3). Aliquot volume is to be 500 µL. Close the caps tightly and place on ice. This process should be completed within 1 hour of centrifugation.

5. Check that all aliquot vial caps are secure and that all vials are labeled.

6. Place all aliquots upright in a specimen box or rack in an -80°C or colder freezer. All specimens should remain at -80°C or colder prior to shipping. The samples should not

be thawed prior to shipping. Plasma should be shipped on dry ice according to the shipping procedures in Section 5.9.3.

5.9.2 Serum Collection Procedures

For patients who consent to consent question #2, serum samples will be used for the studies described in Section 9.2.

1. Collect blood in 10 mL red top tube. After collection, tubes ("vacutainers") should sit upright after the blood is drawn at room temperature for a minimum of 30 to a maximum of 60 minutes to allow the clot to form. Note: Use red top (serum) tubes (silicon-coated)—no additives and not SST (serum separator tubes).

2. Centrifuge the blood sample at the end of the clotting time (30-60 minutes) in a horizontal rotor (swing-out head) for 20 minutes at 1100-1300 g at room temperature.

3. Use a pipette to transfer the serum (Recommendation: do not pour). Pipette serum into the labeled cryovials (recommended cryovials are described in Section 5.9.3). Aliquot volume is to be 500 µL. Close the cap on the vial tightly. This process should be completed within 1 hour of centrifugation. Note: Be very careful not to pick up red blood cells when aliquoting. This can be done by keeping the pipet above the red blood cell layer and leaving a small amount of serum in the tube.

4. Check that all aliquot vial caps are secure and that all vials are labeled.

5. Place all aliquots upright in a specimen box or rack in an -80°C or colder freezer. All specimens should remain at -80°C or colder prior to shipping. The samples should not be thawed prior to shipping. Serum should be shipped on dry ice according to the shipping procedures in Section 5.9.3.

5.9.3 Plasma and Serum Shipping Procedures

The CALGB strongly recommends the usage of 2 mL cryovials for storage of plasma and serum specimens. Acceptable cryovials include:

Company name	Catalog number
Nalgene	03-337-7Y (through Fisher) NNI No.: 5012-0020
Fisher brand	05-669-57 (through Fisher)
Corning	03-374-21 (through Fisher) CLS430659 (through Sigma) Corning: 430488
VWR	16001-102

Specimens for patients registered on this study must be logged and shipped using the online Alliance Biospecimen Management System (BioMS). All institutions may access BioMS using IE9, FireFox, Safari web browsers at: http://bioms.allianceforclinicaltrialsinoncology.org.

A copy of the Shipment Packing Slip produced by BioMS must be printed and placed in the shipment with the specimens.

USE OF THE ALLIANCE BIOSPECIMEN MANAGEMENT SYSTEM (BioMS) IS MANDATORY AND ALL SPECIMENS MUST BE LOGGED AND SHIPPED VIA THIS SYSTEM.

BioMS is a web-based system for logging and tracking all biospecimens collected on Alliance trials. Authorized individuals may access BioMS at the following URL: http://bioms.allianceforclinicaltrialsinoncology.org using most standard web browsers

(Safari, Firefox, Internet Explorer). For information on using the BioMS system, please refer to the 'Help' links on the BioMS web page to access the on-line user manual, FAQs, and training videos. To report technical problems, such as login issues or application errors, please contact: 1-855-55-BIOMS or Bioms@alliancenctn.org. For assistance in using the application or questions or problems related to specific specimen logging, please contact: 1-855-55-BIOMS or Bioms@alliancenctn.org.

All submitted specimens must be labeled with the protocol number (CALGB 80802), CALGB patient ID, patient's initials and date and time of collection, and type of specimen collected (e.g., plasma, serum, whole blood). A copy of the Shipment Packing Slip produced by the Alliance BioMS must be printed and placed in the shipment with the specimens. In addition to the pathology specimen and the BioMS Shipment Packing Slip, send a copy of the pathology report to the Alliance Biorepository at Ohio State University (OSU):

Alliance Biorepository at Ohio State University
The Ohio State University
Innovation Centre
2001 Polaris Parkway
Columbus, OH 43240
Tel: 614-293-7073 Fax: 614-293-7967
path.calgb@osumc.edu

Samples should be shipped on dry ice within 30 days of collection. Please be sure to use a method of shipping that is secure and traceable. Extreme heat precautions should be taken when necessary. Shipment on Monday through Friday by overnight service to assure receipt is encouraged. If shipping on Friday, FedEx or UPS must be used and the air bill must be marked "For Saturday delivery." Do not ship specimens on Saturdays.

5.9.4 Whole Blood Submission for the Pharmacogenomic Substudy (CALGB 60901)

For patients who consent to participate (consent question #3), whole blood will be used for the pharmacogenomic studies described in Section 9.3. Specimens for patients registered on this study must be logged and shipped using the Alliance Biospecimen Management System (BioMS). All institutions may access this system at http://bioms.allianceforclinicaltrialsinoncology.org.

Draw 10 mL of venous blood in a lavender top tube and keep refrigerated until shipped overnight to the Alliance Biorepository at Ohio State University. Label the tube with the patient's initials, CALGB/CTSU patient ID number, study number (CALGB 80802) and date of collection. The sample should be shipped the same day on a cold pack by overnight mail to:

Alliance Biorepository at Ohio State University
The Ohio State University
Innovation Centre
2001 Polaris Parkway
Columbus, OH 43240
Phone: 614-293-7073
Fax: 614-293-7967

Shipment on Monday through Friday by overnight service to assure receipt is encouraged. If shipping on Friday, FedEx or UPS must be used and the air bill must be marked "For Saturday delivery". Do not ship specimens on Saturdays.

6.0 REQUIRED DATA

Pre-Study Testing Intervals

To be completed within 16 DAYS before registration:

- All blood work (including hepatitis labs), history and physical, and pregnancy test.

To be completed within 28 DAYS before registration:

- MUGA/ECHO, ECG, and scans of any type that are utilized for tumor measurements.

	Prior to Registration	Day 1 of each cycle*	Time of Restaging (q 2 cycles, i.e. q 6 weeks)	Post Treatment Follow up**
Tests & Observations				
History and Progress Notes	X	X		X
Physical Examination	X	X		X
Pulse, Blood Pressure #	X	X		
Height	X			
Weight/Body Surface Area †	X	X		
Performance Status	X	X		
Drug Toxicity Assessment		X		
12 lead ECG	X			
MUGA/ECHO^	X		A	
Laboratory Studies				
CBC, Diff, Platelets	X	X		
Creatinine, BUN, Electrolytes (Ca^{2+}, Mg^{2+}, PO_4), Glucose	X	X		
ALT/AST, Alk. Phos., LDH	X	X		
Bilirubin (Total and Direct)	X	B		
Total Protein, Albumin	X	X		
Hep B Surface Antigen, Hep B Core Antibody, Hep C Antibody	C			
PT/INR	X			
Alphafetoprotein	X			
Pregnancy Test (Urine or Serum)	X			
Child-Pugh Score (see Appendix I)	X			
Staging				
CT Scan/MRI	D		D	X
Companion Studies				
Plasma and Serum£	*Please see Section 5.9.*			
Whole Blood$^{\Psi}$	*Please see Section 5.9.*			

* Pre-registration labs may be used for Day 1 of Cycle 1 tests if obtained within 7 days prior to day 1 of Cycle 1. For subsequent cycles, labs may be obtained within 48 hours prior to day of treatment.

** If treatment ended for reasons other than disease progression: Every 3 months for 1 year, then every 6 months until 3 years after registration. After disease progression, report survival status every 6 months until 3 years after registration.

A Only for patients randomized to the sorafenib plus doxorubicin arm: MUGA/ECHO is to be performed every three cycles, up to the maximum cumulative dose of 360 mg/m^2 of doxorubicin, then before every cycle thereafter up to the maximum cumulative dose of doxorubicin of 480 mg/m^2.

B Bilirubin must be obtained within 48 hours of Day 1 of every cycle (including cycle 1) on both arms.

C Hepatitis labs may be obtained within 16 days prior to registration. Patients may receive Day 1, Cycle 1 treatment prior to receiving hepatitis results.

D Preferably CT scan of chest/abdomen/pelvis with triphasic liver scan. If CT contrast is contraindicated despite the use of antihistamines and steroids, CT chest without contrast and MRI of abdomen and pelvis is allowed. A bone scan should also be obtained if bone metastases are suspected. For those patients who consent to participate in CALGB 580901, please refer to Section 5.8 for submission procedures of CT scans. Restaging scans may be performed 7 days in advance of Day 1 of treatment of next cycle.

Blood pressure measurement will be performed in a consistent manner with the patient sitting for 5 minutes prior to the evaluation.

† The dose of chemotherapy need not be changed unless the calculated dose changes by ≥ 10%.

^ If MUGA is not available, an ECHO can be used to assess LVEF. Modality should remain consistent throughout study treatment.

£ For those patients who consent to participate in CALGB 150902.

Ψ For those patients who consent to participate in CALGB 60901.

7.0 TREATMENT PLAN

Protocol treatment is to begin within 7 days of registration. Questions regarding treatment should be directed to the CALGB study chair.

Doses of doxorubicin and sorafenib will be based on the patient's baseline bilirubin level (measured within 48 hours prior to Day 1 of Cycle 1).

One cycle is considered 21 days with an allowed variance of plus or minus (+/-) 3 days. On Cycle 1 Day 1, treatment with sorafenib only once in the evening is permissible.

7.1 Arm A: Doxorubicin plus Sorafenib

For patients with baseline bilirubin ≤ 1.2 mg/dL:

- Doxorubicin = 60 mg/m^2
- Sorafenib = 400 mg **twice daily**

For patients with baseline bilirubin between 1.3 – 3 mg/dL:

- Doxorubicin = 30 mg/m^2
- Sorafenib = 400 mg **once a day**

Total doxorubicin allowed is 360 mg/m^2 and in approved circumstances (patient benefits from therapy i.e., shows evident radiographic response or stability of disease, and continues to have normal EF on MUGA) 480 mg/m^2, after which sorafenib can be continued as a single agent.

