The University of Texas M. D. Anderson Cancer Center
Department of GI Medical Oncology

A Phase II Trial of Erlotinib plus Bevacizumab in Advanced Hepatocellular Carcinoma as a Second-line Therapy in Patients Who Have Received First-line Sorafenib Therapy

Study Drugs
Bevacizumab (Avastin®)
Erlotinib (Tarceva)

Support Provided By
Genentech, Inc.
OSI

Principal Investigator
Ahmed O Kaseb, MD*
akaseb@mdanderson.org

Sub-Investigators
Christopher Garrett, MD*
Milind Javle, MD*
Gauri Varadhachary, MD*
Linus Ho, MD*
Kanwal P. Raghav*

*U. T. M. D. Anderson Cancer Center,
Department of GI Medical Oncology, Unit 426
1515 Holcombe Blvd, Houston, TX 77030

Study Statistician
Jeffrey Morris, PhD
U. T. M. D. Anderson Cancer Center, Department of Biostatistics

Genentech Study Number: AVF4572

Protocol Version Date: 11/1/13

TABLE OF CONTENTS

Page #

REFERENCES

APPENDICES

1.0 BACKGROUND

Hepatocellular cancer (HCC) is the most common primary neoplasm of the liver, accounting for almost half a million deaths annually worldwide. Although the incidence of HCC is particularly high in parts of Asia and Africa, recent studies have documented a clear rise in the number of cases in Japan, Western Europe, and the United States, largely because of the increase in hepatitis C–related liver disease.[1] Unfortunately, most patients with HCC are not candidates for any curative treatments because of advanced disease at presentation and/or a background of chronic liver disease. Furthermore, the growth of HCC depends on stimulatory effects of various growth factors, which bind to tyrosine kinase receptors and hence activate various intracellular signaling pathways which subsequently lead to tumor cell proliferation, survival, migration and metastasis. Therefore, both the extracellular growth factors and the intracellular signaling pathways represent potential molecular targets for therapy of HCC. However, the anti-angiogenic pathway looks more promising in HCC.

1.1 DISEASE BACKGROUND

HCC is potentially curable by surgical resection and liver transplantation. However, the majority of patients present with advanced stage disease, which is most commonly accompanied by severe background liver disease. Hence, surgery is feasible for only a small fraction of patients with localized disease, and liver transplantation is severely limited by the availability of liver donors. Systemic cytotoxic therapies have demonstrated a very limited impact on the natural history of advanced HCC.

Molecular characterization of HCC has led to the recognition of defined aberrant signaling pathways which helped in subsequent development of targeted agents as potential choices for the treatment of this chemoresistant disease. In HCC, several crucial intracellular signaling pathways such as the Ras/Raf/Mek/Erk (Methyl ethyl ketone/Extracellular Signal-regulated kinase) pathway and PI3k/Akt/mTOR (mammalian target of rapamycin) pathway, in addition to several growth and angiogenic factors/receptors such as EGFR (Epidermal Growth Factor Receptor), PDGFR (platelet-derived growth factor receptor), FGFR (fibroblast growth factor receptor), and VEGFR (Vascular Endothelial Growth Factor Receptor) have been recognized as outlined in a recent review. [2] Subsequently, targeted agents have entered clinical trials in HCC patients. This is of particular significance for HCC in light of the lack of existing effective systemic therapy for this cancer.

1.1.1 Targeting Growth Factors in Hepatocellular Carcinoma

EGFR is frequently expressed in human hepatoma cells, and EGF may be one of the mitogens needed for the growth of hepatoma cells.[3, 4] Several strategies have been tested in HCC, including using a neutralizing monoclonal antibody such as cetuximab, and using small molecule tyrosine kinase inhibitor such as gefitinib and erlotinib, as demonstrated in HCC cell cultures.[5, 6] Erlotinib is an orally active and selective inhibitor of the EGFR/HER1 (Human Epidermal Receptor)-related tyrosine kinase enzyme. In two phase II studies of erlotinib in HCC, [7, 8] the response rates were 0% and 9% but the disease control rates were 43% and 50%, and median survival times were 10.75 and 13 months, respectively. EGFR/HER1 expression was detected in 71% and 88% of evaluable patients, respectively, but there was no significant difference in terms of overall survival between the high-EGFR and low-EGFR groups. However, this assay detects the presence of EGFR receptors and does not determine the functional status of the receptor (eg, phosphorylated EGFR), as the latter can be performed on fresh tissue only.

1.1.2 Rationale for Antiangiogenic Therapy of Hepatocellular Carcinoma

The cancer cell has been the only target of anticancer therapy for more than 50 years. However, the cancer cell is genetically unstable, and mutations accumulate. On the other hand, antiangiogenic therapy targets endothelial cells which are genetically stable. The genetic stability of endothelial cells may make them less susceptible to acquired drug resistance. As a result, angiogenesis inhibitors are emerging as a new class of therapeutic agents.

Angiogenesis' role in the initial progression from a pre-malignant tumor to a cancer prompted investigators to study the role of VEGF in the natural history of HCC.[9] In 1999, a group of researchers suggested that the degree of tissue VEGF expression increased according to the stepwise development of HCC.[10] In addition, studies have shown that VEGF was frequently expressed in HCC. In a quantitative analysis study, VEGF expression was demonstrated in 63.9% of encapsulated HCC and 78.3% of non-encapsulated HCC.[11] Another study reported VEGF tissue expression in HCC of 88.8%.[12] Notably, studies have suggested a correlation between the degree of tissue VEGF expression and the intensity of both the magnetic resonance signal and the computed tomographic enhancement of the hepatic artery, which represent radiological vascular signals.[13-15] Hence, the hypervascular nature of HCC has led to increasing interest in exploring the potential of anti-angiogenic therapy in this disease.

1.1.3 Clinical Trials of Anti-angiogenic Agents in Hepatocellular carcinoma

Several vascular targeted agents, including thalidomide, sunitinib, sorafenib, and bevacizumab, have been tested in advanced HCC. Thalidomide's mechanism was not clearly known but was thought to be partly based on its antiangiogenic effects.[16-18] Nevertheless, several clinical trials of thalidomide alone or in combination with epirubicin or interferon showed rare responses ranging from 0-6.3%.[19-25] A recent report in abstract form of 19 patients treated with oral thalidomide 200 mg/day continuously showed a 6-month progression free survival of 41%.[26]Sunitinib, an oral multikinase inhibitor, exerts an antiangiogenic effect by targeting VEGFR and platelet derived growth factor receptor (PDGFR) tyrosine kinases. A phase II study of sunitinib alone in 19 patients with unresectable or metastatic HCC reported a partial response (PR) in one patient.[27]

Sorafenib, an oral multikinase inhibitor, exerts an antiangiogenic effect by targeting VEGFR and PDGFR tyrosine kinases. It exerts its effect through targeting Raf/MEK/ERK signaling at the level of Raf kinase, and exerts an antiangiogenic effect by targeting VEGFR-2/-3. A phase II study of Sorafenib alone in advanced HCC showed 2.2% partial and 5.8% minor response.[28] Recently, a randomized, placebo-controlled phase III trial of Sorafenib in advanced HCC reported a 2.8 month improvement in median overall survival (HR 0.69, 95% CI: 0.55-0.87; p=0.0006) along with increased time to progression and disease control rate.[29]

Bevacizumab is a recombinant, humanized monoclonal antibody that targets VEGF and may augment chemotherapy administration by making tumor vasculature less permeable and decreasing the elevated tumor interstitial pressure.[30, 31] Recent phase II trials of bevacizumab alone, and in combination with cytotoxic therapy, in advanced HCC suggested an improved disease control rate with one trial reporting a response rate of 12.5% (all PR) with disease control rate [PR+ stable disease (SD)] of 67%.[24, 32] Bevacizumab was also combined with gemcitabine and oxaliplatin in a phase II trial of advanced HCC with an overall response rate of 20%. [33] A phase II trial of bevacizumab + capecitabine as a first-line treatment for advanced HCC recently reported response rate Complete Response (CR+PR) of 16% [95% confidence interval (CI) 4.5-36.1%] and disease control rate (CR+PR+SD) of 60% (95% CI 38.7-78.9%) with a median overall survival of 10.7 months (95% CI, 5.3-14.7) and median Progression-free survival (PFS) of 4.1 months.[34] In addition, a phase II study of advanced or unresectable metastatic HCC treating 30 patients with bevacizumab, oxaliplatin and capecitabine reported an 11% response rate with mean PFS of 5.4 months.[35] Another study of 46 patients who received bevacizumab 5 mg/kg (n = 12) or 10

mg/kg (n = 34) every 2 weeks was recently reported.[36] Six patients had objective responses (13%; 95% CI, 3% to 23%), and 65% were progression free at 6 months. Median PFS time was 6.9 months (95% CI, 6.5 to 9.1 months); overall survival rate was 53% at 1 year, 28% at 2 years, and 23% at 3 years. In addition, our group at M. D. Anderson Cancer Center has reported a phase II, single-arm, open-label trial of bevacizumab and erlotinib.[37] Ten patients achieved a PR, for a confirmed overall response rate of 25%. The PFS at 16 weeks of treatment was 62.5%. The median PFS was 39 weeks (95% CI: 24-45 weeks) (9.75 months), and median overall survival of 68 weeks (17 months) (95% CI: 48-78 weeks). Moreover, there are a number of ongoing clinical trials of different vascular targeted agents in HCC. Preclinical studies of agents which target other foci that interact with VEGF, such as Hypoxia-Inducible Factor 1 (HIF-1) alpha and APRIL(a proliferation inducing ligand), have shown promising results with reduced VEGF expression in hepatocellular carcinoma cell cultures.[38, 39] Furthermore, the assessment of systemic treatment response to targeted agents, particularly anti-angiogenesis ones, has changed over the years. It is now well recognized that the conventional markers of radiographic response (World Health Organization [WHO] or RECIST criteria) are poorly related to tumor cell kill in liver tumors and that end points other than radiographic tumor shrinkage, such as time to tumor progression, progression-free survival, and certainly overall survival, are more meaningful measures of therapeutic benefit.

1.2 BEVACIZUMAB CLINICAL EXPERIENCE

Bevacizumab has been studied in a multitude of Phase I, II, and III clinical trials in more than 5000 patients and in multiple tumor types. In addition, data are available from 3,863 patients enrolled in two post marketing studies in metastatic colorectal cancer (CRC). Approximately 130,000 patients have been exposed to bevacizumab as a marketed product or in clinical trials. The following discussion summarizes bevacizumab's safety profile and presents some of the efficacy results pertinent to this particular trial. Please refer to the bevacizumab Investigator Brochure for descriptions of all completed Phase I, II, and III trials reported to date.

In a large phase III study (AVF2107g) in patients with metastatic colorectal cancer, the addition of bevacizumab, a monoclonal antibody directed against vascular endothelial growth factor (VEGF), to irinotecan/5-fluorouracil/leucovorin (IFL) chemotherapy resulted in a clinically and statistically significant increase in duration of survival, with a hazard ratio of death of 0.67 (median survival 15.6 vs. 20.3 months; $p < 0.001$). Similar increases were seen in progression-free survival (6.2 vs. 10.6 months; $p < 0.001$), overall response rate (35% vs. 45%; $p < 0.01$) and duration of response (7.1 vs. 10.4 months; $p < 0.01$) for the combination

arm versus the chemotherapy only arm (bevacizumab Investigator Brochure, October 2005).

Based on the survival advantage demonstrated in Study AVF2107g, bevacizumab was designated for priority review and was approved on 26 February 2004 in the United States for first-line treatment in combination with IV 5-FU–based chemotherapy for subjects with metastatic colorectal cancer.

Additional data from Phase III trials in metastatic CRC (E3200), non–small cell lung cancer (NSCLC; E4599), and metastatic breast cancer (E2100) have also demonstrated clinical benefit from bevacizumab when added to chemotherapy. In Study E3200, the addition of bevacizumab to Folinic acid (leucovorin), Fluorouracil (5-FU), Oxaliplatin (Eloxatin) (FOLFOX) chemotherapy resulted in improved overall survival compared with FOLFOX alone (13.0 vs. 10.8 months, respectively, HR = 0.75; $p < 0.01$) in a population of previously treated CRC patients.

There was also improved overall survival in first-line NSCLC patients (E4599) treated with carboplatin/paclitaxel + bevacizumab compared with chemotherapy alone (12.3 vs. 10.3 months, respectively; HR = 0.80; $p = 0.003$). The results from this trial were the basis for FDA approval of bevacizumab for use in combination with carboplatin + paclitaxel as first-line treatment of patients with unresectable, locally advanced, recurrent or metastatic, non-squamous NSCLC in October 2006. Finally, patients with untreated metastatic breast cancer (E2100) who received bevacizumab in combination with weekly paclitaxel had a marked improvement in PFS compared with chemotherapy alone (13.3 vs. 6.7 months, respectively; HR = 0.48; $p < 0.0001$) (see the Bevacizumab Investigator Brochure for additional details).

