

**NCCTG N0745: Phase I/II Randomized Trial of Sorafenib and Bevacizumab as First-Line Therapy
in Patients with Locally Advanced or Metastatic Hepatocellular Carcinoma**

Fast Facts

Provided Drug: Bevacizumab

Inclusion Criteria

1. ≥ 18 years of age.
2. Histologically or cytologically confirmed diagnosis of hepatocellular carcinoma that is locally advanced or metastatic and is not amenable to treatment with surgery or to orthotopic liver transplant.
3. Child Pugh class A or B7 liver disease (see Appendix VI)
4. Patients must have measurable disease as defined in Section 11.0
5. Prior chemoembolization, radioembolization, radiofrequency ablation (RFA), or other local ablative therapies are permissible if ≥ 6 weeks from procedure with evidence of progression or new metastatic disease, if applicable.
6. Esophagogastroduodenoscopy (EGD) for evaluation and treatment of known or clinically suspected esophageal varices ≤ 6 months prior to registration, if applicable.
7. ECOG Performance Status (PS) 0 or 1.
8. The following laboratory values obtained ≤ 14 days prior to registration.
 - a. ANC $\geq 1,200/\text{mm}^3$ (cells/uL)
 - b. PLT $\geq 75,000/\text{mm}^3$
 - c. HgB ≥ 9.0 g/dL
 - d. Total bilirubin $\leq 1.5 \times$ UNL
 - e. SGOT (AST) $\leq 5 \times$ UNL
 - f. Alkaline phosphatase $\leq 5 \times$ UNL
 - g. Urine protein $\leq 1+$ Urine Protein Creatinine (UPC) ratio or urine dip stick.
If $>1+$, 24-hour urine collection should be performed. If <1 gm of protein, the patient is eligible.
9. Negative pregnancy test done ≤ 7 days prior to registration, for women of childbearing potential only.
10. Men or women of childbearing potential must agree to use adequate contraception (barrier method of birth control) prior to study entry and for the duration of study participation. Men and women should continue to use adequate birth control for at least 2 weeks after the last administration of sorafenib alone or for at least 6 months after the last administration of combined sorafenib and bevacizumab. This study involves agents whose genotoxic, mutagenic and teratogenic effects on the developing fetus and newborn are unknown.
11. Ability to understand and the willingness to sign a written informed consent
12. Willing to return to NCCTG enrolling institution for follow-up every 4 weeks.
13. Willing to provide mandatory blood samples for research purposes
14. Willing to provide mandatory tissue specimen for central review of diagnosis.
15. Life expectancy of ≥ 3 months.

Exclusion Criteria

1. Mixed cholangiocarcinoma/hepatocellular carcinoma.
2. Current or previously resected brain metastases
3. History of allergic reactions attributed to compounds of similar chemical or biologic composition to bevacizumab or sorafenib.
4. Prior systemic chemotherapy regimens for hepatocellular carcinoma
5. Prior external beam radiation to the primary site.
6. Radiation (if given for another malignancy) to ≥ 25 percent of the bone marrow.
7. Prior biologic, hormone, or immune therapy ≤ 4 weeks prior to registration.
8. Uncontrolled hypertension defined as systolic blood pressure > 150 mmHg or diastolic blood pressure > 100 mmHg despite optimal medical management.
9. Congestive heart failure (New York Heart Association classification III or IV). Note: Patients classified as NYHA class II controlled with treatment may participate with increased monitoring as outlined in Section 4.0, footnote 10.
10. Cardiac ventricular arrhythmias requiring anti-arrhythmic therapy.

11. Any of the following ≤ 6 months: transient ischemic attack, cerebrovascular accident, cardiac arrhythmia, unstable angina or angina requiring surgical or medical intervention. Patients with clinical significant peripheral artery disease (i.e., claudication in less than one block) or any other arterial thrombotic event are also ineligible.
12. QTc interval >500 msec on baseline EKG
13. Serious or non-healing wound, ulcer or bone fracture.
14. Major surgical procedure, open biopsy, or significant traumatic injury ≤ 4 weeks prior to registration or anticipation of need for major surgical procedure during the course of the study.
15. Any of the following:
 - Pregnant women
 - Nursing women
 - Men or women of childbearing potential who are unwilling to employ adequate contraception for the duration of study participation. Men and women should continue to use adequate birth control for at least 3 months after the last administration of sorafenib and 6 months after the last administration of bevacizumab. This study involves agents whose genotoxic, mutagenic and teratogenic effects on the developing fetus and newborn are unknown.
16. Co-morbid systemic illnesses or other severe concurrent disease which, in the judgment of the investigator, would make the patient inappropriate for entry into this study or interfere significantly with the proper assessment of safety and toxicity of the prescribed regimens.
17. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, or psychiatric illness/social situations that would limit compliance with study requirements.
18. Receiving any investigational agent which would be considered as a treatment for the primary neoplasm.
19. Active other malignancy ≤ 3 years prior to registration, excepting non-melanotic skin cancer or carcinoma-in-situ of the cervix. If there is a history of prior malignancy, they must not be receiving other specific treatment (other than hormonal therapy) for their cancer.
20. Patients on any anticoagulant except those receiving low-dose warfarin or heparin for deep venous thrombosis prophylaxis [not treatment].
21. History of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess ≤ 6 months prior to registration.
22. Evidence of bleeding diathesis (greater than normal risk of bleeding) or coagulopathy (in the absence of therapeutic anticoagulation).
23. Active or recent history of hemoptysis ($\geq \frac{1}{2}$ teaspoon of bright red blood per episode) ≤ 30 days prior to registration
24. Core biopsy or other minor surgical procedures ≤ 7 days prior to registration. NOTE: Placement of a vascular access device is allowed.
25. Significant vascular disease (e.g., aortic aneurysm, aortic dissection) or recent peripheral arterial thrombosis ≤ 6 months prior to registration.
26. History of hypertensive crisis or hypertensive encephalopathy.
27. Any of the following risk factors for decreased left ventricular ejection fraction (LVEF):
 - Prior treatment with anthracyclines
 - Prior central thoracic radiation therapy (RT), including RT to the heart
 - History of myocardial infarction (MI) within last 12 months

Pre-Study Parameters

1. History and physical including height, weight, BP, performance status, Child-Pugh Classification
2. Labs including CBC with differential, CMP, amylase, lipase, Alpha-fetoprotein, urine protein, pregnancy test for women of child-bearing potential
3. PT/INR, aPTT, fibrinogen (for those patients taking warfarin)
4. EGD, EKG, MUGA or Echo, CT or MRI for tumor measurement, CXR (if CT chest not done)

Treatment

Phase I – Dose finding

Cycle = 28 days

Arm A

Drug	Starting Dose	Route	Frequency
Bevacizumab	1.25 mg/kg*	IV	Days 1 and 15
Sorafenib	400 mg BID*	PO	Every 5 days out of 7

*See section 7.1 for details regarding dose escalation and de-escalation.
Bevacizumab and Sorafenib provided.

Phase II

Cycle = 28 days

Arm B

Drug	Dose	Route	Frequency
Bevacizumab	MTD determined from Phase I	IV	Days 1 and 15
Sorafenib	MTD determined from Phase I	PO	Daily or TBD from Phase I

Arm C

Drug	Dose	Route	Frequency
Sorafenib	MTD determined from Phase I	PO	Daily or TBD from Phase I

MTD = maximum tolerated dose

See section 7.2 for further details.

Bevacizumab and Sorafenib provided.