7.2 Arm B: Sorafenib

For patients with baseline bilirubin ≤ 1.2 mg/dL:

- Sorafenib = 400 mg **twice daily**

For patients with baseline bilirubin between 1.3 – 3 mg/dL:

- Sorafenib = 400 mg **once a day**

7.3 Adherence

Adherence to sorafenib will be monitored using medication calendar. A medication calendar will be provided each time a new supply of sorafenib is dispensed. If a patient cites reasons other than adverse events for not taking the required oral medication, the reasons for missing the doses will be reviewed and the importance of taking all dosages on schedule will be reinforced with the patient.

8.0 DOSE MODIFICATIONS AND MANAGEMENT OF TOXICITY

- If sorafenib is interrupted for > 3 weeks, discontinue all protocol therapy.
- If day 1 doxorubicin is delayed for 3 consecutive times/weeks, discontinue all protocol therapy.
- If dose reductions beyond the lowest dose level are required, discontinue all protocol therapy.
- Doses that have been reduced will not be re-escalated, except in the case of skin toxicity (see Section 8.7).

8.1 Dose Levels

Dose levels are based on the patient's baseline bilirubin level (measured within 7 days prior to Day 1 of Cycle 1). These dose levels will apply regardless of subsequent change in bilirubin during protocol treatment.

8.1.1 Dose levels for patients with baseline bilirubin ≤ 1.2 mg/dL

Doxorubicin Dose Levels

	Doxorubicin
Dose level 0	60 mg/m^2
Dose level -1	45 mg/m^2
Dose level -2	30 mg/m^2
Dose level -3	22.5 mg/m^2

Sorafenib Dose Levels

	Sorafenib
Dose level 0	400 mg **BID**
Dose level -1	400 mg **once a day**
Dose level -2	400 mg **every other day**

8.1.2 Dose levels for patients with baseline bilirubin between 1.3 – 3.0 mg/dL

Doxorubicin Dose Levels

	Doxorubicin
Dose level 0	30 mg/m^2
Dose level -1	22.5 mg/m^2

Sorafenib Dose Levels

	Sorafenib
Dose level 0	400 mg **once a day**
Dose level -1	400 mg **every other day**

8.2 Hematologic Toxicities

The following dose modifications are based on toxicity experienced during a cycle:

8.2.1 Grade 3 neutropenia or thrombocytopenia: Delay doxorubicin until ≤ grade 2, then decrease doxorubicin by one dose level for all subsequent cycles. No dose modifications for sorafenib.

8.2.2 Grade 4 neutropenia, thrombocytopenia, or neutropenic fever: Delay doxorubicin and interrupt sorafenib until ≤ grade 2, then resume with one dose level reduction of doxorubicin and one dose level reduction of sorafenib for all subsequent doses.

8.3 Gastrointestinal Toxicities

- **Grade ≥ 3 diarrhea:** Interrupt sorafenib until diarrhea improves to ≤ grade 2, then resume sorafenib with one dose level reduction. There are no dose modifications for doxorubicin for diarrhea.
- **Grade ≥ 3 nausea or vomiting despite antiemetics**: Delay doxorubicin until nausea or vomiting improve to ≤ grade 2, then resume doxorubicin with one dose level reduction. There are no dose modifications for sorafenib for nausea vomiting.

8.4 Hepatic Dysfunction

For bilirubin 1.3-3.0 mg/dL, delay doxorubicin and interrupt sorafenib. Re-check in one week. Resume treatment once bilirubin returns to less than or equal to baseline value.

- If baseline bilirubin was ≤ 1.2 mg/dL and the current dose of doxorubicin is 60 mg/m^2, decrease doxorubicin by two dose levels and sorafenib by one dose level for all subsequent doses.
- If baseline bilirubin was ≤ 1.2 mg/dL and the current dose of doxorubicin is < 60 mg/m^2, decrease doxorubicin by one dose level and sorafenib by one dose level for all subsequent doses.
- If baseline bilirubin was 1.3-3 mg/dL, continue same dose level of doxorubicin and sorafenib.

For bilirubin > 3.0 mg/dL, delay doxorubicin and interrupt sorafenib. Re-check in one week. Resume treatment once bilirubin returns to less than or equal to baseline value.

- If baseline bilirubin was ≤ 1.2 mg/dL and the current dose of doxorubicin is 60 mg/m^2, decrease doxorubicin by two dose levels and sorafenib by one dose level for all subsequent doses.
- If baseline bilirubin was ≤ 1.2 mg/dL and the current dose of doxorubicin is < 60 mg/m^2, decrease doxorubicin by one dose level and sorafenib by one dose level for all subsequent doses.
- If baseline bilirubin was 1.3-3 mg/dL, decrease doxorubicin by dose level and sorafenib by one dose level for all subsequent cycles.

8.5 Cardiotoxicity (Arm A only)

For grade 3 Ejection Fraction Decreased, discontinue all protocol therapy. Per CTCAE v4.0, grade 3 Ejection Fraction Decreased is described a resting ejection fraction 39-20% or > 20% drop from baseline.

8.6 Sorafenib Dose Modifications for Skin Toxicity

8.6.1 Dose Modifications for Rash (Maculo-Papular) or Palmar-Plantar Erythrodysesthesia (Hand-Foot Syndrome)

- **Grade 2, 1st appearance:** Interrupt sorafenib until skin toxicity improves to ≤ grade 1, then resume sorafenib at the previous dose level.
- **Grade 2, 2nd or 3rd appearance:** Interrupt sorafenib until skin toxicity improves to ≤ grade 1, then resume sorafenib at one reduced dose level.
- **Grade 2, 4th appearance**: Discontinue all protocol therapy.
- **Grade 3, 1st or 2nd appearance**: Interrupt sorafenib until skin toxicity improves to ≤ grade 1, then resume sorafenib at one reduced dose level.
- **Grade 3, 3rd appearance**: Discontinue all protocol therapy.

If sorafenib is interrupted for more than 3 weeks for skin toxicity, discontinue all protocol therapy.

Following a full cycle of reduced dose sorafenib with no rash (maculo-papular) or HFSR (palmar-plantar erythrodysesthesia) of ≥ grade 1 severity, the dose of sorafenib may be re-escalated to the previous dose level. (Note: Re-escalation is only allowed in the case of skin toxicity.)

There are no dose modifications for doxorubicin for skin toxicity, except in the instance of discontinuation of all protocol therapy.

8.6.2 Management of Skin Toxicity: At first occurrence of HFSR, independent of grade, supportive measures such as topical emollients, high-potency topical steroids, or keratolytic cream (urea/salicylic acid) should be administered.

8.7 Sorafenib Dose Modifications for Hypertension

- **For hypertension >140/90 and ≤160/100:** Continue sorafenib. Consider adding or adjusting anti-hypertensive medications (e.g., calcium channel blockers).
- **For persistent (>160/100) or symptomatic hypertension:** Interrupt sorafenib. Resume when blood pressure improves to ≤160/100. If sorafenib is interrupted for > 3 weeks, discontinue all protocol therapy.
- **Grade 4 hypertension**: Discontinue all protocol therapy.

8.8 Other Non-hematologic Toxicities

8.8.1 Grade 3: For other grade 3 toxicity considered at least possibly related to doxorubicin, delay doxorubicin until toxicity improves to ≤ grade 1. If doxorubicin is delayed for 3 consecutive times/weeks, discontinue all protocol therapy.

For other grade 3 toxicity considered at least possibly related to sorafenib, interrupt sorafenib until toxicity improves to ≤ grade 1. If sorafenib is interrupted for more than 3 weeks, discontinue all protocol therapy.

8.8.2 Grade 4: Discontinue all protocol therapy.

8.9 Dose Modifications for Obese Patients

There is no clearly documented adverse impact of treatment of obese patients when dosing is performed according to actual body weight. Therefore, all dosing is to be determined solely by actual weight without any modification unless explicitly described in the protocol. This will eliminate the risk of calculation error and the possible introduction of variability in dose administration. Failure to use actual body weight in the calculation of drug dosages will be considered a major protocol deviation. Physicians who are uncomfortable with calculating doses based on actual body weight should recognize that doing otherwise would be a protocol violation.

9.0 COMPANION STUDIES

9.1 CALGB 580901: The Evaluation of Tumor Necrotic Areas using a New Volumetric Method of Assessing Non-viable Tumor as a Correlate for Response

9.1.1 Background

We developed a computer algorithm for semi-automated delineation of liver metastases from colorectal cancer. The algorithm starts with a manual selection of a seed lesion region-of-interest (ROI). Based on intensity distributions of the seed ROI and the liver parenchyma,

several features were computed and used to adaptively guide the region-growing (24). Figure 1 shows two examples of the segmentation results obtained using the algorithm.

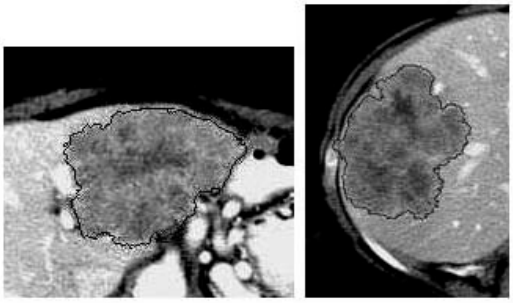


Figure 1 Semi-automated segmentation of liver metastasis using a shape-constrained region-growing algorithm.

Automated/semi-automated segmentation of necrosis:

Once a tumor is delineated, necrosis inside the tumor needs to be detected and segmented. As necrosis will not be enhanced by the contrast material, it appears low attenuation and possesses a certain low range of intensity on contrast-enhanced CT images. We determine this intensity range through manually extracting necroses in a large number of liver tumors and calculating the mean and standard deviation (std) of the necroses' intensity. Volumetric tumor size and necrosis can therefore be calculated simply for an entire tumor or series of tumors.

All assessments will occur at the time of radiologic evaluations, i.e. baseline and every six weeks while on therapy. Patients who cannot have triphasic CT scans will be excluded from this correlative study, but still can join the clinical trial.