Two recent phase II trials of bevacizumab, alone and in combination with cytotoxic therapy, in advanced HCC suggested an improved disease control rate with one trial reporting a response rate of 12.5% (all PR) with disease control rate (PR+SD) of 67%.[24, 32] Bevacizumab was also combined with gemcitabine and oxaliplatin in a phase II trial of advanced HCC with overall response rate of 20%. [33] A phase II trial of bevacizumab + capecitabine as a first-line treatment for advanced HCC recently reported response rate (CR+PR) of 16% (95% CI 4.5-36.1%) and disease control rate (CR+PR+SD) of 60% (95% CI 38.7-78.9%) with a median overall survival of 10.7 months (95% CI, 5.3-14.7) and median PFS of 4.1 months.[34] In addition, a phase II study of advanced or unresectable metastatic HCC treating 30 patients with bevacizumab, oxaliplatin and capecitabine reported an 11% response rate with mean PFS of 5.4 months.[35] More recently, a study of bevacizumab in advanced HCC at 5 mg/kg (n = 12) or 10 mg/kg (n = 34) every 2 weeks reported six patients had objective responses (13%; 95% CI, 3% to 23%), and

65% were progression free at 6 months. Median PFS time was 6.9 months (95% CI, 6.5 to 9.1 months); overall survival rate was 53% at 1 year, 28% at 2 years, and 23% at 3 years. Grade 3 to 4 adverse events included hypertension (15%) and thrombosis (6%, including 4% with arterial thrombosis). Grade 3 or higher hemorrhage occurred in 11% of patients, including one fatal variceal bleed. Bevacizumab was associated with significant reductions in tumor enhancement by dynamic contrast-enhanced magnetic resonance imaging and reductions in circulating VEGF-A and stromal-derived factor-1 levels.[36]

Most recently, our group at M D Anderson Cancer Center has published a phase II, single-arm, open-label trial of bevacizumab and erlotinib.[37] Ten patients achieved a PR, for a confirmed overall response rate of 25%. The PFS at 16 weeks of treatment was 62.5%. The median PFS was 39 weeks (95% CI: 24-45 weeks) (9.75 months), and median overall survival of 68 weeks (17 months) (95% CI: 48-78 weeks). Grade 3-4 drug-related toxicity included fatigue (8 pts, 20%), hypertension (6 pts, 15%), diarrhea (4 pts, 10%) elevated transaminases (4 pts, 10%), gastrointestinal hemorrhage (2 pts, 5%), thrombocytopenia (2 pts, 5%), proteinuria, hyperbilirubinemia, back pain, hyperkalemia, and wound infection (1 pt each).

a. Bevacizumab Safety Profile

In the initial Phase I and II clinical trials, four potential bevacizumab-associated safety signals were identified: hypertension, proteinuria, thromboembolic events, and hemorrhage. Additional completed Phase II and Phase III studies of bevacizumab as well as spontaneous reports have further defined the safety profile of this agent. Bevacizumab-associated adverse events identified in phase III trials include congestive heart failure (CHF) primarily in metastatic breast cancer, gastrointestinal perforations, wound healing complications, and arterial thromboembolic events (ATE). These and other safety signals are described in further detail as follows and in the bevacizumab Investigator Brochure.

Hypertension: An increased incidence of hypertension has been observed in patients treated with bevacizumab. Grade 4 and 5 hypertensive events are rare. Clinical sequelae of hypertension are rare but have included hypertensive crisis, hypertensive encephalopathy, and reversible posterior leukoencephalopathy syndrome (RPLS) (Ozcan et al., 2006; Glusker et al., 2006).

There is no information on the effect of bevacizumab in patients with uncontrolled hypertension at the time of initiating bevacizumab therapy. Therefore, caution should be exercised before initiating bevacizumab therapy in these patients. Monitoring of blood pressure is recommended during bevacizumab therapy. Optimal control of blood pressure according to standard public health guidelines is recommended for patients on treatment with or without bevacizumab.

Temporary interruption of bevacizumab therapy is recommended in patients with hypertension requiring medical therapy until adequate control is achieved. If hypertension cannot be controlled with medical therapy, bevacizumab therapy should be permanently discontinued. Bevacizumab should be permanently discontinued in patients who develop hypertensive crisis or hypertensive encephalopathy.

Proteinuria: An increased incidence of proteinuria has been observed in patients treated with bevacizumab compared with control arm patients. In the bevacizumab-containing treatment arms of clinical trials (across all indications), the incidence of proteinuria (reported as an adverse event) was up to 38% (metastatic CRC Study AVF2192g). The severity of proteinuria has ranged from asymptomatic and transient events detected on routine dipstick urinalysis to nephrotic syndrome; the majority of proteinuria events have been grade 1. NCI-CTC Grade 3 proteinuria was reported in up to 3% of bevacizumab-treated patients, and Grade 4 in up to 1.4% of bevacizumab-treated patients. The proteinuria seen in bevacizumab clinical trials was not associated with renal impairment and rarely required permanent discontinuation of bevacizumab therapy. Bevacizumab should be discontinued in patients who develop Grade 4 proteinuria (nephrotic syndrome)

Patients with a history of hypertension may be at increased risk for the development of proteinuria when treated with bevacizumab. There is evidence from the dose-finding, Phase II trials (AVF0780g, AVF0809s, and AVF0757g) suggesting that Grade 1 proteinuria may be related to bevacizumab dose.

Proteinuria will be monitored by urine protein:creatinine (UPC) ratio at least every 4 weeks. If the UPC ratio is not available, a dipstick urinalysis may be used to allow treatment to proceed.

Thromboembolic Events: Both venous and arterial thromboembolic (TE) events, ranging in severity from catheter-associated phlebitis to fatal, have been reported in patients treated with bevacizumab in the colorectal cancer trials and, to a lesser extent, in patients treated with bevacizumab in NSCLC and breast cancer trials.

Venous thromboembolism (including deep venous thrombosis, pulmonary embolism, and thrombophlebitis: In the phase III pivotal trial in metastatic CRC, there was a slightly higher rate of venous TE events in patients treated with bevacizumab plus chemotherapy compared with chemotherapy alone (19% vs. 16%).

In Study AVF2107g, a Phase III, pivotal trial in metastatic CRC, VTE events, including deep venous thrombosis, pulmonary embolism, and thrombophlebitis, occurred in 15.2% of patients receiving chemotherapy alone and 16.6% of patients receiving chemotherapy + bevacizumab.

The incidence of NCI-CTC Grade ≥ 3 venous VTE events in one NSCLC trial (E4599) was higher in the bevacizumab-containing arm compared to the chemotherapy control arm (5.6% vs. 3.2%). One event (0.2%) was fatal in the bevacizumab-containing arm; not fatal events were reported in the carboplatin/paclitaxel arm (see Bevacizumab Investigator Brochure). In metastatic CRC clinical trials, the incidence of VTE events was similar in patients receiving chemotherapy + bevacizumab and those receiving the control chemotherapy alone.

In clinical trials across all indications the overall incidence of VTE events was 2.8%–17.3% in the bevacizumab-containing arms compared with 3.2%–15.6% in the chemotherapy control arms. The use of bevacizumab with chemotherapy does not substantially increase the risk of VTE event compared with chemotherapy alone. However, patients with metastatic CRC who receive bevacizumab and experienced a VTE event may be at higher risk for recurrence of VTE event.

Arterial Thromboembotic Events: An increased incidence of ATE events was observed in patients treated with bevacizumab compared with those receiving control treatment. ATE events include cerebrovascular accidents, myocardial infarction, transient ischemic attacks (TIAs), and other ATE events. In a pooled analysis of data from five randomized Phase II and III trials (mCRC [AVF2107g, AVF2192g, AVF0780g]; locally advanced or metastatic NSCLC [AVF0757g]; metastatic breast cancer [AVF2119g]), the incidence rate of ATE events was 3.8% (37 of 963) in patients who received chemotherapy+bevacizumab compared with 1.7% (13 of 782) in patients treated with chemotherapy alone. ATE events led to a fatal outcome in 0.8% (8 of 963) of patients treated with chemotherapy+bevacizumab and 0.5% (4 of 782) of patients treated with chemotherapy alone. Cerebrovascular accidents (including TIAs) occurred in 2.3% of patients treated with chemotherapy+bevacizumab and 0.5% of patients treated with chemotherapy alone. Myocardial infarction occurred in 1.4% of patients treated with chemotherapy+bevacizumab compared with 0.7% of patients treated with chemotherapy alone (see the Bevacizumab Investigator Brochure for additional details).

Aspirin is a standard therapy for primary and secondary prophylaxis of arterial thromboembolic events in patients at high risk of such events, and the use of aspirin ≤ 325 mg daily was allowed in the five randomized studies discussed above. Use of aspirin was assessed routinely as a baseline or concomitant medication in these trials, though safety analyses specifically regarding aspirin use were not preplanned. Due to the relatively small numbers of aspirin users and arterial thromboembolic events, retrospective analyses of the ability of aspirin to affect the risk of such events were inconclusive. However, similarly retrospective analyses suggested that the use of up to 325 mg of aspirin daily does not increase the risk of grade 1-2 or grade 3-4 bleeding events, and similar data with

respect to metastatic colorectal cancer patients were presented at ASCO 2005 (Hambleton et al., 2005). Further analyses of the effects of concomitant use of bevacizumab and aspirin in colorectal and other tumor types are ongoing.

Gastrointestinal perforation Patients with metastatic carcinoma may be at increased risk for the development of gastrointestinal perforation and fistula when treated with bevacizumab and chemotherapy. Bevacizumab should be permanently discontinued in patients who develop gastrointestinal perforation. A causal association of intra-abdominal inflammatory processes and gastrointestinal perforation to bevacizumab treatment has not been established. Nevertheless, caution should be exercised when treating patients with intra-abdominal inflammatory processes with bevacizumab. Gastrointestinal perforation has been reported in other trials in non-colorectal cancer populations (e.g., ovarian, renal cell, pancreas, breast, and NSCLC) and may be higher in incidence in some tumor types.

Fistula: Bevacizumab use has been associated with serious cases of fistulae including events resulting in death. Fistulae in the GI tract are common (1%–10% incidence) in patients with metastatic CRC, but uncommon (0.1%–1%) or rare (0.01%–0.1%) in other indications. In addition, fistulae that involve areas of the body other than the GI tract (e.g., tracheoesophageal, bronchopleural, urogenital, biliary) have been reported uncommonly (0.1%–1%) in patients receiving bevacizumab in clinical studies and post marketing reports. Events were reported at various time points during treatment, ranging from 1 week to > 1 year following initiation of bevacizumab, with most events occurring within the first 6 months of therapy.

Permanently discontinue bevacizumab in patients with tracheoesophageal fistulae or any Grade 4 fistula. Limited information is available on the continued use of bevacizumab in patients with other fistulae. In cases of internal fistula not arising in the GI tract, discontinuation of bevacizumab should be considered.

Wound healing complications: Wound healing complications such as wound dehiscence have been reported in patients receiving bevacizumab. In an analysis of pooled data from two trials in metastatic colorectal cancer, patients undergoing surgery 28-60 days before study treatment with 5-FU/LV plus bevacizumab did not appear to have an increased risk of wound healing complications compared to those treated with chemotherapy alone (Scappaticci et al., 2005). Surgery in patients currently receiving bevacizumab is not recommended. No definitive data are available to define a safe interval after bevacizumab exposure with respect to wound healing risk in patients receiving elective surgery; however, the estimated half life of bevacizumab is 21 days. Bevacizumab should be discontinued in patients with severe wound healing complications.

If patients receiving treatment with bevacizumab require elective major surgery, it is recommended that bevacizumab be held for 4–8 weeks prior to the surgical procedure. Patients undergoing a major surgical procedure should not begin or restart bevacizumab until 4 weeks after that procedure (in the case of high-risk procedures such as liver resection, thoracotomy, or neurosurgery, it is recommended that chemotherapy be restarted no earlier than 6 weeks and bevacizumab no earlier than 8 weeks after surgery).

Hemorrhage: Overall, grade 3 and 4 bleeding events were observed in 4.0% of 1132 patients treated with bevacizumab in a pooled database from eight phase I, II, and III clinical trials in multiple tumor types (bevacizumab Investigator Brochure, October 2005). The hemorrhagic events that have been observed in bevacizumab clinical studies were predominantly tumor-associated hemorrhage (see below) and minor mucocutaneous hemorrhage.

Tumor-Associated Hemorrhage: Major or massive pulmonary hemorrhage or hemoptysis has been observed primarily in patients with NSCLC. Life-threatening and fatal hemoptysis was identified as a bevacizumab-related adverse event in NSCLC trials. These events occurred suddenly and presented as major or massive hemoptysis. Among the possible risk factors evaluated (including squamous cell histology, treatment with anti-rheumatic/anti-inflammatory drugs, treatment with anticoagulants, prior radiotherapy, bevacizumab therapy, previous medical history of atherosclerosis, central tumor location, and cavitation of tumors during therapy), the only variables that showed statistically significant correlations with bleeding were bevacizumab therapy and squamous cell histology.