The nature of HCC tumors and their embedment in liver parenchyma may make them difficult to assess radiologically, especially when it comes to evaluating response to a novel therapeutic. In a phase II study evaluating sorafenib, we reported that despite tumors appearing to have grown, many patients' scans displayed central tumor necrosis (25). We recently completed the evaluation on 12 patients and found an association between response and tumor necrosis/tumor volume ratio (N/T). N/T as a surrogate of response obviously needs to be evaluated as part of a large clinical study. Its validation requires a positive association with patients' overall survival (26).

We have developed a system with a practical user interface that allows the operator to synchronously view baseline and corresponding follow-up images of the liver side-by-side, semi automatically delineate tumor contours, and segment necrosis with an optimal threshold determined by observing segmentation results while varying thresholds or setting a system-wide threshold value. If a segmentation result is suboptimal, the system allows the operator to make a manual correction.

The software has been validated in one other published trial (25, 27). The assessment of necrotic tumor volume has been widely used in GIST tumors and anecdotally noted in many other tumors. Our approach here is to make a qualitative assessment of necrosis quantitative and highly reproducible. Many other treatment options for HCC involve estimations of the degree of necrosis, therefore, using the technique in this study may help with other treatments in HCC.

9.1.2 Objectives

To correlate outcome based on OS, PFS, and response by RECIST with tumor necrosis as estimated by N/T ratio.

9.1.3 Methods

For each patient, the tumor or series of tumors in the liver will be evaluated at baseline and every 6 weeks while on protocol therapy.

For each triphasic CT study, a tumor volume, necrosis volume, and a ratio of tumor necrosis volume to tumor volume will be recorded by the Imaging Core Laboratory (ICL). All investigators, including radiologists, will be blinded to the patient data until completion of the study when correlation of outcome based on OS, PFS and response by RECIST with necrosis will be studied.

In addition to evaluation of tumor necrosis (TN) by radiologists, the semi-automated, computerized technique described above will be used to quantify TN for each patient at baseline and at the first 6-week radiologic assessment. Radiologists will be blinded to the patients' clinical data. Tumor volume (TV), TN and the ratio of TN and TV (TN percent) will be recorded. The primary endpoint will be percent TN after the first radiologic assessment at 6 weeks post initiation of therapy. The change from baseline will also be determined for each of these measures at the assessment time.

Sites will be asked to perform their standard tri-phasic CT of the liver with additional post contrast CT of the chest and pelvis.

Sites are provided with the triphasic imaging protocol in Section 9.1.4, utilizing a standard dose and contrast regimen. Sites will reconstruct thin section CTs from the triphasic CT and will send centrally for volumetric and necrosis calculations. The use of standard triphasic CT will enable sites to utilize their standard imaging protocols. In general, triphasic CT is standardized across multiple centers. The data will be centrally collected at the Alliance ICL. This will allow image analysis as described in the protocol and estimations of necrosis to be calculated. Their standard protocol should be carried through all time points while the patient is on study treatment.

9.1.4 CT Scan Requirements

Optimal Technique: The requirements listed below are to be used for the triphasic CT scan whenever possible.

- Scanning mode: Helical
- Patient position: Supine, arms up
- Scan extent: Thoracic inlet through pubic symphysis
- Scan time: Single breath-holding period, in full inspiration
- Section thickness: 2.5 mm or less
- Enhancement: Intravenous contrast unless contraindicated by allergy. Liver only is required to be triphasic. Chest and pelvis can be post contrast only.
- Reconstruction: Contiguous or overlapping sections; no gaps

Minimum CT requirements are listed below. Note that a CT scan made as part of a PET-CT is acceptable if it meets these requirements. **Any CT scan that does not meet these minimal requirements must be repeated.**

- Scanning mode: Helical
- Patient position: Supine
- Scan extent: Thoracic inlet through liver
- Scan time: Single breath-holding period, in full inspiration
- Section thickness: 5 mm or less

- Enhancement: Required if not clinically contraindicated. Triphasic of liver only.
- Reconstruction: Contiguous or overlapping sections; no gaps

9.2 CALGB 150902: Correlative Science Studies in CALGB 80802

9.2.1 Evaluation of Circulating Biomarkers

It has been previously reported that changes in glycosylation on liver derived glycoproteins is a function of cancer (HCC) development. The most notable change is an increase in the level of core and outer arm fucosylation. Using a glycoproteomic platform, investigators have identified many of the proteins containing this altered glycosylation and have developed plate-based assays to measure these changes or in some cases, to just examine the identified protein. Studies to date have shown that the serum levels of the biomarkers we discovered correlate with a diagnosis of HCC. It has been reported that these biomarkers can be used to detect HCC in a setting of cirrhosis (28). However, the extent to which these biomarkers alter with treatment intervention has not been fully determined. There is encouraging preliminary evidence to suggest that these markers do alter with treatment outcome. Briefly, the fate of 11 patients was followed as a function of initial Fc-hemopexin levels immediately after treatment. Although the numbers are small, a clear trend was seen. Those patients who remain tumor free (up to 6 years post tumor treatment) have drops in fucosylated hemopexin and GP73. In contrast, those patients who had high levels of fucosylated hemopexin or GP73 after treatment all had multiple lesions detected in follow up. These data are preliminary but dramatically imply that these markers may have value in the monitoring of patients and may be elevated even when small, undetectable tumors are present. If this indeed is the case, it would imply that markers like GP73 may be elevated in patients well before an imageable tumor mass is visible.

9.2.2 Evaluation of Viral Titers in Patients with HBV and/or HCV

In HCV-replicating cells, c-Raf is recruited to the replicon complex via NS5A, resulting in the activation of c-Raf (29). It has been shown that sorafenib efficiently blocks HCV replication and viral gene expression. The sorafenib antiviral effects were demonstrated to be c-Raf mediated (30). Others have demonstrated that the VEGF expression of HepG2 once inhibited with sorafenib, can promote cellular polarization and form tight junctions, which inhibits HCV entry. This is commensurate with increased HCV infectivity once the cells are treated with VEGF. This effect could be also be blocked by sorafenib. In Huh-7 cells, it was found that HCV infection induces VEGF expression that acts to depolarize hepatocytes and disrupt tight junctions, thereby making cells more susceptible to further HCV infection in an autocrine fashion. Sorafenib treatment was able to block this cycle. These data highlight a potential role for VEGF antagonists to help control HCV infection in addition to their known properties of regulating HCC growth and development (31).

The current study objective is to evaluate a possible synergistic effect between sorafenib and doxorubicin. This possible synergy may be partly driven by inhibiting the Raf-1–dependent bFGF-mediated protection of endothelial cells against stress-mediated apoptosis (32). The release of the Raf-1, Ask-1 dimer and ultimate inhibition of Raf-1 via sorafenib, will most likely differ in the two arms, in the presence and absence of doxorubicin. The implication of this modulation on HCV is unknown, thus the need for evaluating the objectives in both arms of the study.

From the SHARP trial, it is suggested that patients with hepatitis C may have an added advantage for sorafenib therapy (33). In a sub-group analysis of patients with hepatitis C based HCC, it was noted that these patients treated with sorafenib (n=93) had a median

survival advantage of 14 months compared to the entire sorafenib treated group of 10.7 months.

Similarly, in a retrospective evaluation of the phase II trial evaluating sorafenib in patients with advanced HCC (34), it was noted that patients who were infected with hepatitis C but not hepatitis B (n=13) had a longer time to progression of 6.5 months compared to 4 months for hepatitis B but not C patients (n=33) (p=0.05) and to 4.2 months for the whole population of the study (n=137). The small sample size, of course, makes definitive conclusions impossible. Data from hepatitis B patients from the SHARP trial have not yet been reported. Obviously, these observations are limited by their retrospective nature.

9.2.3 Objectives

9.2.3.1 To determine if the serum biomarkers GP73, fucosylated hemopexin, fucosylated fetuin-A and fucosylated kininogen correlate with treatment outcome following therapy with sorafenib plus doxorubicin or in patients with sorafenib alone.

9.2.3.2 To examine additional plasma markers of interest, including VEGF, soluble sVEGFR-2, sVEGFR-3, sc-Kit, HGF, Ras p21, and pERK, a tumor biomarker related to sorafenib's mechanism of action to identify predictors of survival or clinical correlates with sorafenib treatment responses.

9.2.3.3 To determine the proportion of patients with undetectable viral load with <50 copies/mL at 15 weeks.

9.2.3.4 To assess and compare the HCV antiviral effect, if any, of sorafenib or sorafenib plus doxorubicin at 6, 9 and 15 weeks.

9.2.3.5 To study and compare patients' rate of undetectable viral load (< 50 copies per mL), 2 log decline in viral load, and a continuum of viral load at 6, 9 and 15 weeks, and any association with OS of the whole study population, and patients treated with sorafenib or sorafenib plus doxorubicin.

9.2.3.6 To study and compare patients with detectable versus undetectable viral load (< 50 copies per mL) at 6, 9 and 15 weeks, and any association with PFS of the whole study population, and patients treated with sorafenib or sorafenib plus doxorubicin.

9.2.3.7 To study and compare patients with detectable versus undetectable viral load (<50 copies per mL) at 6, 9 and 15 weeks, and any association with response rate as defined by RECIST criteria of the whole study population, and patients treated with sorafenib or sorafenib plus doxorubicin.

9.2.3.8 To assess retesting of genotype changes.

9.2.3.9 To assess quasi-species in patients with virologic failure defined as reversing from undetectable (<50 copies per mL) to detectable viral load, or increase in 2 logs above nadir, at any point in time.

9.2.4 Methods

Both serum and plasma will be collected prior to registration; every 3 weeks (i.e., every cycle) for the first 6 cycles, then every 6 weeks (i.e., every 2 cycles); and at progression using the procedures described in Section 5.9.

The levels of GP73, fucosylated hemopexin, fucosylated fetuin-A and fucosylated kininogen will be performed either via traditional ELISA or via lectin-ELISA as has been

done previously (35). The relative change in these proteins will be compared to the imaging results obtained and with survival. In total, 250 µL of serum and 250 µL of plasma will be required for analysis.

Aliquots of frozen plasma will be sent to the laboratory of Dr. Gregory Tsongalis for HCV analysis. HCV RNA levels will be measured by TaqMan PCR (36) and by genotype (37). Specimens will be evaluated by PCR and genotype at baseline on Day 1 of Cycle 1 and those patients with detectable virus, defined as an HCV RNA ≥50 copies/mL, will have HCV RNA levels obtained on Day 1 of Cycles 2, 3, and 5. On the last time point (Day 1 of Cycle 5), the virus genotype will be retested.

9.3 CALGB 60901: Pharmacogenomic Studies in CALGB 80802

9.3.1 Candidate Marker Study

In CALGB 80303, it was discovered that the rs763780 variant in the IL17F gene was a prognostic factor (38) in advanced pancreatic cancer patients treated with chemotherapy (39). Germline DNA was isolated from peripheral blood on 352 patients, and was typed for more than 550,000 SNPs using the Illumina550 platform. The associations between overall survival (OS) and SNPs were investigated using the log-rank test. A review of the clinical data and ancestry genomic analysis identified 294 patients who were clinically eligible and determined to be genetically European, and this subset was used for the primary analysis.

For the analysis of OS, patients in both arms were pooled, and a nonsynonymous SNP in the IL17F gene (rs763780) with an allelic frequency of 3.9% (H161R, $p<2.7x10-8$) was associated with OS. Median OS was significantly shorter for the H/R heterozygotes (3.1 months, 95% CI 2.3-4.3, n=23), as compared to the H/H homozygotes (6.8 months, 95% CI 5.8-7.3, n=271). This association remained highly significant when the analysis was stratified by extent of disease or previous radiotherapy. There was no evidence of an interaction with bevacizumab, suggesting that this SNP is prognostic rather than predictive.

Wild-type (161H) IL17F is a pro-inflammatory, anti-angiogenic cytokine (40). The 161R mutant IL17F antagonizes wild-type IL17F (41), potentially resulting in a pro-angiogenic effect.

Heritable variation in IL17F may be a prognostic marker for prostate cancer and other cancers.

9.3.2 Genome-wide Association Study (GWAS)

In addition to the investigation of the candidate gene variation and its association with treatment outcomes, DNA of patients extracted from peripheral blood will be used to scan their entire genome. Using genetic information collected from selected candidate genes might have the disadvantage of relying on existing data regarding the role of those genes in the pharmacology of the study drugs or the biology of a specific tumor. Novel high-density SNP platforms are now available to survey the pattern of variation of the entire genome of an individual, allowing the identification of genes that have not previously identified as candidate genes. This comprehensive and unbiased genome-wide approach has the potential to lead to new discoveries of genes of clinical importance in pharmacogenomics.

Currently, platforms with hundreds of thousands of SNPs have been extensively used in case-control studies of cancer risk in germ line DNA of subjects. These platforms do not only provide information on the SNP pattern of an individual, but also on the quantitative pattern on copy number variation.

The fact that this study is relatively large, placebo-controlled, and randomized, would put the genome-wide investigation in the perfect position to identify new genes (additional to

the candidate genes) that are associated with the treatment outcomes. Ultimately, subsets of patients with better response and/or less risk of toxicity can be identified based upon their genetic make-up.

9.3.3 Objectives

The primary statistical objective for the candidate-marker pharmacogenetic companion of this study is to investigate the association between IL17F (rs763780) and overall survival (OS) in the Caucasian population. It is assumed that the presence of the G allele is associated with higher risk of death.

The primary objective for the genome-wide association study (GWAS) is to identify single-nucleotide polymorphphisms (SNPs) associated with overall survival (OS)

Other endpoints of interest are other relevant clinical endpoints such as adverse events and progression-free survival (PFS). The clinical definitions for these endpoints will coincide with those of specified in the CALGB 80802 protocol.

Additionally, we will seek to identify potential SNP by doxorubicin interactions with respect to outcome, and seek to develop prediction models for the outcomes based on SNPs adjusted for important clinical and demographics co-variables.

We will also validate results found in other CALGB studies (e.g., 80303, 40101 and 90401) and perform a risk analysis by comparing the 80802 SNP data to SNP data from controls (patient thought not to have cancer). The latter will be obtained from public databases.

9.3.4 IL17F Methods

Aliquots of DNA will be sent to the PET committee colleagues for genotype analysis. Gentoyping for IL17F variants will be performed based on established and published methods (42). If more efficient alternative genotyping methods become available in the future, the PET committee colleagues will change the genotyping approach to optimize the resource utilization. The genotyping information will be correlated with clinical and correlative data collected in this study.

9.3.5 Genome-wide Association Samples and Platform

DNA will be available from patients who will consent to the isolation of DNA for genetic investigation. Phenotypic data will be extracted from research databases by the Alliance Statistics and Data Center. No additional samples will be obtained from patients for purposes of this research. Samples will be banked by the Alliance Biorepository at OSU. DNA quality will be assessed by UV spectrophotometry and by agarose gel electrophoresis.

Illumina's HumanHap550 Genotyping BeadChip enables whole-genome genotyping of over 555,000 single nucleotide polymorphisms (SNP) loci efficiently and accurately on a single BeadChip. The HumanHap550 BeadChip is powered by the Infinium™ II assay, which uses a single-tube, whole-genome amplification method that does not require PCR and enables intelligent SNP selection using tagSNPs. TagSNPs are loci that can serve as proxies for many other SNPs. The use of tagSNPs greatly improves the power of association studies, as the same information and power from a larger number of SNPs can be gathered by genotyping only a subset of loci. TagSNPs on the HumanHap550 BeadChip were selected from the recently completed International HapMap Project. The Illumina's HumanHap550 Genotyping BeadChip is one of the platforms that might be used in this study. However, additional platforms, including high-throughput resequencing, might be also used to interrogate the germline genomic variation of patients.

10.0 DRUG FORMULATION, AVAILABILITY, AND PREPARATION

10.1 Qualified Personnel

Qualified personnel who are familiar with procedures that minimize undue exposure to themselves and to the environment should undertake the preparation, handling, and safe disposal of chemotherapeutic agents in a self-contained, protective environment.

10.2 Dose Instructions

The total administered dose of chemotherapy may be rounded up or down within a range of 5% of the actual calculated dose.

It is not necessary to change the doses of doxorubicin due to changes in weight unless the calculated dose changes by ≥ 10%.

10.3 Sorafenib (Nexavar®) (IND 69896/NSC 724772)

AVAILABILITY

Sorafenib will be supplied and distributed by the Pharmaceutical Management Branch (PMB), Cancer Therapy Evaluation Program (CTEP), Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI).

The commercially labeled 200 mg tablets are round, biconvex, red film-coated tablets, debossed with the "Bayer cross" on one side and "200" on the other side and packaged in HDPE bottles of 120 tablets. The 200 mg tablet formulation contains: sorafenib and the excipients croscarmellose sodium, microcrystalline cellulose, hydroxypropylmethylcellulose, sodium lauryl sulfate, magnesium stearate and the coating consisting of hypromellose, polyethylengylcol, titanium dioxide and ferric oxide red. This tablet is film coated with a water-soluble polymer (hypromellose) that has no effect on the release rate of the active sorafenib. It has a red color in appearance, weighs approximately 350 mg, and is 10 mm round in shape. The active compound of sorafenib is 4-{4-[3-(4-Chloro-3-trifluoromethyl-phenyl) -ureido]-phenoxy}-pyridine-2-carboxylic acid methylamide-4-methylbenzenesulfo-nate, and its molecular weight is 465 Daltons (free base).

NOTE: Sorafenib tablets may be repackaged in HDPE pharmacy dispensing bottle other than the original container with expiration date not to exceed 30 days.

AGENT ORDERING

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

Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees 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) account < https://eapps-ctep.nci.nih.gov/iam/ > and the maintenance of an "active" account status and a

"current" password. For questions about drug orders, transfers, returns, or accountability, call (301) 496-5725 Monday through Friday between 8:30 am and 4:30 pm (ET) or email PMBAfterHours@mail.nih.gov anytime.

AGENT ACCOUNTABILITY

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

The agent supplied by CTEP, DCTD, NCI used in this protocol (Bayer/Onyx) is provided to the NCI under a Clinical Research and Development Agreement (CRADA, CTA) between Bayer/Onyx Pharmaceuticals (hereinafter referred to as Collaborator) 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) contained within the terms of the award, apply to the use of the Agent in this study:

1. Agent may not be used outside the scope of this protocol, nor can Agent be transferred or licensed to any party not participating in the clinical study. Collaborator data for Agent are confidential and proprietary to Collaborator and should 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 a 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 the NCI's participation in the proposed combination protocol.
    b. Each Collaborator shall agree to permit the 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 the 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 for Phase III 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 should be provided to CTEP by the Group Office for Cooperative Group Studies or by the 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)'s intellectual property rights, are protected. Copies of abstracts should be provided 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 should be sent to:

   Regulatory Affairs Branch, CTEP, DCTD, NCI
   NCI Shady Grove
   Room 5W520, MSC 9740
   9609 Medical Center Drive
   Bethesda, Maryland 20892
   Fax: 301-402-1584
   Email: ncicteppubs@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 the Collaborator's confidential proprietary information.

STORAGE

Store intact bottles at controlled room temperature, not to exceed 25ºC; brief excursions are permitted between 15°C and 30°C (59°F and 86°F). If a storage temperature excursion is identified, promptly return sorafenib to controlled room temperature (not to exceed 25ºC) and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

STABILITY

Stability studies are ongoing for investigationally-labeled supplies. Refer to package labeling for shelf life of commercially-labeled supplies.

ADMINISTRATION

Patients will take 2 tablets of sorafenib (200 mg tablets) twice daily, orally on a continuous basis. Patients will take two tablets two times daily, swallowed whole with approximately 250 mL of water, each morning and evening (i.e., 12-hourly). Study drug may be taken either with a moderate fat meal or without food. After a dose, patients do not have to wait before eating.