GI hemorrhages, including rectal bleeding and melena have been reported in patients with CRC, and have been assessed as tumor-associated hemorrhages.

Tumor-associated hemorrhages were also seen rarely in other tumor types and locations, including a case of CNS bleeding in a patient with hepatoma with occult CNS metastases and a patient who developed continuous oozing of blood from a thigh sarcoma with necrosis.

Mucocutaneous Hemorrhage: Across all bevacizumab clinical trials, mucocutaneous hemorrhage has been seen in 20%-40% of patients treated with bevacizumab. These were most commonly NCI-CTC Grade 1 epistaxis that lasted less than 5 minutes, resolved without medical intervention and did not require any changes in bevacizumab treatment regimen.

There have also been less common events of minor mucocutaneous hemorrhage in other locations, such as gingival bleeding and vaginal bleeding.

Reversible Posterior Leukoencephalopathy Syndrome: There have been rare reports of bevacizumab-treated patients developing signs and symptoms that are consistent with RPLS, a rare neurologic disorder that can present with the following signs and symptoms (among others): seizures, headache, altered mental status, visual disturbance, or cortical blindness, with or without associated hypertension. Brain imaging is mandatory to confirm the diagnosis of RPLS. In patients who develop RPLS, treatment of specific symptoms, including control of hypertension, is recommended along with discontinuation of bevacizumab. The safety of reinitiating bevacizumab therapy in patients previously experiencing RPLS is not known (Glusker et al. 2006; Ozcan et al. 2006).

Congestive heart failure: In clinical trials CHF was observed in all cancer indications studied to date, but predominantly in patients with metastatic breast cancer. In the Phase III clinical trial of metastatic breast cancer (AVF2119g), 7 (3%) bevacizumab-treated patients experienced CHF, compared with two (1%) control arm patients. These events varied in severity from asymptomatic declines in left ventricular ejection fraction (LVEF) to symptomatic CHF requiring hospitalization and treatment. All the patients treated with bevacizumab were previously treated with anthracyclines (doxorubicin cumulative dose of 240–360 mg/m^2). Many of these patients also had prior radiotherapy to the left chest wall. Most of these patients showed improved symptoms and/or left ventricular function following appropriate medical therapy (Miller et al. 2005).

In a randomized, Phase III trial of patients with previously untreated metastatic breast cancer (E2100), the incidence of LVEF decrease (defined as NCI-CTC Grade 3 or 4) in the paclitaxel + bevacizumab arm was 0.3% versus 0% for the paclitaxel alone arm

No information is available on patients with preexisting CHF of New York Heart Association (NYHA) Class II–IV at the time of initiating bevacizumab therapy, as these patients were excluded from clinical trials.

Prior anthracyclines exposure and/or prior radiotherapy to the chest wall may be possible risk factors for the development of CHF. Caution should be exercised before initiating bevacizumab therapy in patients with these risk factors.

A Phase II trial in patients with refractory acute myelogenous leukemia reported 5 cases of cardiac dysfunction (CHF or LVEF decrease to < 40%) among 48 patients treated with sequential cytarabine, mitoxantrone, and bevacizumab. All but 1 of these patients had significant prior exposure to anthracyclines as well (Karp et al. 2004).

Other studies in patients with various tumor types and either a history of anthracycline exposure or concomitant use with bevacizumab are ongoing.

Patients with prior exposure to systemic anthracyclines will have, as a standard of care procedure, a baseline Multi Gated Acquisition (MUGA) scans or echocardiograms (ECHOs).

Neutropenia: Increased rates of severe neutropenia, febrile neutropenia, or infection with severe neutropenia (including some fatalities) have been observed in patients treated with some myelotoxic chemotherapy regimens plus bevacizumab in comparison to chemotherapy alone (Sandler et al. 2006).

Additional Adverse Events: See the bevacizumab Investigator Brochure for additional details regarding the safety experience with bevacizumab.

1.3 ERLOTINIB (TARCEVA) BACKGROUND

The control of cell growth is mediated by a complex network of signaling pathways responsive to external influences, such as growth factors, as well as to internal controls and checks. Epidermal growth factor (EGF) was one of the first growth factors to be described. It was shown to be mitogenic, an effect mediated by the binding of EGF (or other ligands) to the cell surface EGF receptor (EGFR), stimulating autophosphorylation of the intracellular tyrosine kinase domain of the receptor. Subsequent investigations revealed EGFR to be one of a family of closely related receptors that includes EGFR (HER1), HER2, HER3, and HER4.

EGFR and other HER family members are considered to be important in the development, progression, and aggressive behavior of human epithelial malignancies and to be relevant therapeutic targets. A number of human malignancies are associated with aberrant or over-expression of EGFR (Salomon et al. 1995). Stimulation of tumor cells via the EGFR is important for both tumor growth and tumor survival in vivo. Over-expression of EGFR in certain human tumors, including non–small cell lung carcinoma (NSCLC), has been correlated with both chemo-resistance and poor prognosis (Rusch et al. 1996, 1997; Davies and Chamberlin 1996; Veale et al. 1987, 1993; Sekine et al. 1998; Pfeiffer et al. 1996; Cerny et al. 1986; IMPATH Inc 1998–1999; Reissmann et al. 1999; Fujino 1996; Fontanini et al. 1995; Lei et al. 1999). Inhibitors of EGFR tyrosine kinase activity have been in development for a number of years, and although earlier compounds lacked specificity and potency, newer compounds have proven active in nonclinical and clinical studies.

Erlotinib (previously known as OSI-774) is an orally active, potent, selective inhibitor of the EGFR tyrosine kinase. Early clinical data with Erlotinib indicate that the compound is generally safe and well tolerated at doses that provide the targeted effective concentration based on nonclinical experiments. A recently completed, randomized, double-blind, placebo-controlled trial has shown that Erlotinib as a single agent

significantly improves the survival of patients with incurable Stage IIIb/IV NSCLC who have failed standard therapy for advanced or metastatic disease (Shepherd et al; Proceedings of American Society of Clinical Oncology (ASCO) 2004; Abst 7022).

The epidermal growth factor receptor (EGFR) is frequently expressed in human hepatoma cells, and EGF may be one of the mitogens needed for the growth of hepatoma cells.[3, 4] Several strategies have been tested in HCC, one is through using neutralizing monoclonal antibody such as cetuximab, and another is through using small molecule tyrosine kinase inhibitor such as gefitinib and erlotinib, as demonstrated in HCC cell cultures.[5, 6] Erlotinib is an orally active and selective inhibitor of the EGFR/HER1-related tyrosine kinase enzyme. In two phase II studies of erlotinib in HCC, [7, 8] the response rates were 0% and 9% but the disease control rate was 43 % and 50%, and median survival times were 10.75 and 13 months, respectively. EGFR/HER1 expression was detected in 71% and 88% of evaluable patients, respectively, but there was no significant difference in terms of overall survival between the high-EGFR and low-EGFR groups. However, this assay detects the presence of EGFR receptors and does not determine the functional status of the receptor (eg, phosphorylated EGFR), as the latter can be performed on fresh tissue only.

1.3.1 Nonclinical Experience Data

a. Pharmacology

Erlotinib, a quinazoline, directly and reversibly inhibits the human EGFR tyrosine kinase with an Inhibition Concentration $(IC)_{50}$ of 2 nM (0.79 ng/mL) in an in vitro enzyme assay and reduces EGFR autophosphorylation in intact tumor cells with an IC_{50} of 20 nM (7.9 ng/mL). This potent inhibition is selective for the EGFR tyrosine kinase both in assays assessing the effects of erlotinib on a variety of other isolated tyrosine kinases and in cellular bioassays designed to isolate this functional pathway. Erlotinib is designed to inhibit EGF-dependent proliferation of cells at submicromolar concentrations and blocks cell cycle progression in the G1 phase.

Data on drug exposure and anti-tumor responses in human tumor xenograft models (HN5 and A431) were analyzed in order to estimate the plasma concentration of erlotinib associated with anti-tumor activity. Based on these efficacy models, the minimum steady-state plasma concentration targeted for clinical activity in humans is projected to be 500 ng/mL.

b. Toxicology

Toxicology studies have been performed in mice, rats (up to 6 months), dogs (up to 1 year), and monkeys (1 week). Treatment-related effects observed in at least one species or study included effects on the cornea (atrophy, ulceration), skin (follicular degeneration and inflammation, redness, and alopecia), ovary (atrophy), liver (necrosis), kidney (papillary necrosis and tubular dilatation), lacrimal glands (atrophy), salivary glands (atrophy), mandibular lymph nodes (inflammation), spleen (hematopoiesis), gastrointestinal tract (delayed gastric emptying and diarrhea), and embryo-fetal toxicity. Red blood cell parameters were decreased, and white blood cells (primarily neutrophils) were increased. There were treatment-related increases in asparte aminotransferase (AST) and alanine aminotransferase (ALT), triglyceride and bilirubin and decreases in albumin; increases in bilirubin were likely caused by a treatment-related impairment of bilirubin metabolism.

1.3.2 Clinical Experience Data

a. Dose Selection for Single-Agent Trials of Erlotinib

Phase I trials of Erlotinib explored both schedule and dose to evaluate the safety, tolerability, and pharmacokinetic profile of the compound given as a single agent. A number of pharmacokinetic trials in healthy subjects have been conducted, along with three classic Phase I trials in patients with advanced cancer. The single-agent maximum tolerated dose (MTD) was estimated to be 150 mg administered once daily.

The primary toxicities of single-agent Erlotinib consisted of rash (dermatosis), diarrhea, nausea, fatigue, stomatitis, vomiting, and headache. When given daily, dose-limiting toxicity (diarrhea) was observed at 200 mg/day. At 150 mg/day, diarrhea was manageable with the addition of loperamide therapy; this dose was considered the maximal tolerated dose.

Rash (variously referred to as dermatitis, acneiform rash, or maculopapular rash) has been variable in onset, duration, and severity, but typically appears on the face, neck, scalp, chest, and back starting after ~1 week of treatment. The mechanistic basis of the rash remains uncertain; histopathologic examination of biopsies of the rash demonstrated inflammatory cell infiltrate and mild epidermal hyperproliferation. In some cases, the rash gradually improved despite continued dosing and, in general, resolved without sequelae following Erlotinib discontinuation. The rash did not result in study discontinuation in patients with cancer in the Phase I trials. Laboratory abnormalities

observed infrequently with single-agent Erlotinib involved primarily liver function tests, including elevation of ALT, AST, and/or bilirubin.

Selection of the 150 mg/day dose of Erlotinib for subsequent single-agent studies was based on pharmacokinetic parameters, as well as the safety and tolerability profile of this dose in Phase I trials in heavily pretreated patients with advanced cancer. Drug levels seen in patients with cancer receiving the 150 mg/day dose were consistently above the average plasma concentration of 500 ng/mL targeted for clinical efficacy.

b. Pharmacokinetics

Oral Erlotinib is well absorbed and has an extended absorption phase, with mean peak plasma levels occurring at 3 hours after oral dosing of 150 mg/dL at steady state. A study in healthy subjects provided an estimate of bioavailability of 59% (95% CI: 55%, 63%). The time to reach steady-state plasma concentration was ~5 days. The accumulation ratio with daily dosing of Erlotinib was estimated to be 2.0. From a population pharmacokinetic analysis of 708 patients, the median trough concentration (C_{min}) 24 hours following the previous dose was 1041 ($\pm$697) ng/mL. Median AUC achieved during the dosing interval at steady state was 19,801 ng • hr/mL. Exposure after an oral dose is increased by food.

There is extensive binding of Erlotinib and metabolites to both serum albumin and AAG (alpha-1-acid glycoprotein), with total plasma protein binding for Erlotinib and OSI-420 of ~95% and 91%, respectively. Erlotinib is extensively metabolized in the liver by the hepatic cytochromes in humans–primarily by CYP3A4 and to a lesser extent by CYP1A2. The primary metabolite of Erlotinib, OSI-420, has potency comparable to that of erlotinib, but is present at levels that are $<$10% of erlotinib levels. Erlotinib is excreted predominantly via the feces ($>$90%). The elimination half-life after a 150-mg oral dose is ~30 hours. In population-based data analyses, no relationships were identified between predicted steady-state trough concentration and patient age, body weight, sex, ethnicity, or creatinine clearance.

d. Phase II and III Trials in Patients with Advanced Cancer

Multiple Phase II trials evaluating the safety, tolerability, and antitumor activity of Erlotinib have been conducted in patients with advanced, refractory malignancies including cancer of the head and neck, lung, aerodigestive tract, ovary, breast, central nervous system (glioma), and others. Erlotinib has been evaluated both as a single agent and administered concurrently with conventional chemotherapy agents using various doses and schedules.