TOXICITIES

In the phase III study of sorafenib versus placebo (12), adverse events that were reported for patients receiving sorafenib were predominantly grade 1 or 2 in severity and gastrointestinal, constitutional, or dermatologic in nature. Diarrhea, weight loss, hand–foot skin reaction,

alopecia, anorexia, and voice changes also occurred. Grade 3 drug-related adverse events included diarrhea (8%), hand–foot skin reaction (8%), hypertension (2%), and abdominal pain (2%). Grade 3 hypophosphatemia (11%) and grade 3 or 4 thrombocytopenia (4%) were also noted.

In the reported randomized phase II study of doxorubicin plus sorafenib and doxorubicin plus placebo, fatigue noted in 6% of patients on each arm; and hand-foot skin reaction noted in the doxorubicin plus sorafenib arm only (6%). Diarrhea (11% and 8%); leucopenia (13% and 6%); and neutropenia (38% and 42%) were noted on the doxorubicin plus sorafenib arm and the doxorubicin plus placebo arm respectively. Most toxicities were noted to be at about the same incidence as would have been expected with the individual agents alone. Treatment emergent left ventricular systolic dysfunction (LVSD) occurred at a higher rate with doxorubicin/sorafenib compared with doxorubicin/placebo arm (19% versus 2%), but was in most cases NCI-CTC-Grade 1 and 2. One patient (2%) on the doxorubicin plus sorafenib arm had a grade 3-4 left ventricular dysfunction. Grade 1 and 2 treatment-emergent hypertension was reported in 8 subjects (17.0%) receiving doxorubicin/sorafenib and in none receiving doxorubicin/placebo. 19.1% in the doxorubicin plus sorafenib arm and five 10.2% in the doxorubicin plus placebo experienced any grade treatment emergent bleeding events. Grade 3 and 4 treatment related bleeding events occurred in two patients in the doxorubicin plus sorafenib arm, both of which were related to gastrointestinal bleeds.

10.4 Doxorubicin

Please refer to the FDA-approved package insert for doxorubicin for product information, extensive preparation instructions, and a comprehensive list of adverse events.

AVAILABILITY

Doxorubicin is commercially available as a lyophilized powder for reconstitution in 10, 20, 50 and 100 mg vials. Also available are 2 mg/mL solutions for injection in 10, 20, 50 and 200 mg vials.

STORAGE AND STABILITY

Intact vials of doxorubicin solution should be stored in the refrigerator. Intact vials of powder for reconstitution should be stored at room temperature. Reconstituted solutions are stable for 7 days at room temperature and 15 days under refrigeration when protected from light. Commercially available solutions labeled as such are intended to be multi-dose vials.

PREPARATION

Reconstitute the vials of doxorubicin powder with 5, 10, 25 or 50 mL of sodium chloride, resulting in a concentration of 2 mg/mL.

ADMINISTRATION

Doxorubicin is administered intravenously, according to institutional procedures. Avoid extravasation as severe local tissue necrosis may result.

TOXICITIES

Hematologic: leukopenia (dose-limiting), thrombocytopenia, anemia; nadir in 10-14 days with recovery usually in 21 days.

Dermatologic: alopecia (usually complete; reversible); radiation recall reactions; increased sensitivity to sunlight.

Gastrointestinal: nausea and vomiting (doxorubicin is generally considered moderately to highly emetogenic), anorexia, diarrhea, mucositis (stomatitis, esophagitis).

Cardiovascular: Cardiomyopathy may occur and is related to total cumulative lifetime dose. The risk for cardiomyopathy increases with total doses > 450 mg/m^2. ECG changes and less often, arrhythmias are seen. Rarely, sudden death has occurred.

Other: Red discoloration of urine for 24-48 hours after drug administration. Doxorubicin is a vesicant and can cause tissue necrosis if extravasated.

11.0 ANCILLARY THERAPY

11.1 Supportive Care

Patients should receive full supportive care, including transfusions of blood and blood products, erythropoietin (unless otherwise specified in the protocol), antibiotics, antiemetics, etc., when appropriate. The reason(s) for treatment, dosage, and the dates of treatment should be recorded on Form C-260 and/or C-1912 via Medidata Rave®.

11.2 Concurrent Therapy

Treatment with hormones or other chemotherapeutic agents may not be administered except for steroids given for adrenal failure; hormones administered for non-disease-related conditions (e.g., insulin for diabetes); and intermittent use of dexamethasone as an antiemetic in solid tumor protocols.

Sorafenib may prolong the QT/QTc interval. Avoid concomitant drugs that may induce QTc prolongation.

11.3 Palliative Radiation Therapy

Palliative radiation therapy may not be administered while the patient is on study treatment. A symptomatic lesion or one which may produce disability (e.g., unstable femur) may be irradiated before study initiation, provided other measurable or evaluable disease is present and radiation therapy is completed ≥ 4 weeks before start of therapy.

Patients who require radiation therapy during protocol treatment will be removed from protocol therapy due to disease progression.

11.4 Other Drug Considerations

Rifampin or St John's Wort is not allowed. Patients taking concomitant medications known to be metabolized by the liver should be closely observed for side effects. Patients taking narrow therapeutic index medications that are hepatically metabolized should be monitored proactively. These medications include warfarin, phenytoin, quinidine, carbamazepine, phenobarbital, cyclosporin, and digoxin.

Use caution when co-administering with strong CYP3A4 inducers, such as phenytoin, carbamazepine, phenobarbital and dexamethasone as they can reduce sorafenib exposure. CYP3A4 inhibitors are not expected to cause clinically relevant changes to sorafenib exposure.

Clinical data suggests sorafenib does not increase exposure of other drugs metabolized by CYP pathways and therefore does not appear to be clinically relevant. Use caution when co-administered with sensitive substrates of UGT1A1.

11.5 Alliance Policy Concerning the Use of Growth Factors

11.5.1 Filgrastim (G-CSF), Sargramostim (GM-CSF), and Pegfilgrastim

The use of a growth factor is encouraged. It is recommended to administer G-CSF or GM-CSF x 3 days, or pegfilgrastim x 1 day after each doxorubicin dose. Document details on the Form C-260 and/or C-1912 via Medidata Rave®.

11.5.2 Epoetin (EPO)

Use of epoetin in this protocol is permitted at the discretion of the treating physician.

12.0 CRITERIA FOR RESPONSE, PROGRESSION, AND RELAPSE

For the purposes of this study, patients should be reevaluated every 6 weeks. In addition to a baseline scan, confirmatory scans should also be obtained at least 6 weeks following initial documentation of objective response.

12.1 Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, and should be chosen based on their suitability for accurate repetitive measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible repeated measurements in which case the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum LD will be used as reference to further characterize the objective tumor response of the measurable dimension of the disease.

12.1.1 Complete Response: Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

12.1.2 Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

12.1.3 Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: The appearance of one or more new lesions is also considered progression).

12.1.4 Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as references the smallest sum diameters while on study.

12.2 Non-target Lesions

All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

12.2.1 Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis). Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

12.2.2 Non-complete response (non-CR)/Non-progression (non-PD): Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

12.2.3 Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally

trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of non-target lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed later on by the review panel (or study chair).

12.3 Cytology and Histology

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

These techniques can be used to differentiate between PR and CR in rare cases (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

12.4 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria (see Section 12.6.1).

For Patients with Measurable Disease (i.e., Target Disease):

Target Lesions	Non-target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required
CR	CR	No	CR	≥ 4 wks confirmation*
CR	Non-CR/Non-PD	No	PR	≥ 4 wks confirmation*
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥ 4 wks from baseline*
PD	Any	Yes or No	PD	No prior SD, PR or CR
Any	PD**	Yes or No	PD	
Any	Any	Yes	PD	

* Only for non-randomized trials with response as the primary endpoint.

** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note:

- Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration" on the Off-

treatment Form (C-300) under "other" via Medidata Rave®. Every effort should be made to document the objective progression even after discontinuation of treatment.

For Patients with Non-measurable Disease (i.e., Non-target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

12.5 Guidelines for Evaluation of Measurable Disease

If patients are enrolled on CALGB 580901, then specific image acquisition guidelines, involving triphasic CT are to be utilized.

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

12.5.1 Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g., for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

12.5.2 PET-CT: At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

12.6 Confirmation Measurement/Duration of Response

12.6.1 Confirmation

To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat studies that should be performed 6 weeks after the criteria for response are first met. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 6 weeks.

12.6.2 Duration of Overall Response

The duration of overall response is measured from the time measurement criteria are met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

12.6.3 Duration of Stable Disease

Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

13.0 REMOVAL OF PATIENTS FROM PROTOCOL THERAPY

13.1 Duration of Treatment

13.1.1 CR, PR, or SD: Continue treatment at the highest tolerable dose until the appearance of disease progression (see Section 12) or unacceptable toxicity. Doxorubicin treatment is limited (see Section 7.1).

13.1.2 Disease Progression: Give a minimum of 2 cycles of therapy. Remove from protocol therapy any patient with rapid disease progression. Document details, including tumor measurements, on Form C-1914 via Medidata Rave®.

13.2 Extraordinary Medical Circumstances

If, at any time the constraints of this protocol are detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, protocol therapy shall be discontinued. In this event:

- Notify the study chair.
- Document the reason(s) for discontinuation of therapy on Form C-1912 via Medidata Rave®.
- Follow the patient for progression, survival, or secondary malignancy for a minimum of 3 years following registration.

14.0 STATISTICAL CONSIDERATIONS

The study is based on a phase III design, with a primary endpoint of overall survival (OS). The study will enroll 480 patients over 2 years (20 patients/month) and will follow patients for an additional 15 months. Three hundred sixty-four (364) events are expected at the time of final analysis. The study will have 90% power to detect a 37% increase in median OS (10.7 to 14.7 months; 1-sided $\alpha = 0.05$). Median OS of 10.7 months is assumed for patients treated with sorafenib alone based on the results of the SHARP trial. Sample size estimates are not inflated for ineligibility; only patients ineligible due to incorrect disease histology will be omitted from analysis. Patients will be followed a maximum of three years from study entry.

The trial will employ an early stopping rule based on PFS in the first 170 patients enrolled. Analyses of OS and PFS will be stratified by extent of disease (locally advanced; metastatic). Hepatitis status (no hepatitis; hepatitis B; hepatitis C; hepatitis B and C) will be considered as a covariate.