Evidence of activity has been observed in squamous cell carcinoma of the head and neck, ovarian, breast and pancreatic carcinoma, non–small cell lung cancer (NSCLC), and glioblastoma multiforme (GBM). Patients received 150 mg/day of Erlotinib in all of these studies except the GBM study where dose escalation was allowed until limited by rash and where a higher starting dose was tested in subjects receiving concomitant enzyme inducing anti-epileptic drugs. Dose reduction was allowed in all studies in the case of intolerance. Diarrhea was treated with loperamide therapy and/or dose reduction. Rash was treated with a variety of agents, including oral and topical antibiotics, corticosteroids, and other agents.

Patients receiving Erlotinib in combination with various chemotherapy agents have generally experienced the same type of adverse events (AEs) as with either agent alone.

The first randomized placebo controlled trial to demonstrate a survival advantage for an EGFR inhibitor was the Phase III study, BR21. This international trial, conducted by the National Cancer Institute of Canada Clinical Trial Group (NCIC CTG), included 731 patients with incurable Stage IIIb/IV NSCLC who have failed standard therapy for advanced or metastatic disease. Patients randomized in a 2:1 ratio to single-agent Erlotinib 150 mg/day obtained a 42.5% improvement in median survival over placebo, from 4.7 to 6.7 months. The one-year survival increased significantly (from 22% to 31%) as did the median and 6 month PFS, response rate, and the time to deterioration of tumor related symptoms of pain, cough, and dyspnea. (Shepherd 2004).

In BR-21, of the 727 patients evaluable for safety (485 Erlotinib, 242 placebo), the most common AEs in the Erlotinib arm were rash (75% Erlotinib, 17% placebo), diarrhea (54% Erlotinib, 18% placebo) and stomatitis (17% Erlotinib, 18% placebo) events. The majority of these events were mild to moderate in severity. The incidence of interstitial lung disease (ILD) reported was the same in the placebo and Erlotinib groups at 0.8% in each arm.

Two large, Phase III, randomized studies in first-line NSCLC patients evaluated Erlotinib in combination with platinum-based two-drug combination chemotherapy. A total of 1079 previously untreated patients received carboplatin/paclitaxel with either Erlotinib or placebo in the TRIBUTE trial (OSI2298g) conducted in the United States. An additional 1172 patients received cisplatin/gemcitabine plus either Erlotinib or placebo in the TALENT trial (BO16411) conducted in 27 countries in Europe and other ex-U.S. locations. Neither study met its primary endpoint of improved overall survival or a secondary endpoint of improved time to disease progression or overall response rate. Overall, the number of adverse events and serious adverse events were well balanced

between the two arms of each study, with two exceptions. As expected, rash and diarrhea occurred more frequently in the Erlotinib arms. In the TRIBUTE study, more serious adverse events resulting in death were seen in the Erlotinib arm compared with the placebo arm (53 vs. 27). Most of the apparent imbalance was due to events reported as pneumonia or progression of underlying cancer. (Gatzemeier U. et al.- Talent trial - ASCO 2004 - Abstract 7010 and Herbst R. et al. – Tribute trial - ASCO 2004 - Abstract 7011).

e. Patients with Hepatic or Renal impairment

The influence of hepatic metastases and/or hepatic dysfunction on the pharmacokinetics of Erlotinib is not yet known. However, Erlotinib is cleared predominately by the liver, and caution should be used when administering Erlotinib to patients with hepatic dysfunction. Erlotinib is also a strong inhibitor of the Uridine 5'-diphospho-(UDP)-glucuronosyltransferase UGT1A1 enzyme responsible for the glucuronidation of bilirubin. Hyperbilirubinemia appears most often to be a side effect related to genetic polymorphisms of UGT1A1. Rare cases of hepatic failure (including fatalities) have been reported during the post marketing use of Erlotinib. Confounding factors for severe hepatic dysfunction have included pre-existing liver disease such as cirrhosis, viral hepatitis, hepatocellular carcinoma, hepatic metastases, or concomitant treatment with potentially hepatotoxic drugs.

Rare cases of myocardial infarction (including fatalities) have been reported during the post marketing use of Erlotinib.

No clinical studies have been conducted in patients with compromised renal function since Erlotinib and its metabolites are not significantly excreted by the kidneys.

f. Adverse Events Associated with ERLOTINIB

Common adverse events associated with erlotinib administration include rash and diarrhea. Other common adverse events include nausea/vomiting, mucositis/stomatitis, headache, and fatigue.

A rash occurred in 75% of Erlotinib-treated NSCLC patients enrolled in BR.21. Similar incidences of rash have occurred when erlotinib was administered concurrently with chemotherapy including gemcitabine, paclitaxel/carboplatin, and gemcitabine/cisplatin. A papular, pustular rash manifesting most often on the face and upper trunk was common across all studies, but rash was rarely the cause of study drug discontinuation. Other dermatologic manifestations reported in clinical studies or post marketing use of Erlotinib include nail changes, paronychia, painful fissures or cracking of the skin on the hands and feet, and hair growth

abnormalities (alopecia, thinning hair, eyelash/eyebrow changes, hirsutism).

Wearing of contact lenses while receiving Erlotinib therapy is not recommended. The incidence of diarrhea in BR.21 was 54% of Erlotinib-treated NSCLC patients. The median time to onset of skin rash was 8 days and median time to occurrence of first diarrheal symptom was 9 days.

There have been infrequent reports of serious (including fatal) interstitial lung disease (ILD) in patients receiving Erlotinib for treatment of NSCLC or other advanced solid tumors. In Study BR.21, the incidence of ILD (0.8%) was the same in the placebo and Erlotinib groups. The overall incidence in Erlotinib-treated patients from all studies (including uncontrolled studies and studies with concurrent chemotherapy) is approximately 0.6%. Included in this rate of ILD are reported diagnoses of pneumonitis, radiation pneumonitis, hypersensitivity pneumonitis, interstitial pneumonia, interstitial lung disease, obliterative bronchiolitis, pulmonary fibrosis, acute respiratory distress syndrome, alveolitis, and lung infiltration, irrespective of investigator assessed causality. Most of the cases were associated with confounding or contributing factors such as concomitant/prior chemotherapy, prior radiotherapy, preexisting parenchymal lung disease, metastatic lung disease, or pulmonary infections.

Rare cases of acute renal failure or renal insufficiency have been reported (including fatalities). Many of these cases have been associated with dehydration associated with nausea, vomiting, diarrhea, and/or anorexia. There have been rare reports of renal failure in patients receiving Erlotinib in combination with platinum-containing chemotherapy regimens. Febrile neutropenia has been reported in patients receiving concomitant chemotherapy.

Erlotinib is both protein bound (92%–95%) and metabolized by hepatic cytochromes CYP3A4 and CYP3A5 and pulmonary cytochrome CYP1A1. Therefore, a potential for drug–drug interaction exists when Erlotinib is co-administered with drugs that are highly protein bound or that are CYP3A4 inhibitors/inducers.

Co-administration of Erlotinib with omeprazole, a proton pump inhibitor, decreased the exposure of Erlotinib (AUC) by 46% and the maximum concentration (C_{max}) by 61%. There was no change to Tmax or half-life. Therefore, drugs that alter the pH of the GI tract may alter the solubility of Erlotinib and hence its bioavailability.

The exposure to Erlotinib (AUC) increased to a moderate extent, by 39%, and the maximum concentration (C_{max}) by 17%, when Erlotinib was co-administered with ciprofloxacin, an inhibitor of both CYP3A4 and CYP1A2.

Co-administration of Erlotinib with an inhibitor of CYP3A4 metabolism (ketoconazole, 200 mg po BID for 5 days) resulted in increased exposure to Erlotinib as measured by an 86% increase in median Erlotinib AUC and a 69% increase C_{max}, compared with administration of Erlotinib alone.

Induction of CYP3A4 metabolism by a known enzyme inducer (rifampin, 600 mg po QD for 7 days) resulted in a 69% decrease in the median Erlotinib AUC, compared with administration of Erlotinib alone. However, the effect of rifampin on C_{max} was negligible. In another study, rifampicin pretreatment followed by co-administration of rifampicin with a single 450 mg dose of Erlotinib resulted in a mean Erlotinib exposure (AUC) that was 57.6% of that observed following a single 150 mg Erlotinib dose in the absence of rifampicin treatment. Therefore, a potential for drug-drug interaction exists when Erlotinib is co-administered with drugs that are highly protein bound or that are potent CYP3A4 inhibitors or inducers.

International normalized ratio (INR) elevations and/or bleeding events have been reported in some cancer patients while on Erlotinib alone and in combination with other chemotherapeutic agents, and concomitant Non-steroidal anti-inflammatory drugs (NSAIDS) or anticoagulants, including warfarin.

1.4 STUDY RATIONALE

In HCC, several crucial intracellular signaling pathways such as the Ras/Raf/Mek/Erk pathway and PI3k/Akt/mTOR pathway, in addition to several growth and angiogenic factors/receptors such as EGFR (Epidermal Growth Factor Receptor), PDGFR (platelet-derived growth factor receptor), FGFR (fibroblast growth factor receptor), and VEGFR (Vascular Endothelial Growth Factor Receptor) have been recognized. Subsequently, targeted agents have entered clinical trials for HCC patients and, most recently, sorafenib was approved by FDA for treatment of advanced HCC. Sorafenib exerts its effect through targeting Raf/MEK/ERK signaling at the level of Raf kinase, and exerts an antiangiogenic effect by targeting VEGFR-2/-3. It is currently considered the standard of care for HCC, based on a phase III study conducted in Europe that demonstrated survival benefit, although modest activity was observed. This is of particular significance for HCC in light of the lack of existing effective systemic therapy for this cancer. Evolution of sorafenib resistance is going to be a major challenge and dealing with this clinical dilemma is obviously an unmet need. Furthermore, sorafenib effects are suggested to be related to inhibition of angiogenesis (VEGFR and PDGFR), and direct effects on tumor cell proliferation/survival (Raf kinase signaling-dependent and signaling-independent mechanisms). Thus, sorafenib resistance may be attributed to failure of one of these two mechanisms, which further indicates the importance of studying more effective mechanisms of targeting one of those two most important

pathways in HCC.

The hypervascular nature of HCC has led to increasing interest in exploring the potential of anti-angiogenic therapy in this disease. While the cancer cell has been the only target of anticancer therapy for more than 50 years, it is genetically unstable, and mutations accumulate. On the other hand, antiangiogenic therapy targets endothelial cells which are genetically stable. Thus, the genetic stability of endothelial cells may make them less susceptible to acquired drug resistance. As a result, angiogenesis inhibitors are emerging as a new class of therapeutic agents. Antiangiogenic strategy has been shown to be very promising in HCC, as indicated by recent phase II trials of bevacizumab, alone and in combination with cytotoxic agents in advanced HCC that suggested an improved disease control.[33, 36, 40-42] In addition, two Phase II studies of erlotinib in HCC have been conducted. The first study was conducted by our group at M. D. Anderson Cancer Center, Thomas MB et al,[43] and the other study was conducted by Philip P et al.[7] Both of these studies suggested that a dose of 150 mg/day was effective and well tolerated.

Bevacizumab and Erlotinib in HCC:

Journal of Clinical Oncology (JCO) has published the results from our front-line phase II study with erlotinib and bevacizumab combination for advanced HCC, with very promising data that was previously reported at ASCO 2007 as well.[37] Ten patients achieved PR for a confirmed overall response rate of 25%. The PFS at 16 weeks of treatment was 62.5%. The median PFS was 39 weeks (95% CI 24-45 weeks) (9.75 months), and median overall survival of 68 weeks (17 months) (95% CI: 48-78 weeks). Grade 3-4 drug-related toxicity included fatigue (8 pts, 20%), hypertension (6 pts, 15%), diarrhea (4 pts, 10%) elevated transaminases (4 pts, 10%), gastrointestinal hemorrhage (2 pts, 5%), thrombocytopenia (2 pts, 5%), proteinuria, hyperbilirubinemia, back pain, hyperkalemia, and wound infection (1 pt each).

As a major referral center, we have noted a recent change in referral patterns by local oncologists treating patients with advanced HCC. Patients are being started on sorafenib, the standard of care for HCC since its FDA approval in November 2007, based on a phase III study that showed a modest increase in overall survival of 2.8 months.[44] Therefore, patients who have progressed on sorafenib were allowed to participate in the study, after it was extended for a second cohort of 20. Analysis of this cohort is still ongoing with similar promising preliminary results in this important setting. We have seen a signal of activity of bevacizumab and erlotinib in this setting. Therefore, we propose to use this combination as a second-line systemic therapy for patients with advanced HCC who have progressed on sorafenib.

2.0 OBJECTIVES

2.1 Primary

This is a Phase II, single-arm open-label study of erlotinib plus bevacizumab in advanced hepatocellular carcinoma as a second-line therapy in patients who have progressed on first-line Sorafenib therapy.

- The primary objective will be to assess progression-free survival (PFS) measured at 16 weeks following initiation of therapy with the combination of bevacizumab and erlotinib in patients who progressed on sorafenib treatment. Progression-free survival is defined as the time from initiation of therapy until documented disease progression or death.