14.1 Analysis Plan and Plans for Formal Interim Analysis

Early Stopping (Original)

The study will initially enroll 170 patients, then suspend accrual and follow for PFS for 6 months. With 170 patients enrolled over 8.5 months and followed for an additional 6 months, 90% power is achieved to detect a 50% increase in median PFS (4.0 to 6.0 months; 1-sided $\alpha = 0.15$). One hundred twenty-eight PFS events are expected at the time of this analysis. The hypothesized median PFS for sorafenib alone of 4 months is based on results from the phase II

study of sorafenib in advanced HCC (43). If the test results are favorable, accrual will resume and the trial will continue to completion (n = 480). If test results are unfavorable, the trial will close to further accrual.

14.1.1 Administrative Summary (to Update #7)

The accrual rate to this trial has been slower than expected with an average of 5.67 patients per month accrued since the first patient enrollment. Due to the longer accrual period to reach the total of 170 patients no additional follow-up is required to observe the number of expected PFS events for this analysis. The timing of the interim analysis is now estimated to occur by April 1, 2013 with results reported soon afterward. Moreover, due to revisions in eligibility criteria and trial promotion, the accrual rate in the recent six-month period from September 1, 2012 through January 31, 2013 has increased to an average of 8.8 patients per month. Suspending the trial at this time may impede the momentum of increased enrollment if the trial continues. For these reasons, the trial will not be suspended while the interim analysis is being conducted.

14.1.2 Power Estimation

One hundred seventy patients (n=170) were randomized on CALGB 80802 between June 15, 2010 and January 3, 2013. With 5.67 patients enrolled per month over 30 months and no additional follow-up, approximately 90% power is achieved to detect a 50% increase in median PFS (4.0 to 6.0 months; 1-sided $\alpha = 0.15$). One hundred thirty PFS events (d=130) are expected at the time of this analysis. The hypothesized median PFS for sorafenib alone of 4 months is based on results from the phase II study of sorafenib in advanced HCC (43). If PFS is statistically superior on the sorafenib plus doxorubin treatment arm versus the sorafenib alone treatment arm at the 0.15 significance level, accrual will resume and the trial will continue to completion (n = 480). If PFS is not statistically superior on the sorafenib plus doxorubin treatment arm versus the sorafenib alone arm at the 0.15 significance level, the trial will close to further accrual.

Interim Analysis

The total expected number of OS events is 364. Formal interim analyses for OS begin when 15% of expected events (n=55) are observed and subsequently occur every 6 months coinciding with Alliance Data Safety Monitoring Board meetings. Five interim analyses are anticipated when 0.15, 0.32, 0.54, 0.76 and 0.91 of the expected events have been observed. Three interim analyses are expected during the accrual period. The Lan-DeMets boundaries (O'Brien-Fleming analogue) will be used to test the superiority hypothesis at each interim (1-sided $\alpha = 0.05$). Futility based on the OS endpoint will be monitored using a confidence interval approach. If at any interim analysis the log of the targeted hazard ratio of 1.37 lies above the adjusted 95.0% upper confidence bound for the observed log hazard ratio, the trial will be terminated. The confidence bound estimates for futility will also be adjusted according to the Lan-DeMets analogue of the O'Brien-Fleming boundaries (44).

Adverse Event Monitoring

Cardiac toxicity will be formally monitored in the 240 patients randomized to sorafenib plus doxorubicin when approximately 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9 and 1.00 of the 240 patients have been enrolled. Cardiac toxicity will be defined as the development of grade 3 or more Ejection Fraction Decreased (per CTCAE v 4.0). The null hypothesis that cardiac toxicity is 0.05 versus the alternative that it is 0.084 will be tested using a one-sample exact test of a binomial proportion. The unadjusted power to test this hypothesis with 240 patients studied is 80% (1-sided, $\alpha = 0.10$). The 1-sided, $\alpha = 0.10$, Lan-DeMets boundaries (Pocock analogue) will be used to test this hypothesis when the specified proportions of data are available. If at any

interim analysis the proportion of patients with cardiac toxicity is found to be significantly greater than 0.05 (an interim boundary is crossed) a review of the toxic events and a determination regarding the toxicity will be made. Accrual to the trial will be suspended while this review is ongoing. Excess cardiac toxicity will be addressed, as appropriate, for example, by amending the treatment schedule. Trial closure may also be considered.

14.2 Accrual Information

Accrual Rate: 20 patients/month.

The accrual is based on an initial estimate reflecting the accrual of previous phase II studies in HCC conducted by different institutions or groups, and upon the participation of additional groups including ECOG, SWOG, and NCI-C.

Total Expected Accrual: 170 min 480 max.

We expect to accrue more men than women because of the epidemiology of the disease. We also expect in sites to have certain ethnic groups over- or under-represented because of the association of risk factors with certain ethnicities. However, we do not expect any differences in accrual compared to historical controls.

The Alliance Statistics and Data Center will submit quarterly reports to CTEP by electronic means using the Clinical Data Update System (CDUS).

14.3 Statistical Considerations for Imaging Companion 580901

The distributional characteristics of each measure after the first radiologic assessment will be described overall and by treatment arm. The relationships between tumor necrosis (TN) and tumor volume (TV) over time will also be described.

The association between percent TN after the first radiologic assessment and OS will be investigated. Analyses will be conducted within each treatment arm and, if appropriate, across treatment arms. No preliminary data regarding a %TN cut point are available. Patients will be categorized according to tertiles based on the percent TN distribution. Estimates of OS will be computed within each category. OS within the third tertile will each be compared to OS within the lowest tertile. It is hypothesized that increases in the percent TN will result in prolonged OS.

We anticipate TN measurements to be available on at least 75% of patients (n=360; 180 per treatment arm) enrolled. No preliminary data are available regarding a %TN cut point that distinguishes patients by OS.

With 180 patients studied for TN per treatment arm an OS hazard ratio of 1.66 between the highest and lowest tertiles (within the sorafenib treatment arm) is detectable with approximately 80% power (2-sided α=0.1; based on approximately 96 expected deaths in the lowest and highest tertiles in the sorafenib treatment arm). Similarly, an OS hazard ratio of 1.71 between the highest and lowest tertiles within the combination treatment arm is detectable with approximately 80% power (2-sided α=0.1; based on 84 expected deaths in the lowest and highest tertiles).

14.4 Statistical Considerations for Correlative Substudy 150902

Evaluation of circulating biomarkers: We expect to obtain plasma and serum samples for at least two time points on 85% of patients (n=408). For power estimation, differences between the baseline and first post-treatment biomarker measurement of glycosylation will be categorized as low and high at the median. A test of interaction between treatment and change in the biomarker for OS will be run using the Cox proportional hazards model. With approximately 309 expected events, an interaction hazard ratio of approximately 1.77 can be detected with 80% power (2-sided α=0.1) (45). If no interaction is detected, differences in change (categorized as low vs. high) in the biomarker will be studied in the combined treatment

groups. With approximately 309 expected events, a hazard ratio of 1.4 for OS can be detected with 90% power (2-sided α=0.05).

Evaluation of viral titers: We expect to obtain viral titers for at least two time points on 33% of patients (n=158). Samples will be stored and analyzed retrospectively at the end of the follow-up period. Laboratory investigators will be blinded to patient identity and outcomes.

The primary endpoint for this analysis is the proportion of patients with undetectable viral load determined as < 50 copies/mL at 15 weeks. The number of copies/mL will be measured by TaqMan PCR. Secondary endpoints include change in viral load defined as: 1) > 2 log decrease in viral load versus ≤ 2 log decrease in viral load at 6 weeks, 9 weeks, and 15 weeks versus baseline viral load and 2) change in the number of copies/mL at 6 weeks, 9 weeks, and 15 weeks versus the number of copies/mL at baseline.

The proportion of patients with undetectable viral load at Week 15 will be estimated within each treatment group. With 79 patients studied in each treatment group, the proportion of patients with undetectable viral load at 15 weeks on the two treatment regimens can be estimated to within at most +/- 0.11. The numbers of copies/mL and the proportions of patients with undetectable viral load will be estimated at each time point (6 weeks, 9 weeks, and 15 weeks from the start of therapy) and within each treatment arm (sorafenib; sorafenib + doxorubicin). Descriptive statistics will be computed for the number of copies/mL within each treatment group at each time point. No preliminary data are available for these measurements. Differences over time and between treatments will be investigated using regression methods. Measurements may be transformed by log 10 to achieve normality. Prior exposure to IFN will also be considered as a covariate.

Associations between the proportions of patients with undetectable viral load, change in viral load, and OS and PFS outcomes will be studied. Approximately 120 deaths (OS events) and 152 recurrences or deaths (PFS events) are expected among the 158 patients studied at the time of the final analysis.

For power estimation, differences in viral load will be categorized as undetectable and detectable (< 50 copies/mL; ≥ 50 copies/mL) at Week 15. A test of interaction between viral load at Week 15 and treatment with sorafenib or sorafenib plus doxorubicin for OS and PFS will be run using the Cox proportional hazards model. With 120 expected OS events, an interaction hazard ratio of approximately 2.5 can be detected with 80% power (2-sided α=0.1) (46). If no interaction is detected and 120 OS events are observed, a hazard ratio of 1.57 for OS can be detected with 80% power (2-sided α=0.1). With approximately 152 expected PFS events, an interaction hazard ratio of approximately 2.25 can be detected with 80% power (2-sided α=0.1) (46). If no interaction is detected and 152 PFS events are observed, a hazard ratio of 1.49 for PFS can be detected with 80% power (2-sided α=0.1). These analyses will be stratified by prior IFN exposure (no prior exposure; exposure).

Similarly, associations between viral load at Week 15, change in viral load (as defined above) and response as measured by RECIST criteria will also be studied. The logistic regression model will be used to test these hypotheses (47).

Specimens will be genotyped at baseline and at 15 weeks after the start of treatment. Greater than 80% of patients are expected to be genotype 1 (versus 2+3) at baseline. Response and decline in viral load will be described by genotype (1; 2+3). Quasispecies changes (resistant mutations) will be investigated for patients who exhibit "virologic failure" (a reversal from undetectable (<50 copies/mL) to detectable (≥ 50 copies/mL) viral load, or an increase of 2 logs above nadir) during the study period. These analyses will be descriptive.

If accrual to the trial stops at the interim analysis based on PFS (n=170), we will have approximately 56 patients (28 patients per treatment group) with HCV for study. This sample

size may limit the ability to achieve the objectives. In this case, analyses will be considered exploratory and hypothesis-generating.

14.5 Statistical Considerations for PET Companion 60901

14.5.1 Candidate Gene Analysis

A total of 480 patients are to be randomized to the study. It is assumed that 85% of these patients will provide consent and usable samples for this companion study. The analysis population will consist of those self-reported as Caucasian on the CRF form. The expected proportion for this population is 0.85. As such, the companion study will be powered based on a sample size of 346 (=480*0.85*0.85).

According to the clinical design, the assumed times to death distributions for the two arms are hypothesized to be exponential with medians of 10.7 and 14.7 months, respectively. The follow-up distribution is assumed to be uniform on the interval (15,24+15) months.

Based on the CALGB genome-wide association study, the relative genotypic frequencies were 0.92, 0.08 and 0 for AA, AG and GG respectively. We will power the analyses for the dominant (in the G allele) model assuming relative frequencies of 0.92 and 0.08 for the {AA} and {AG, GG} groups, respectively. For the power calculations, it will be assumed that the OS distribution for the control arm is expressible as a mixture of exponential laws of the form P(T1>t)=0.92*exp[-lam1,0*t]+0.08*exp[-lam1,0*D*t] where D>=1. Similarly for the experimental arm, the OS distribution will be expressed as P(T2>t)=0.92*exp[-lam2,0*t]+0.08*exp[-lam2,0*D*t]. In the power calculations, we will set P(T1>t)=0.5 for t=10.7, P(T2>t)=0.5 for t=14.7 and then solve for lam1,0 and lam2,0.

Under the above assumptions, the power of the two-sample log-rank test, at the one-sided 0.05 level, is 0.85 and 0.94 for hazard ratios of 1.8 and 2, respectively. The power was approximated using B=10,000 simulation replicates. It is noted that the estimated hazard ratio, within a proportional hazards framework, was 3.2 (95%CI=2.1,5.1).

It is also noted that this is a hypothesis of association (gene by outcome) and not a hypothesis of interaction (gene by drug with respect to outcome). Any potential interaction will be investigated using a log-linear multiplicative logistic model.

The addition of other important clinical and demographic co-variables will be considered. Multivariable models, with molecular, clinical and demographic variables, will be constructed using conditional inference trees and random forests. The primary objective will be tested at the one-sided level of 0.05. All secondary and exploratory objectives will be tested at an unadjusted two-sided level of 0.05.

Secondary analyses will also look into additional candidate genes of treatment outcomes, including PFS and toxicity of chemotherapy.

14.5.2 GWAS Pre-processing

For pre-processing (quality control and genotype calls) the Illumina chips, we will use the commercial program Bead Studio, developed by Illumina. Although Illumina does not provide a Linux port of Bead Studio, one can run the software on VMWARE, running on a Linux host. A two CPU dual core (four cores) AMD Operation Socket F workstation, with 16GB of RAM, will be available for this purpose. The statistical analyses will be carried out on a Linux server with 8 dual core Operation Socket F CPUs (16 cores) with 64GB of RAM (expandable to 128GB if needed).

14.5.3 Analyses to assess genotyping quality and population stratifications

Initial quality studies will be conducted to identify SNPs that have generated sufficiently poor quality genotype data that they should be removed from analyses. Call rate, patterns of missing data, and departures from Hardy-Weinberg equilibrium (HWE) using an exact test will all be scrutinized to identify markers that will not be used in analysis. In general, SNPs with call rates < 95% and those with highly significant departures from HWE ($p<10^{-7}$) will not be included in analyses. Non-random patterns of missing data are sometimes encountered in data generated on high-throughput genotyping platforms; the most common non-random missing data problem is that heterozygous genotypes are more likely to be assigned as missing than either homozygous genotype. We will perform analyses using blind duplicates as well as analyses assessing the relationship between heterozygous call rates and missing data to identify any SNPs in which data are clearly not missing at random. Depending on the number and degree of difficulty observed, we will either remove problematic SNPs from analysis, or assign quality scores to reflect the extent of the non-random missing data.

Additional preliminary quality control analyses will be conducted to ensure that the sample does not include duplicated samples or closely related individuals. These analyses can be rapidly conducted using PLINK (48). Duplicated samples (or unrecognized identical twins) will be reduced to a single sample for further analyses. Although we do not expect to have closely related individuals included in this sample, only one member of any set of first-degree relatives will be included in subsequent analysis.

Population structure that is not appropriately recognized and accommodated can lead to both false positive and false negative results in association studies. We will conduct studies using structure (49) to estimate ancestry proportions using 10,000 SNPs chosen for having no pairwise LD with unrelated individuals from the HapMap CEU, YRI and CHB+JPT samples used to model the ancestral populations. Substantial previous research has shown this to be a rapid and effective approach to defining historical geographic ancestry. Although self-identified race/ethnicity is usually highly correlated with estimated historical geographic ancestry, there are often a few individuals who appear to be misclassified with self-defined labels, and it is the genetically defined ancestry that is critical to correctly accommodate to insure robust results from association studies.

Each individual will then have estimates of European, African and Asian ancestry. For individuals with high ancestry proportion for a single group (> 98%), we will conduct further analyses with eigenstrat (50) using all SNPs to determine whether there are additional important sources of variation among individuals leading to detectable stratification by allele frequencies (reflecting, for example, differences in ethnic make-up within individuals of European descent from different U.S. cities from which subjects for the trial were obtained). Primary analyses, described below, will be conducted within groups defined by historical geographic ancestry. Secondary analyses will be conducted using logistic regression with ancestry proportions (and any additional stratification identified using eigenstrat) as covariates.

14.5.4 Feature discovery

The association between the genotype call (say AA, AB or BB) for each autosomal SNP and OS will be carried out using a univariable Cox model. Let lam0[t],lam1[t] and lam2[t], denote the hazard rate at time t conditional on having 0, 1 or 2 copies of the B allele.

For the power calculations we will assume that the SNPs satisfy HWE and that the OS distribution for the control arm is expressible as a mixture of exponential laws of the form P(T1>t)=(1-q)2exp[-lam1,0*t]+2*q*(1-q)exp[-lam1,1*t]+q2exp[-lam 1,2*t] where q

denotes the relative frequency of the B allele and lam1 the exponential hazard rate specified in the clinical protocol. Similarly for arm 2, we will assume a mixture distribution of the form P(T2>t)=(1-q)2exp[-lam2,0*t]+2*q*(1-q)exp[-lam 2,1*t]+q2exp[-lam2,2*t]. In the power calculations, we will set P(T1>t)=0.5 for t=10.7, P(T2>t)=0.5 for t=14.7 and then solve for lam1,0 and lam2,0.

We will power the study for the additive genetic model with no drug interaction. In other words, for some D>1,

P(T1>t)=(1-q)2exp[-lam1,0*t]+2*q*(1-q)exp[-lam1,0*D*t]+q2exp[-lam1,0*D2*t] and

P(T2>t)=(1-q)2exp[-lam2,0*t]+2*q*(1-q)exp[-lam2,0*D*t]+q2exp[lam2,0*D2*t] for some 0<lam2,0<lam1,0.

A total of 480 patients are to be randomized to the study. It is assumed that 85% of these patients will provide consent and usable samples for this companion study. The analysis population will consist of those self-reported as Caucasian on the CRF form. The expected proportion for this population is 0.85. As such, the companion study will be powered based on a sample size of 346 (=480*0.85*0.85).

According to the clinical design, the assumed times to death distributions for the two arms are hypothesized to be exponential with medians of 10.7 and 14.7 months respectively. The follow-up distribution is assumed to be uniform on the interval (15,24+15) months.

A feature (SNP) will be considered significant if the corresponding nominal unadjusted two-sided P-value is less than 0.05/K, where K is number of features which pass the pre-processing step. Needless to say, this approach may be conservative. It does however guarantee strict type I error control. It is expected that these samples will be genotyped on the Illumina 610Quad platform. The power, at the two-sided 0.05/600000 level (i.e., assuming K=600,000 autosomal SNP markers pass through the pre-processing step), is illustrated in Table 1. The Cox statistics, coding the genotypes AA, AB, and BB as 0, 1, and 2 is used. Each case is based on 10,000 simulation replicates. In addition to the additive model, we provide power calculations for the recessive (i.e., lam0=lam1,lam2-lam0*D) and dominant (i.e., lam1=lam2=lam0*D) models if the test based on the additive model is used.