2.2 Secondary

- The secondary objective will be to assess time to progression (TTP): this endpoint will reflect the time between treatment assignment and radiological progression as defined by the amendments of the Response Evaluation Criteria in Solid Tumors (RECIST). Due to the fact that death often occurs as a result of liver failure in patients with liver cancer, deaths during follow-up without evidence of radiological progression will be censored. This concept has been proposed by a group of experts most recently.[45]

- Other secondary objectives include: response rate, median and overall survival, safety, toxicity and tolerability, stable disease at 16, 24, and 36 weeks, and duration of response.

3.0 STUDY DESIGN

3.1 Description of the Study

This will be a single-arm study. Bevacizumab will be administered intravenously at 10 mg/kg once every 2 weeks, and erlotinib at 150 mg will be taken orally once a day. Patients will be evaluated every 28 days (a cycle is defined as 28 days), and will undergo restaging evaluation every 2 cycles. Treatment will be administered on an outpatient basis at M. D. Anderson Cancer Center. Patients will continue on therapy until disease progression as defined in modified RECIST, until development of

intolerable toxicity, or withdrawal of patient consent. Evaluable patients include any patient who receives at least one 28-day cycle. Patients who do not complete 1 cycle of therapy will be replaced.

3.2 Rationale for Study Design

Because erlotinib and bevacizumab act on two different pathways critical to tumor growth and dissemination, our group designed and completed a phase II study that demonstrated clinical benefits to HCC patients with advanced disease. We propose that the combination of bevacizumab plus erlotinib may prove to be a viable second-line therapy for advanced HCC patients who have failed sorafenib therapy.

We will follow the same design of our phase II study at MDACC, in unresectable HCC given its tolerability record in this patient population. An initial cohort of 40 patients with advanced HCC was completed and published at JCO.[37] An additional cohort of 20 additional patients is currently finishing accruing patients. The study objective was to determine the proportion of patients with HCC treated with the combination of bevacizumab and erlotinib, who were alive and progression-free at 16 weeks (PFS16) of continuous therapy. Secondary objectives included response rate, median PFS, survival, and toxicity. Patients received bevacizumab at 10 mg/kg every 14 days, and erlotinib at 150 mg orally daily, continuously, for 28 day cycles. Tumor response was evaluated every 2 cycles using modified RECIST criteria.

The median age was 64, 31 males (77%), 27 (67.5%) patients had pathologic or radiographic evidence of cirrhosis, 25 patients (62%) were Caucasian, 35 patients (87.5%) had Childs-Pugh A liver function, 8 patients (20%) had prior systemic therapy; 19 patients (47.5%) had ”Cancer for the Liver Italian Program” (CLIP) score 0-2, with 21 patients (52.5%) with a CLIP score of 3-4.

Ten patients achieved a partial response (PR) for a confirmed overall response rate (ORR) of 25%. The PFS at 16 weeks of treatment was 62.5%. The median time to progression was 39 weeks (95% CI 24-45 weeks), and median overall survival (MS) was 68 weeks (95% CI:48-78 weeks), all of which are substantially higher than any other regimen tested in HCC and higher than the results in both the Phase II and Phase III sorafenib trials.

Overall the frequency of grade 3-4 events in this study such as neutropenic fever, myelosuppression, nausea, vomiting and fatigue, was low relative to studies of cytotoxic agents in HCC. Several grade 1-2 drug-related adverse events were commonly experienced by a majority of patients and represented chronic side effects that affected patients’ quality of life. These included dry skin, acne, anorexia, diarrhea, dry mouth/mucositis, and fatigue. These occurred most frequently during the

first 1-4 months of therapy, and generally resolved and/or responded to supportive care measures including oral and topical antibiotics for acne, low-dose steroids for appetite stimulation and fatigue, and anti-diarrhea medications. Nine patients required one dose reduction of erlotinib (150 mg to 100 mg daily) and 2 patients required 2 dose reductions (to 50 mg daily) of erlotinib. Seven patients were removed from the study for toxicity including: fatigue (1 patient), proteinuria (2 patients), delayed wound healing (1 patient), gastrointestinal hemorrhage, (3 patients). Two patients with known portal hypertension developed life-threatening gastrointestinal hemorrhage while on study. One patient recovered and the other patient succumbed within 30 days due to complications of the bleeding event. One patient had grade 1 esophageal varices but was receiving concurrent warfarin. At the time of the bleeding event the prothrombin time (PT) was significantly prolonged. Two patients had known portal hypertension but had poor tolerance to beta blockade therapy and thus remained at risk for variceal bleeding. Following implementation of PillCam™ screening, which was utilized due to its low cost and low morbidity, there were no further episodes of variceal hemorrhage.

3.3 Outcome Measures

3.3.1 Primary Outcome Measures

- Progression-free survival: measured at 16 weeks

3.3.2 Secondary Outcome Measures

- Time to Progression: the time between assignment and radiological progression as defined by the amendments of the Response Evaluation Criteria in Solid Tumors (RECIST).
- Response rate (CR and PR) by RECIST amendments
- Median and Overall survival
- Stable Disease at 16, 24, and 36 weeks
- Duration of response

4.0 SAFETY PLAN

4.1 GENERAL PLAN TO MANAGE SAFETY

A number of measures will be taken to ensure the safety of patients participating in this trial. These measures will be addressed through exclusion criteria (see Section 5.3) and routine monitoring as follows.

Patients enrolled in this study will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study. Safety evaluations will consist of medical interviews, recording of adverse events, physical examinations, blood pressure, and laboratory measurements. Patients will be evaluated for adverse events (all grades), serious adverse events, and adverse events requiring study drug interruption or discontinuation at each study visit for the duration of their participation in the study. Patients discontinued from the treatment phase of the study for any reason will be evaluated ~30 days (28–42 days) after the decision to discontinue treatment (see Section 12.0).

a. Bevacizumab-Specific

Specific monitoring procedures are as follows:

- Hypertension will be monitored through routine evaluation of blood pressure prior to each bevacizumab treatment. Optimal control of blood pressure according to standard public health guidelines is recommended for patients on treatment with or without bevacizumab.
- Proteinuria will be monitored by urine protein:creatinine (UPC) ratio or dipstick every 4 weeks. A 24-hour urine specimen will be collected if proteinuria is ≥ Grade 3.
- If patients on treatment with bevacizumab require elective major surgery, it is recommended that bevacizumab be held for 4-8 weeks prior to the surgical procedure. Patients undergoing a major surgical procedure should not begin/restart bevacizumab until 4 weeks after that procedure (in the case of high risk procedures such as liver resection, thoracotomy, or neurosurgery, it is recommended that chemotherapy be restarted no earlier than 6 weeks and bevacizumab no earlier than 8 weeks after surgery).

b. Erlotinib-Specific

- Skin toxicities will be monitored by routine physical examination and managed symptomatically. The following agents may be used to treat rash: diphenhydramine, topical or oral corticosteroids, and topical (clindamycin) or oral antibiotics (tetracycline, minocycline, doxycycline). Topical drying agents are not recommended.
- Diarrhea will be monitored and managed symptomatically. Guidelines for management include administration of loperamide and Erlotinib dose reduction/interruption as described in Section 7.3.2 and Table 3.
- Although quite rare, ILD can be life threatening. Therefore, patients should be monitored closely for symptoms consistent with ILD, such as new onset dyspnea without an obvious cause. In the event that ILD is suspected, Erlotinib treatment should be discontinued and the patient should receive appropriate medical management. Although there is no

proven therapy, systemic corticosteroids are often provided. Erlotinib should not be restarted in those patients suspected of having drug-related ILD. See Section 7.3.2 and Table 3 for management guidelines, including Erlotinib dose interruption.

- Liver function abnormalities, including elevated serum ALT, AST, and/or bilirubin, have been observed infrequently with single-agent Erlotinib and occasionally with Erlotinib in combination with concomitant chemotherapy. Periodic monitoring of liver function is recommended. Erlotinib dosing should be interrupted if changes in liver function are severe.
- Women of childbearing potential should have a negative pregnancy test prior to starting therapy with Erlotinib and should use adequate contraceptive methods during and after Erlotinib therapy.
- It is not known whether Erlotinib is excreted in human milk. Because many drugs are excreted in human milk and because the effects of Erlotinib on infants have not been studied, women should be advised against breast-feeding while receiving Erlotinib therapy.

5.0 STUDY SUBJECTS

5.1 Subject Selection

Potential study patients will be screened according to the Eligibility Criteria. Study-specific evaluations may be performed only after written informed consent has been obtained.

5.2 Inclusion Criteria

1. Patients with histological or cytologically documented HCC not amenable to curative resection (documentation of original biopsy for diagnosis is acceptable if tumor tissue is unavailable) or clinical diagnosis by American Association for the Study of Liver Diseases (AASLD) criteria (see Appendix Q) in cirrhotic subjects is required. For subjects without cirrhosis, histological or cytological confirmation is mandatory.
2. Patients must have measurable disease as per the modified RECIST criteria (Appendix E). Measurable target lesions are defined at baseline as lesions that can be accurately measured in at least one dimension (longest diameter to be recorded) ≥ 20 mm using conventional techniques (CT or MRI) or ≥10 mm using spiral CT scan. Lesion must not be chosen from a previously irradiated field, unless there has been documented disease progression in that field after irradiation.

3. Patients who have progressed on, or were intolerant to, one prior systemic therapy with sorafenib, completed ≥ 14 days prior to treatment day 1. Previous treatments also allowed that do not count as systemic therapy include: surgical resection, transarterial embolization/chemoembolization (TAE/TACE), radiofrequency ablation (RFA), percutaneous ethanol injection (PEI), provided that the lesion(s) to be evaluated in this study are separate from the previously treated lesions(s).
4. Eastern Cooperative Oncology Group (ECOG) performance status of </= 2 (Appendix B)
5. Childs-Pugh liver function status (Appendix D) of A or B (only 7 points allowed).
6. Organ function: Absolute peripheral granulocyte count of >/= 1500 mm^3, platelet count of >/= 40,000 mm^3, hemoglobin >/= 10 gm/dL. Total bilirubin </= 2.0 gm/dL; serum albumin >/= 2.5 gm/dL; asparte aminotransferase (AST) and alanine aminotransferase (ALT) up to 5 X the upper limit of institutional normal (AST – 46 and ALT – 56); and prothrombin time prolonged not more than 3 seconds greater than institutional normal, once attempts to correct a prolonged PT have been made. Patients who require full dose anticoagulation, who are otherwise eligible for this trial, are allowed to have an appropriately prolonged International Normalized Ratio (INR).
7. Negative serum pregnancy test in women with childbearing potential (those who are not surgically sterilized or who are not amenorrheic for ≥ 12 months), within one week prior to initiation of treatment.
8. Men and women of childbearing potential must agree to use effective means of contraception prior to study entry and for at least 180 days after the last dose of study treatment. They must agree to use two forms of birth control, for example, barrier methods (such as a diaphragm, cervical cap, contraceptive sponge, female condom, or male condom), and an intrauterine device (IUD).
9. Age ≥ 18 years. The agents bevacizumab and erlotinib have not been studied in pediatric patients, thus the doses to be used in this study cannot be assumed to be safe in children.
10. Radiographic evidence of disease progression during or following prior treatment with sorafenib.
11. Patients must have proteinuria < 2+ **or** a urine protein:creatinine (UPC) ratio < 1.0 (Appendix C). Patients who have proteinuria ≥ 2+ **and** UPC ratio ≥ 1.0 must undergo a 24 hour urine collection and must demonstrate ≤ 1g of protein in 24 hours to be eligible.

5.3 Exclusion Criteria

a. Disease-Specific Exclusions

1. Patients who have had prior systemic therapy other than sorafenib. Patients may not have received any systemic chemotherapy </=14 days of Treatment Day 1.
2. Active malignancy other than superficial basal cell and superficial squamous (skin) cell, or carcinoma in situ of the cervix within last five years.
3. Current, recent (within 4 weeks of Treatment Day 1) or planned participation in an experimental drug study, other than this study.
4. Gastrointestinal disease resulting in an inability to take oral medication or a requirement for intravenous hyperalimentation.
5. History of rupture of existing HCC lesion, or HCC lesion with large necrotic areas seen on conventional imaging studies, as determined by the Principal Investigator, if there is no measurable solid tumor area > 1.5 cm.
6. Inadequately controlled hypertension (defined as systolic blood pressure >140 and/or diastolic blood pressure > 90).
7. Prior history of hypertensive crisis or hypertensive encephalopathy.
8. New York Heart Association (Appendix A) Class II or greater congestive heart failure
9. Cardiac arrhythmia not controlled by medication.
10. History of myocardial infarction or unstable angina within 6 months of Treatment Day 1.
11. History of stroke or transient ischemic attack within 6 months prior to Day 1 of treatment.
12. Significant vascular disease (e.g., aortic aneurysm requiring surgical repair or recent peripheral arterial thrombosis) within 6 months prior to Day 1.
13. Evidence of clinically significant (CTC Grade 3 or 4) venous or arterial thrombotic disease within previous 6 months.
14. Radiographic evidence of major tumor thrombus in the vena cava.
15. History of hemoptysis (≥ 1/2 teaspoon of bright red blood per episode) within 1 month prior to Day 1.
16. Evidence of bleeding diathesis or significant coagulopathy (in the absence of therapeutic anticoagulation).
17. History of significant gastrointestinal bleeding requiring procedural intervention (eg variceal banding, Transjugular Intrahepatic Portosystemic

Shunt (TIPS) procedure, arterial embolization) within three months prior to treatment day 1. Patients at risk for varices (based on the following: known history of esophageal or gastric varices; evidence of hepatic cirrhosis and/or portal hypertension including biopsy-proven cirrhosis, radiographic evidence of cirrhosis, hypersplenism, or radiographic findings of varices) will be screened for esophageal varices. If varices are identified that require intervention (banding) that patient will not be eligible for the trial until the varices have been adequately treated.

18. Known CNS disease, except for treated brain metastases. Treated brain metastases are defined as having no evidence of progression or hemorrhage after treatment and no ongoing requirement for dexamethasone, as ascertained by clinical examination and brain imaging (MRI or CT) during the screening period. Anticonvulsants (stable dose) are allowed. Treatment for brain metastases may include whole brain radiotherapy (WBRT), radiosurgery [RS; Gamma Knife, Linear Accelerator (LINAC), or equivalent] or a combination as deemed appropriate by the treating physician. Patients with CNS metastases treated by neurosurgical resection or brain biopsy performed within 3 months prior to Day 1 will be excluded.
19. Major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to Day 1, or anticipation of need for major surgical procedure during the course of the study.
20. Core biopsy, fine needle aspiration, or other minor surgical procedure, excluding placement of a vascular access device, within 7 days prior to Day 1.
21. History of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 6 months prior to Day 1.
22. Serious, non-healing wound, active ulcer, or untreated bone fracture.
23. Ongoing or active infection requiring parenteral therapy.
24. Known HIV disease.
25. Uncontrolled psychiatric illness.
26. Known hypersensitivity to any component of bevacizumab and erlotinib.
27. Pregnancy (positive pregnancy test) or lactation.
28. Inability to comply with study and/or follow-up procedures.

6.0 STUDY DESIGN

6.1 Treatment Plan

This is an open-label single arm single institution phase II study designed to evaluate the efficacy and safety of bevacizumab and erlotinib in patients with HCC who progressed on first-line sorafenib therapy. Bevacizumab 10 mg/kg will be administered intravenously once every 2 weeks and erlotinib 150 mg will be taken orally daily. Treatment may continue until occurrence of disease progression, unacceptable toxicity, or patient withdrawal from the study. Patients will be evaluated every 28 days (a cycle is defined as 28 days), and will undergo restaging evaluation every 2 cycles. Treatment will be administered on an outpatient basis at M. D. Anderson Cancer Center.

The estimated number of patients to be enrolled is 44, the estimated rate of accrual is 1-2 patients per month, with an estimated date of study completion of 3 years from initiation of enrollment, including follow-up.

Doses and Schedule

Bevacizumab	10 mg/kg IV	Once every 2 weeks
Erlotinib	150 mg Oral	Once Daily

For patients who experience treatment-related toxicity, criteria for study drug(s) reduction and/or dose withholding are provided in section 7.

7.0 STUDY MEDICATION

7.1 BEVACIZUMAB DOSAGE AND FORMULATION

Bevacizumab will be administered intravenously at 10 mg/kg once every 2 weeks. Bevacizumab is a clear to slightly opalescent, colorless to pale brown, sterile liquid concentrate for solution for intravenous (IV) infusion. Bevacizumab may be supplied in 20-cc (400-mg) glass vials containing 16 mL bevacizumab (25 mg/mL). Vials contain bevacizumab with phosphate, trehalose, polysorbate 20, and Sterile Water for Injection (SWFI), United States Pharmacopeia (USP). Vials contain no preservative and are suitable for single use only.

For further details and molecule characterization, see the bevacizumab Investigator Brochure.

7.1.1 Bevacizumab Administration

Bevacizumab will be diluted in a total volume of 100mL of 0.9% Sodium Chloride Injection, USP. Administration will be as a continuous IV infusion. Anaphylaxis precautions should be observed during study drug administration. It is not necessary to correct dosing based on ideal weight.

The initial dose will be delivered over 90±15 minutes. If the first infusion is tolerated without infusion-associated adverse events (fever and/or chills), the second infusion may be delivered over 60±10 minutes. If the 60-minute infusion is well tolerated, all subsequent infusions may be delivered over 30±10 minutes.

If a subject experiences an infusion–associated adverse event, he or she may be premedicated for the next study drug infusion; however, the infusion time may not be decreased for the subsequent infusion. If the next infusion is well tolerated with premedication, the subsequent infusion time may then be decreased by 30±10 minutes as long as the subject continues to be premedicated. If a subject experiences an infusion-associated adverse event with the 60-minute infusion, all subsequent doses should be given over 90±15 minutes. Similarly, if a subject experiences an infusion-associated adverse event with the 30-minute infusion, all subsequent doses should be given over 60±10 minutes.

7.1.2 Bevacizumab Storage

Upon receipt of the study drug, vials are to be refrigerated at 2°C–8°C (36°F–46°F) and should remain refrigerated until just prior to use. DO NOT FREEZE. DO NOT SHAKE. Vials should be protected from light.

Opened vials must be used within 8 hours. VIALS ARE FOR SINGLE USE ONLY. Vials used for 1 subject may not be used for any other subject. Once study drug has been added to a bag of sterile saline, the solution must be administered within 8 hours..

Any unused or expired study drug will be destroyed per institutional policy.

7.2 ERLOTINIB DOSAGE AND FORMULATION

7.2.1 Formulation

Erlotinib oral tablets are conventional, immediate-release tablets containing erlotinib as the hydrochloride salt. In addition to the active ingredient, Erlotinib contains lactose (hydrous), microcrystalline cellulose, sodium starch glycolate, sodium lauryl sulfate, and magnesium stearate.

Tablets containing 25 mg, 100 mg, and 150 mg of Erlotinib are available. Each bottle will contain 30 tablets, a quantity sufficient for 4 consecutive weeks of dosing, with overage.

For further details, see the Erlotinib Investigator's Brochure.

7.2.2 Dosage, Administration, and Storage

Erlotinib will be administered at 150 mg, one tablet orally once a day. Erlotinib will be self-administered in an open-label, unblinded manner to all patients enrolled in the study. Tablets should be taken at the same time each day with 200 mL of water at least 1 hour before or 2 hours after a meal. On Day 1 of treatment, since the dispensing time may vary, patients should take the dose as soon as it is dispensed.

Erlotinib tablets will be supplied for this clinical trial in white, high-density polyethylene (HDPE) bottles with child-resistant closures and should be stored at temperatures between 15°C and 30°C (59°F and 86°F).

For each cycle, patients will be instructed to return any leftover erlotinib. Patients will also be given a diary to document erlotinib dosing. The diary plus returned drug will be used to assess compliance with the treatment.

Any unused or expired study drug returned by the patient will be destroyed per institutional policy.

7.3 Dose Modifications

7.3.1 Bevacizumab Dose Modification and Toxicity Management

There are no reductions in the bevacizumab dose. If adverse events occur that require holding bevacizumab, the dose will remain the same once treatment resumes.

Any toxicities associated or possibly associated with bevacizumab treatment should be managed according to standard medical practice. Discontinuation of bevacizumab will have no immediate therapeutic effect. Bevacizumab has a terminal half-life of 21 days; therefore, its discontinuation results in slow elimination over several months. There is no available antidote for bevacizumab.

Subjects should be assessed clinically for toxicity prior to, during, and after each infusion. If unmanageable toxicity occurs because of bevacizumab at any time during the study, treatment with bevacizumab should be discontinued.

Infusion Reaction: Infusion of bevacizumab should be interrupted for subjects who develop dyspnea or clinically significant hypotension. Subjects who experience a NCI CTCAE v. 3.0 Grade 3 or 4 allergic reaction / hypersensitivity, adult respiratory distress syndrome, or bronchospasm (regardless of grade) will be discontinued from bevacizumab treatment.

The infusion should be slowed to 50% or less or interrupted for subjects who experience any infusion-associated symptoms not specified above. When the subject's symptoms have completely resolved, the infusion may be continued at no more than 50% of the rate prior to the reaction and increased in 50% increments every 30 minutes if well tolerated. Infusions may be restarted at the full rate during the next cycle.

Adverse events requiring delays or permanent discontinuation of bevacizumab are listed in Table 1

Regardless of the reason for holding study drug treatment, the maximum allowable length of treatment interruption is 2 months.

Table1:
Bevacizumab Dose Management Due to Adverse Events

Event	Action to be Taken
Hypertension	
No dose modifications for grade 1/2 events	
Grade 3	If not controlled to 150/100 mmHg with medication, discontinue bevacizumab.
Grade 4 (including hypertensive encephalopathy)	Discontinue bevacizumab.
Hemorrhage	
No dose modifications for grade 1/2 non-pulmonary and non-CNS events	
Grade 3 Non-pulmonary and non-CNS hemorrhage	Subjects who are also receiving full-dose anticoagulation will be discontinued from receiving bevacizumab. All other subjects will have bevacizumab held until all of the following criteria are met: • The bleeding has resolved and hemoglobin is stable. • There is no bleeding diathesis that would increase the risk of therapy. • There is no anatomic or pathologic condition that significantly increases the risk of hemorrhage recurrence. Subjects who experience a repeat Grade 3 hemorrhagic event will be discontinued from receiving bevacizumab.
Grade 4 non-pulmonary or non-CNS hemorrhage	Discontinue bevacizumab.
Grade 1pulmonary or CNS hemorrhage	Subjects who are also receiving full-dose anticoagulation will be discontinued from receiving bevacizumab. All other subjects will have bevacizumab held until all of the following criteria are met: • The bleeding has resolved and hemoglobin is stable. • There is no bleeding diathesis that would increase the risk of therapy. • There is no anatomic or pathologic condition that significantly increases the risk of hemorrhage recurrence.
Grade 2, 3, or 4 pulmonary or CNS hemorrhage	Discontinue bevacizumab
Venous Thrombosis	
No dose modifications for grade 1/2 events	

Bevacizumab Dose Management due to Adverse Events (continued)

Grade 3 or 4	Hold study drug treatment. If the planned duration of full-dose anticoagulation is <2 weeks, bevacizumab should be held until the full-dose anticoagulation period is over. If the planned duration of full-dose anticoagulation is >2 weeks, bevacizumab may be resumed during the period of full-dose anticoagulation if all of the following criteria are met: • The subject must have an in-range INR (usually between 2 and 3) if on warfarin; LMWH, warfarin, or other anticoagulant dosing must be stable prior to restarting bevacizumab treatment. • The subject must not have had a Grade 3 or 4 hemorrhagic event while on anticoagulation.
Arterial Thromboembolic event	
(New onset, worsening, or unstable angina, myocardial infarction, transient ischemic attack, cerebrovascular accident, and any other arterial thromboembolic event)	
Any grade	Discontinue bevacizumab.
Congestive Heart Failure (Left ventricular systolic dysfunction)	
No dose modifications for grade 1/2 events	
Grade 3	Hold bevacizumab until resolution to Grade ≤ 1.
Grade 4	Discontinue bevacizumab.
Proteinuria	
No dose modifications for grade 1/2 events	
Grade 3 (UPC> 3.5, urine collection > 3.5 g/24 hr)	Hold bevacizumab treatment until ≤ Grade 2, as determined by either UPC ratio ≤ 3.5 or 24 hr collection ≤ 3.5 g
Grade 4 (nephritic syndrome)	Discontinue bevacizumab
GI Perforation	Discontinue bevacizumab.
Fistula	
Any grade (TE fistula)	Discontinue bevacizumab.
Grade 4 fistula	Discontinue bevacizumab.
Bowel Obstruction	
Grade 1	Continue patient on study for partial obstruction NOT requiring medical intervention.

Bevacizumab Dose Management due to Adverse Events (continued)	
Grade 2	Hold bevacizumab for partial obstruction requiring medical intervention. Patient may restart upon complete resolution.
Grade 3/4	Hold bevacizumab for complete obstruction. If surgery is necessary, patient may restart bevacizumab after full recovery from surgery, and at investigator's discretion.
Wound dehiscence Any grade (requiring medical or surgical therapy)	**Discontinue bevacizumab.**
Reversible Posterior Leukoencephalopathy	
Any grade (confirmed by MRI)	Discontinue bevacizumab.
Other Unspecified Bevacizumab-Related Adverse Events	
Grade 3	Hold bevacizumab until recovery to ≤ Grade 1
Grade 4	Discontinue bevacizumab.

7.3.2 Erlotinib Dose Modification and Toxicity Management

Dose Modification

Dose reduction or interruption of erlotinib for toxicity may take place at any time during the study. Toxicity grading is based on NCI-CTCAE, v 3.0. Dose level reductions are presented in Table 2. If patients do not tolerate the second dose reduction, erlotinib is to be discontinued.