Table 1. Power illustration

Hazard Ratio (D)										
q	**model**	**2**	**2.2**	**2.4**	**2.6**	**2.8**	**3.0**	**3.2**	**3.4**	**3.6**
0.1	additive	0.4068	0.6636	0.8300	0.9369	0.9767	0.9931	0.9980	0.9993	0.9998
	dominant	0.2408	0.4482	0.6656	0.8250	0.9143	0.9634	0.9853	0.9938	0.9965
	recessive	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
0.2	additive	0.8623	0.9689	0.9961	0.9996	1.0000	1.0000	1.0000	1.0000	1.0000
	dominant	0.4260	0.6905	0.8639	0.9527	0.9864	0.9960	0.9994	1.0000	1.0000
	recessive	0.0001	0.0002	0.0000	0.0006	0.0001	0.0002	0.0008	0.0005	0.0005
0.3	additive	0.9678	0.9958	0.9999	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000
	dominant	0.3575	0.6119	0.8143	0.9215	0.9705	0.9893	0.9979	0.9991	0.9999
	recessive	0.0006	0.0018	0.0033	0.0067	0.0095	0.0165	0.0191	0.0272	0.0337
0.4	additive	0.9827	0.9987	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000
	dominant	0.1903	0.3671	0.5577	0.7305	0.8487	0.9193	0.9642	0.9801	0.9910
	recessive	0.0104	0.0256	0.0509	0.0912	0.1525	0.2144	0.2814	0.3534	0.4274
0.5	additive	0.9860	0.9988	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000
	dominant	0.0512	0.1125	0.2143	0.3421	0.4595	0.5796	0.6774	0.7574	0.8263
	recessive	0.0631	0.1589	0.2912	0.4445	0.5887	0.7241	0.8254	0.8852	0.9280
0.6	additive	0.9685	0.9966	0.9996	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000
	dominant	0.0070	0.0154	0.0298	0.0484	0.0817	0.1286	0.1705	0.2181	0.2782
	recessive	0.1911	0.3989	0.6151	0.8037	0.9030	0.9585	0.9817	0.9936	0.9975
0.7	additive	0.8850	0.9807	0.9973	0.9994	1.0000	1.0000	1.0000	1.0000	1.0000
	dominant	0.0004	0.0007	0.0016	0.0030	0.0033	0.0069	0.0076	0.0110	0.0145
	recessive	0.2957	0.5436	0.7618	0.9040	0.9667	0.9877	0.9967	0.9988	0.9998
0.8	additive	0.5817	0.8194	0.9327	0.9822	0.9957	0.9986	0.9998	1.0000	1.0000
	dominant	0.0000	0.0000	0.0001	0.0000	0.0001	0.0001	0.0000	0.0002	0.0001
	recessive	0.2332	0.4609	0.6755	0.8372	0.9282	0.9708	0.9882	0.9968	0.9985
0.9	additive	0.0613	0.1668	0.2977	0.4486	0.5924	0.7114	0.7994	0.8720	0.9152
	dominant	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
	recessive	0.0374	0.0928	0.2019	0.3193	0.4670	0.5888	0.6998	0.7729	0.8415

14.5.5 Submission of molecular data

The laboratory of Dr. Yusuke Nakamura will submit the Illumina*.idat image files using secure means to the Alliance Statistics and Data Center. The lab will also submit a table along with this transmission, which at the minimum will provide the following information for each sample received from the repository.

- The lab ID number provided by the repository.
- The experimental ID, a concatenation of the plate, well and replicate information, generated by the lab.
- The idat file names (the file string name will contain Lab ID).
- The md5sum signature of the idat files to ensure data integrity.
- The date the specimen was received from the repository.
- The date the sample was analyzed by the RIKEN laboratory.

Additionally, the lab will also provide the complete results from any quality control measurers carried out. If a sample had to be redone (e.g., defective or poor quality array), the lab will provide all replicate idat files and add an appropriate column to the supplementary table. The molecular data generated for this aim may not be shared with other investigators or used for any analysis not specified in the protocol until a formal approval from the Alliance Statistical Center is obtained.

14.5.6 Secondary objectives

Other clinical endpoints such as overall-survival and toxicity are of interest. The definitions for these will coincide with those of the clinical protocol. Note that due to small sample size, we are primarily focusing on finding prognostic features. From a pharmacogenetic point of view, what is of greater interest is to validate existing or find novel predictive markers. This will be done in the context of multiplicative two-way ANOVA log-linear Cox (logistic) for censored (binary) outcomes.

Logistic regression models and conditional inference trees (or more generally conditional random forests) will be used to construct multi-variable models based on the SNPs identified as interesting. These models also allow for inclusion of other potentially relevant clinical demographic variables.

The Illumina HuamaHap610 Quad contains 4,300 SNPs in regions with common copy number variants (CNVs). Given the complex structure of CNVs, it is not always clear how to define the genotype of a CNV. Instead of categorizing copy numbers into genotypes, we will estimate relative genomic abundance probe intensities. This approach allows for the consideration of other CNVs beyond deletions, including duplications and combinations of both. For notational brevity, we shall refer to these as CNV markers.

For each objective, the association between each CNV marker and the clinical AE endpoint will be assessed using the Wilcoxon two-sample test. The family-wise error rate will be controlled at the 0.05 level using permutation resampling (based on B=10,000 replicates).

Regression methods, as in the case of the SNP markers, will be employed to construct multivariable models based on the CVN markers.

Secondary relevant clinical endpoints include other adverse events (e.g., proteinuria, hypertension, and other common side effects of study drugs) and overall survival. For censored time-to-event outcomes, the stratified log-rank test will be primarily used for assessment of significance.

A risk analysis will be carried out by comparing the genotypic distributions of the SNPs from the CALGB 80802 data to those from controls (thought to not have cancer). The SNP data from the controls will be obtained from public databases.

In addition to conduction analyses on all features directly assessed on the high-throughput platform used in these studies, we will also interrogate all additional HapMap SNPs that are not in strong pairwise LD with any genotyped SNP, but for which there is sufficient multi-locus LD to SNPs on the high-throughput platform. Testing UNtyped Alleles (TUNA) is a robust approach for conducting such analyses that provides inexpensive in silico follow up to the initial analysis and allows us to more efficient design any follow up genotyping studies (51, 52). For example, use of Illumina HumanHap300 enables direct testing of 270K-450K SNPs, and indirect testing of 750K-1.5M additional SNPs (i.e., these SNPs are so highly correlated with SNPs that are directly tested for association that testing them would provide little additional information). The ranges given above, bracket the expectations for different human populations, with European populations at the high end of the range, and populations of recent African descent at the lower end. Use of TUNA enables interrogation of an additional 100K-250K SNPs that are neither on the platform nor highly correlated with any individual SNP on the platform. Note that use of TUNA will facilitate comparisons to genome-wide association studies on potentially related phenotypes (e.g., clinical trials of the same or related drugs) conducted using other high-throughput platforms or candidate gene studies utilizing SNPs not directly genotyped on the high-throughput platform chosen for our studies.

Finally, we note that the methodology field for the analysis of genome-wide SNP data is in its infancy. We will consider the employment of "newer" methods if they are deemed to be statistically sound and enable us to better interrogate, and more importantly, understand the data.

14.5.7 Statistical software

The R statistical environment (53) and Bioconductor (54) packages will be used for all of the primary statistical analyses relating features to phenotypes. Specialized statistical genetics software, including PLINK (48) structure (49), eigenstrat (50) and TUNA (51, 52) will be used for some of the quality or secondary analyses, and R will be used for logistic regression analyses allowing for ancestry covariates.

15.0 ADVERSE EVENT REPORTING (AER)

Investigators are required by Federal Regulations to report serious adverse events as defined in the table below. Alliance investigators are required to notify the Investigational Drug Branch (IDB), the Alliance Protocol Operations Program Office, the study chair, and their Institutional Review Board if a patient has a reportable serious adverse event. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting beginning October 1, 2010. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP Web site (http://ctep.cancer.gov). All reactions determined to be "reportable" in an expedited manner must be reported using the NCI CTEP Adverse Event Reporting System (CTEP-AERS).

Phase 2 and 3 Trials Utilizing an Agent under a CTEP IND or non-CTEP IND: CTEP-AERS Expedited Reporting Requirements for Adverse Events That Occur Within 30 Days[1] of the Last Dose of the Investigational Agent

	Grade 1	Grade 2	Grade 2	Grade 3		Grade 3		Grades 4 & 5[2]	Grades 4 & 5[2]
				Unexpected		Expected			
	Unexpected and Expected	Unexpected	Expected	with Hospitalization	without Hospitalization	with Hospitalization	without Hospitalization	Unexpected	Expected
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-Hrs; 5 Calendar Days	10 Calendar Days

[1] **Adverse events with attribution of possible, probable, or definite that occur greater 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.

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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 defined:
  - "24 hours; 5 calendar days" – The investigator must initially report the AE via CTEP-AERS within 24 hours of learning of the event followed by a complete CTEP-AERS report within 5 calendar days of the initial 24-hour report.
  - "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 (see below).

- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via CTEP-AERS if the event occurs following treatment with an agent under a CTEP IND.
- Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.
- In the rare occurrence when Internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once Internet connectivity is restored, the 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.

Additional Instructions or Exclusion to CTEP-AERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing an Agent Under a CTEP IND or non-CTEP IND:

- All adverse events reported via CTEP-AERS (i.e., serious adverse events) should also be forwarded to your local IRB.
- CALGB 80802 uses a drug under a CTEP IND. The reporting requirements for investigational agents under a CTEP IND should be followed for all agents (any arm) in this trial.
- Grade 3/4 hematosuppression and hospitalization resulting from such do not require CTEP-AERS, but should be submitted as part of study results. All other grade 3, 4, or 5 adverse events that precipitate hospitalization or prolong an existing hospitalization must be reported via CTEP-AERS.
- Reporting of cases of secondary AML/MDS and any new primary malignancy is to be done using CTEP-AERS. New primary malignancies should also be reported using study form C-1001 via Medidata Rave®.
- Treatment expected adverse events include those listed in Section 10.0 in the package insert and in the CAEPR for sorafenib. Note: the ASAEL column of the sorafenib CAEPR has been replaced with the specific protocol exceptions to expedited reporting (SPEER) list. This list now includes “expected” severity grades in addition to event terms.

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

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)***
	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)***

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%)**	
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)		
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)***

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%)**	
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)***
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[5]		
	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)***

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%)**	
		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.

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APPENDIX I

Child-Pugh Classification

Child-Pugh classification of severity of hepatocellular carcinoma according to the degree of encephalopathy and ascites, prothrombin time, and concentrations of total bilirubin and albumin.

	Points Scored for Observed Findings		
	1	**2**	**3**
Encephalopathy grade*	None	1 or 2	3 or 4
Ascites	Absent	Slight	Moderate
Total bilirubin, mg/dL	<2	2 to 3	>3.0
Albumin, g/dL	>3.5	2.8-3.5	<2.8
Prothrombin time, PT/INR	<1.7	1.7-2.3	>2.3

A total score of 5-6 points is considered grade A (low risk); 7-9 points is grade B (moderate risk); and 10-15 points is grade C (poor operative risk).

*Encephalopathy grades:

Grade 0: normal consciousness, personality, neurological examination, electroencephalogram

Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cps waves

Grade 2: lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves

Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves

Grade 4: unarousable coma, no personality/behavior, decerebrate, slow 2-3 cps delta activity