Table 2

Erlotinib Dose Level Reductions

Starting Dose	First Reduction	Second Reduction
150 mg/day	100 mg/day	50 mg/day

Dose modification guidelines are summarized in Table 3.

Management of a tolerable Grade 2 or 3 rash should include continuation of erlotinib at the current dose and symptomatic management. If skin rash is intolerable, dose reduction according to Table 3 should be considered. When skin toxicity improves by at least one grade level, the dose may be re-escalated as tolerated. In Phase II trials, this approach enabled dose re-escalation for the majority of patients requiring dose reduction for skin toxicity. Patients experiencing Grade 4 skin toxicity should be discontinued from study treatment.

For Grade 1 or 2 diarrhea, early intervention should include continuation of erlotinib at the current dose and initiation of loperamide therapy as described in Table 3. Grade 2 diarrhea that persists over 48–72 hours, despite optimal medical management, should be managed by dose reduction according to Table 3. Patients experiencing Grade 3 diarrhea should interrupt erlotinib until resolution to Grade ≤1 and re-start at a reduced dose according to Table 3. Patients should be maintained at the reduced dose without attempt at dose re-escalation. Patients experiencing Grade 4 diarrhea should be discontinued from study treatment.

Erlotinib should not be restarted in those suspected of having drug-related ILD.

Table 3

Dosage Modification Criteria and Guidelines for Management of Erlotinib-Related Toxicities

NCI-CTCAE (v 3.0) Grade	Erlotinib Dose Modification	Guideline for Management
Diarrhea		
Grade 1	None	Consider loperamide (4 mg at first onset, followed by 2 mg q 2–4 hours until free of diarrhea for 12 hours)
Grade 2	None (Dose reduction of Erlotinib is necessary if diarrhea persists over 48–72 hours despite optimal medical management)	Loperamide (4 mg at first onset, followed by 2 mg q 2–4 hours until diarrhea free for 12 hours)
Grade 3	Interrupt then dose reduce Erlotinib. Erlotinib should not be re-escalated.	Interrupt Erlotinib until resolution to Grade ≤1, and restart at next reduced dose
Grade 4	Discontinue study treatment.	
Pulmonary Events if possibly ILD		
All Grades	Temporarily interrupt Erlotinib pending the diagnostic evaluation. If the pulmonary adverse event is assessed as related to Erlotinib, discontinue the patient from study treatment.	Unexplained dyspnea, either new or progressive, should be aggressively evaluated.
Rash		
Grade 1 and 2 Tolerable rash	None	Any of the following: oral antibiotics (tetracycline, minocycline, doxycycline) topical clindamycin, diphenhydramine, topical or oral corticosteroids at discretion of investigator
Grade 3 Intolerable rash	Consider interruption and or dose reduction if unresponsive to symptomatic management. Re-escalation is allowed.	Manage as described above
Grade 4	Discontinue study treatment.	Manage as described above

7.4 CONCOMITANT AND EXCLUDED THERAPIES

Use of anti-neoplastic or anti-tumor agents not part of the study therapy, including chemotherapy, radiation therapy, immunotherapy, and hormonal

anticancer therapy, is not permitted while participating in this study. Use of concurrent investigational agents is not permitted.

Low-dose aspirin (≤ 325 mg/d) may be continued in subjects at higher risk for arterial thromboembolic disease. Subjects developing signs of arterial ischemia or bleeding on study should be evaluated for possible bevacizumab discontinuation per Table 1, Bevacizumab Dose Management Due To Adverse Events.

There are potential interactions between Erlotinib and CYP3A4 inhibitors and CYP3A4 promoters. Although caution and careful monitoring are recommended when use of these compounds is necessary, use of these compounds does not exclude patients from participating in this trial (see Appendix F for a list of CYP3A4 inhibitors and inducers).

Grapefruit juice is a CYP3A4 inhibitor, therefore, consumption of grapefruit or grapefruit juice should be avoided during Erlotinib treatment.

The solubility of Erlotinib is pH dependent. Erlotinib solubility decreases as pH increases. Co-administration of Erlotinib with omeprazole, a proton pump inhibitor, decreased the exposure of Erlotinib (AUC) by 46% and the maximum concentration (C_{max}) by 61%. There was no change to Tmax or half-life. Therefore, drugs that alter the pH of the GI tract may alter the solubility of Erlotinib and hence its bioavailability.

The exposure to Erlotinib (AUC) increased to a moderate extent, by 39%, and the maximum concentration (C_{max}) by 17%, when Erlotinib was co-administered with ciprofloxacin, an inhibitor of both CYP3A4 and CYP1A2.

Erlotinib clearance can be induced by smoking via CYP1A2 induction. Potential drug-drug interaction is expected when erlotinib is taken with CYP1A2 inducers or inhibitors. In a single-dose study in healthy volunteers, the AUC was reduced by 64% in smokers when compared with nonsmokers. In BR.21, current smokers achieved Erlotinib trough plasma concentrations that were approximately 2-fold lower than never smokers. Smokers should be advised to stop smoking while taking Erlotinib as plasma concentrations of erlotinib are reduced due to the effect of cigarette smoking.

Pretreatment or co-administration of erlotinib did not alter the clearance of a prototypical CYP3A4 substrate, midazolam. Therefore, significant metabolic interactions with other CYP3A4 substrates are unlikely. However, the oral bioavailability of midazolam decreased by up to 24% following Erlotinib treatment, which was not attributed to a metabolic interaction.

Patients taking warfarin or other warfarin-derivative anticoagulants should be monitored regularly for changes in prothrombin time or INR.

8.0 CLINICAL AND LABORATORY EVALUATIONS

	Pre-Study@	Cycle 1, Day 1	Cycle 1, Day 15	Cycle 2 & Sub-sequent Cycles, Day 1g#	Cycle 2 & Sub-sequent Cycles, Day 15	End of Cycle 2, 4, & every 2 subsequent cycles	End of Treat-ment	Post Treat-ment Follow-up
Informed Consent	X							
Demographics	X							
Medical History	X			X			X	
Concurrent Medications*	X			X			X	
Physical Exam	X			X			X	
Height	X							
Weight	X	X		X			X	
Vital Signs (Includes SBP/DBP)	X	X	X	X	X		X	
Urinalysis w/urine protein determination	X[m]			X[k]			X	
Performance status	X			X			X	
HBV and HCV serology	X							
PT/PTT/INR[a]	X			X			X	
CBC with differential, platelets	X			X			X	
Serum chemistry [b]	X			X			X	
Liver function tests [c]	X			X			X	
ECG[l]	X							
Serum ß-HCG (women of child-bearing potential)	X							
AFP[d]	X			X			X	
CT/MRI chest/abdomen/pelvis tumor Assessment [e]	X					X	X	
Esophageal-gastric (EGD) endoscopy[i]	X							
Bevacizumab		**X**	**X[f]**	**X[f]**	**X[f]**			
Erlotinib		**Once daily continuously until treatment discontinuation**						
Adverse events	Continuous monitoring during study participation							X[j]
Survival								X[h]

@ Prestudy evaluations except for imaging studies, HBV, & HCV must be obtained within 7 days prior to first day of treatment. Baseline imaging studies may be obtained up to 28 days prior to first day of treatment. HBV & HCV must be obtained within 3 months prior to first day of treatment

Evaluations may be obtained within 72 hours prior to starting a new cycle, except for imaging studies which may be obtained within 7 days prior to starting a new cycle.

*All medications, including prescription and over-the-counter, vitamins, supplements and "herbal" preparations must be disclosed by the patient and recorded. Patients will be instructed to check with study staff before taking any new prescription or over-the-counter medication(s), vitamins, supplements and/or “herbal" preparations

[a] Weekly monitoring of INR for patients on warfarin, however, these patients will be switched to enoxaparin if possible.

[b] Includes BUN, creatinine, sodium, potassium, carbon dioxide, chloride, phosphorus, magnesium. calcium, protein, glucose.

[c] Includes AST (SGOT), ALT (SGPT); total, direct and indirect bilirubin; LDH, alkaline phosphatase, albumin; (GGT will be run for alkaline phosphatase that is >/= 150 IU/L. GGT will be run with the first elevation of alkaline phosphatase and will not be repeated for future alkaline phosphatase elevations)

[d] Alpha-feto protein.

[e] CT will be the radiographic study of choice for baseline and re-staging evaluations; MRI may be substituted at any time in the course of the study as clinically warranted (eg iodine dye intolerance, elevated creatinine). At baseline, CT/MRI scans of chest/abdomen/pelvis will be performed. At restaging, CT/MRI scans of abdomen/pelvis will be performed and chest scan as needed.

[f] Treatment may be given within a 72-hour window (Cycle 1, Day 15 and subsequent treatment days of each cycle).

[g] Treatment may continue after Course 2, including the same study assessment schedule, until one of the criteria for treatment discontinuation applies.

[h] Every 3 months after discontinuation of study treatment until death.

[i] If not done within 6 months prior to study enrollment, esophageal-gastric (EGD) endoscopy will be performed in patients at risk for varices based on the following: known history of esophageal or gastric varices, evidence of hepatic cirrhosis and/or portal hypertension including biopsy-proven cirrhosis, radiographic evidence of cirrhosis, hypersplenism, or radiographic findings of varices.

[j] Patients who have an ongoing Grade ≥ 3 or serious adverse event that is at least possibly related to treatment will be contacted by the investigator or designee every week until the event is resolved or determined to be irreversible.

[k] Proteinuria will be monitored by urine protein:creatinine (UPC) ratio or dipstick every 4 weeks. A 24-hour urine specimen will be collected if proteinuria is ≥ Grade 3.

[l.] Patients with prior exposure to systemic anthracyclines will have a baseline Multi Gated Acquisition (MUGA) scans or echocardiograms (ECHOs).

m. Patients who have proteinuria ≥ 2+ and UPC ratio ≥ 1.0 will undergo a 24 hour urine collection

8.1 POST-TREATMENT EVALUATIONS

The visit at which a response assessment shows disease progression or the decision was made to discontinue treatment for other reasons, such as toxicity, will be considered the End of Treatment visit.

After the treatment completion visit, patients will continue to be followed for adverse events by phone call or clinic visit as needed until at least 30 days after the last dose of study drug.

Patients who have an ongoing Grade ≥ 3 or serious adverse event that is at least possibly related to treatment will be contacted by the investigator or designee every week until the event is resolved or determined to be irreversible.

Patients will be followed for survival by clinic visit, review of medical record, and/or telephone call every 3 months from treatment discontinuation date, until death. Information to be obtained will include post-study discontinuation HCC therapy, as available.

9.0 SUBJECT DISCONTINUATION

Subjects who meet the following criteria should be discontinued from study treatment:

- Grade 4 hypertension or Grade 3 hypertension not controlled with medication
- Nephrotic syndrome
- Grade ≥ 2 pulmonary or CNS hemorrhage; any Grade 4 hemorrhage
- Symptomatic Grade 4 venous thromboembolic event (for lung protocols: any venous thromboembolic event requiring full dose warfarin or equivalent (i.e., unfractionated or low molecular weight heparin)
- Any grade arterial thromboembolic event
- Grade 4 congestive heart failure
- Gastrointestinal perforation
- Tracheoesophageal fistula (any grade) or Grade 4 fistula
- Grade ≥ 2 bowel obstruction that has not fully recovered despite medical or surgical intervention
- Wound dehiscence requiring medical or surgical intervention
- ILD
- Grade 4 skin toxicity
- Grade 4 diarrhea
- Unwillingness or inability of subject to comply with study requirements
- Determination by the investigator that it is no longer safe for the subject to continue therapy
- All Grade 4 events thought to be related to study drug(s) by the investigator

Patients who have an ongoing study drug -related Grade ≥ 3 or serious adverse event at the time of discontinuation from study treatment will continue to be followed until resolution of the event or until the event is considered irreversible.

10.0 STUDY DISCONTINUATION

If, after 14 patients are enrolled and are evaluable for PFS, the criteria for proceeding to the second stage of accrual are not met, the study will be discontinued. Otherwise, the study will continue to the planned maximum accrual.

11.0 STATISTICAL METHODS

This is a single-arm phase II trial assessing the efficacy of erlotinib and bevacizumab in 44 patients with unresectable HCC who have progressed on sorafenib treatment.

11.1 STUDY DESIGN

44 patients evaluable for response will be included in the study. The primary endpoint is the binary variable progression free survival (PFS) at 16 weeks of treatment with the combination of bevacizumab and erlotinib. A patient is said to be failure free at 16 weeks if they are alive, and their disease has not progressed. Success is considered stable disease or objective response by 16 weeks of continuous treatment.

This trial will follow a Simon's two-stage design. The optimal two-stage design to test the null hypothesis that P<=0.350 versus the alternative that P>=0.550 with 80% power at one-sided alpha level of 0.05 will be used. After testing the drug on 14 patients in the first stage, the trial will be terminated if 5 or fewer are alive and progression free at 16 weeks. If the trial goes on to the second stage, a total of 44 patients will be studied. If the total number responding is less than or equal to 20, the drug is rejected. This design has an expected sample size of 24.78 and a probability of early termination of 0.641. If the drug is actually not effective, there is a 0.046 probability of concluding that it is (the target for this value was 0.050). If the drug is actually effective, there is a 0.200 probability of concluding that it is not (the target for this value was 0.200).

A competing risks approach will be used to analyze the secondary endpoint; TTP; where deaths from other causes and discontinuation due to adverse event will be considered competing risks.
Other secondary endpoints of interest will include overall survival, defined as the time from initiation of therapy until documented disease progression or death, or time from initiation of therapy to death, respectively. We will also include response rate, median and overall survival, toxicity and tolerability, and time to radiologic progression defined as time from initiation of therapy until documeted radiologic disease progression. These will be summarized by their corresponding Kaplan-Meier curves.

11.2 PLANNED EFFICACY EVALUATIONS

11.2.1 Primary Efficacy Variables

The primary endpoint, PFS at 16 weeks, will be summarized by the estimated proportion and 95% confidence interval. For this analysis, patients will be considered success if they are alive and progression free at 16 weeks; otherwise they will be considered failures.

11.2.2 Secondary Efficacy Variables

The secondary endpoint is TTP. Time to progression is defined as the time from initiation of therapy until documented radiologic disease progression. 44 patients evaluable for response will be included in the study. A competing risks approach will be used to analyze TTP where deaths from other causes and discontinuation due to adverse event will be considered competing risks. Specifically, patients will be
(a) censored if they have had neither death nor disease progression by study end
(b) treated as a progression if they have disease progression prior to death or study end, or if death is due to disease
(c) treated as a death from other cause if they have died due to a cause unrelated to disease
(d) treated as an AE discontinuation if they are removed from the study due to an study-related AE
Statistical methods for estimation and comparison of competing risks are well-described.[46]
Other secondary objectives are: response rate, median and overall survival, toxicity and tolerability. Overall survival will be analyzed using Kaplan-Meier methods. Proportions and their exact 95% confidence intervals will be estimated for binary outcomes (i.e., response, toxicity and tolerability). Responders will include complete and partial responders as defined by modified RECIST criteria.*

*The original RECIST publication did not address measures of antitumor activity other than tumor shrinkage.[47] In 2000, however, a panel of experts convened by European Association for the Study of the Liver (EASL) recommended that the response criteria be amended to take into account tumor necrosis induced by treatment.[48] That panel considered estimation of the reduction in viable tumor area using contrast-enhanced radiological imaging to be the optimal method to assess treatment response. Viable tumor was defined as uptake of contrast agent in the arterial phase of dynamic CT or MRI.

12.0 Safety Monitoring Plan

A number of measures will be taken to ensure the safety of patients participating in this trial. These measures will be addressed through exclusion criteria and routine monitoring as follows.

Patients enrolled in this study will be evaluated clinically and with standard laboratory tests before and at regular intervals defined in the protocol during their participation in this study. Safety evaluations will consist of medical interviews, recording of adverse events, physical examinations, blood pressure, and laboratory measurements. Patients will be evaluated for adverse events (all grades), serious adverse events, and adverse events requiring study drug interruption or discontinuation at each study visit for the duration of their participation in the study. Patients discontinued from the treatment phase of the study for any reason will be evaluated ~30 days (28–42 days) after the decision to discontinue treatment.

The P.I. will meet with the Research Nurse as necessary to discuss patients' status. Any serious adverse events (SAEs) occurring in study patients will be reviewed by the GI Medical Oncology Department Head and clinical research faculty, including sub-investigators, as part of a weekly departmental Clinical Research Review meeting. The PI also will present updated reports on the study status, including accrual, efficacy, and any safety issues, every 4-5 weeks at this same meeting when hepatobiliary clinical studies are reviewed.

In the event of any significant safety concerns, the P.I. will take all action necessary to protect study participants, such as modifying the protocol, holding accrual until safety concerns are addressed, and/or discontinuing participants from study drugs if warranted.

13.0 Data Confidentiality

The Principal Investigator will take steps to guard against any loss of confidentiality. The Principal Investigator and authorized research staff have completed training in Health Insurance Portability and Accountability Act of 1996 (HIPAA) requirements for protection of Private Health Information (PHI). Only the Principal Investigator and the authorized research staff will have access to the participant's identifiable information from this study. Data will be kept on the institutional password - protected computer system known as Protocol Data Management System (PDMS). Employees must have clearance through the M. D. Anderson Cancer Center Information Services Security Department to be authorized as a PDMS user.

Clinical trial data and results obtained during the conduct of the study will be made available exclusively to M. D. Anderson Cancer Center, Genentech, OSI, and the FDA, as appropriate and unless additional disclosure is required by law or court order. Data provided to Genentech and OSI will be encrypted with all potential personal identifiers stripped from the file.

Additionally, all clinical data and results will be collected, used, and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects including, the *Standards for Privacy of Individual Health Information* set forth in 45 C.F.R. Part 164.

14.0 Reporting Requirements

14.1 Serious Adverse Event Reporting (SAE) for M. D. Anderson-Sponsored IND Protocols

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.

- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center

Institutional Review Board Policy for Investigators on Reporting Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).

• **All life-threatening or fatal events,** that are unexpected, and related to the study drug, must have a written report submitted within **24 hours** (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.

• Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.

• Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.

• Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.

Reporting to FDA:

• Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

14.2 Investigator Communication with Supporting Companies:

All serious adverse events will be faxed (using the safety reporting fax cover sheet) to

Genentech Drug Safety
Fax: (650) 225-4682 or (650) 225-5288

14.3 Adverse Events Reporting (AE)

Adverse events for this protocol will be recorded using the Recommended Adverse Event Recording Guidelines for phase II protocols.

The Investigator is responsible for verifying and providing source documentation for all adverse events and assigning attribution for each event for all subjects enrolled on the trial.

Adverse events will be documented in the medical record (event name, grade, start/stop date, and attribution) and entered into the electronic case report form (PDMS).

Recommended Adverse Event Recording Guidelines					
Attribution	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Unrelated			Phase II	Phase II	Phase II
Unlikely			Phase II	Phase II	Phase II
Possible	Phase II	Phase II	Phase II	Phase II	Phase II
Probable	Phase II	Phase II	Phase II	Phase II	Phase II
Definitive	Phase II	Phase II	Phase II	Phase II	Phase II

References

1. El-Serag, H.B. and A.C. Mason, *Rising incidence of hepatocellular carcinoma in the United States.* N Engl J Med, 1999. **340**(10): p. 745-50.
2. Pang, R.W., et al., *Biology of hepatocellular carcinoma.* Ann Surg Oncol, 2008. **15**(4): p. 962-71.
3. Fausto, N., *Growth factors in liver development, regeneration and carcinogenesis.* Prog Growth Factor Res, 1991. **3**(3): p. 219-34.
4. Hisaka, T., et al., *Expressions of epidermal growth factor family and its receptor in hepatocellular carcinoma cell lines: relationship to cell proliferation.* Int J Oncol, 1999. **14**(3): p. 453-60.
5. Hopfner, M., et al., *Targeting the epidermal growth factor receptor by gefitinib for treatment of hepatocellular carcinoma.* J Hepatol, 2004. **41**(6): p. 1008-16.
6. Huether, A., et al., *Erlotinib induces cell cycle arrest and apoptosis in hepatocellular cancer cells and enhances chemosensitivity towards cytostatics.* J Hepatol, 2005. **43**(4): p. 661-9.
7. Philip, P.A., et al., *Phase II study of Erlotinib (OSI-774) in patients with advanced hepatocellular cancer.* J Clin Oncol, 2005. **23**(27): p. 6657-63.
8. Thomas, M.B., et al., *Phase 2 study of erlotinib in patients with unresectable hepatocellular carcinoma.* Cancer, 2007. **110**(5): p. 1059-1067.
9. Hanahan, D. and J. Folkman, *Patterns and emerging mechanisms of the angiogenic switch during tumorigenesis.* Cell, 1996. **86**(3): p. 353-64.
10. Park, Y.N., et al., *Increased expression of vascular endothelial growth factor and angiogenesis in the early stage of multistep hepatocarcinogenesis.* Arch Pathol Lab Med, 2000. **124**(7): p. 1061-5.
11. Zhao, J., et al., *Vascular endothelial growth factor expression in serum of patients with hepatocellular carcinoma.* Chin Med J (Engl), 2003. **116**(5): p. 772-6.
12. Huang, G.W., L.Y. Yang, and W.Q. Lu, *Expression of hypoxia-inducible factor 1alpha and vascular endothelial growth factor in hepatocellular carcinoma: Impact on neovascularization and survival.* World J Gastroenterol, 2005. **11**(11): p. 1705-8.

13. Kanematsu, M., et al., *Expression of vascular endothelial growth factor in hepatocellular carcinoma and the surrounding liver: correlation with angiographically assisted CT.* AJR Am J Roentgenol, 2004. **183**(6): p. 1585-93.
14. Kanematsu, M., et al., *Magnetic resonance imaging and expression of vascular endothelial growth factor in hepatocellular nodules in cirrhosis and hepatocellular carcinomas.* Top Magn Reson Imaging, 2005. **16**(1): p. 67-75.
15. Wang, B., Z.Q. Gao, and X. Yan, *Correlative study of angiogenesis and dynamic contrast-enhanced magnetic resonance imaging features of hepatocellular carcinoma.* Acta Radiol, 2005. **46**(4): p. 353-8.
16. D'Amato, R.J., et al., *Thalidomide is an inhibitor of angiogenesis.* Proc Natl Acad Sci U S A, 1994. **91**(9): p. 4082-5.
17. Kenyon, B.M., F. Browne, and R.J. D'Amato, *Effects of thalidomide and related metabolites in a mouse corneal model of neovascularization.* Exp Eye Res, 1997. **64**(6): p. 971-8.
18. Kumar, S., T.E. Witzig, and S.V. Rajkumar, *Thalidomid: current role in the treatment of non-plasma cell malignancies.* J Clin Oncol, 2004. **22**(12): p. 2477-88.
19. Zhu, A.X., *Systemic therapy of advanced hepatocellular carcinoma: how hopeful should we be?* Oncologist, 2006. **11**(7): p. 790-800.
20. Hsu, C., et al., *Low-dose thalidomide treatment for advanced hepatocellular carcinoma.* Oncology, 2003. **65**(3): p. 242-9.
21. Wang, T.E., et al., *Salvage therapy for hepatocellular carcinoma with thalidomide.* World J Gastroenterol, 2004. **10**(5): p. 649-53.
22. Lin, A.Y., et al., *Phase II study of thalidomide in patients with unresectable hepatocellular carcinoma.* Cancer, 2005. **103**(1): p. 119-25.
23. Patt, Y.Z., et al., *Thalidomide in the treatment of patients with hepatocellular carcinoma: a phase II trial.* Cancer, 2005. **103**(4): p. 749-55.
24. Schwartz, J.D., et al., *Thalidomide in advanced hepatocellular carcinoma with optional low-dose interferon-alpha2a upon progression.* Oncologist, 2005. **10**(9): p. 718-27.
25. Zhu, A.X., et al., *A phase II study of epirubicin and thalidomide in unresectable or metastatic hepatocellular carcinoma.* Oncologist, 2005. **10**(6): p. 392-8.
26. Fazio, N., Petralia, G., Mancuso, P., Lorizzo, K., Jemos, C., Boselli, S., Porcu, C., Bertolini, F., Bellomi, M., de Braud, F. , *Thalidomide in patients with advanced hepatocellular carcinoma: a clinical/biological study.* Journal of Clinical Oncology, 2007. **25**(18S): p. 15076.
27. Zhu, A.X., et al., *A phase II study of sunitinib in patients with advanced hepatocellular carcinoma.* Journal of Clinical Oncology, 2007. **25**(18S): p. 4637.
28. Abou-Alfa, G.K., et al., *Phase II study of sorafenib in patients with advanced hepatocellular carcinoma.* J Clin Oncol, 2006. **24**(26): p. 4293-300.

29. Llovet, J., et al., *Randomized phase III trial of sorafenib versus placebo in patients with advanced hepatocellular carcinoma (HCC) (SHARP Investigators Study Group).* Journal of Clinical Oncology, 2007. **25**(18S): p. LBA1.
30. Jain, R.K., *Normalizing tumor vasculature with anti-angiogenic therapy: a new paradigm for combination therapy.* Nat Med, 2001. **7**(9): p. 987-9.
31. Willett, C.G., et al., *Direct evidence that the VEGF-specific antibody bevacizumab has antivascular effects in human rectal cancer.* Nature Medicine, 2004. **10**(2): p. 145-147.
32. Malka, D., et al., *Bevacizumab in patients (pts) with advanced hepatocellular carcinoma (HCC): preliminary results of a phase II study with circulating endothelial cell (CEC) monitoring.* Journal of Clinical Oncology, 2007. **25**(18S): p. 4570.
33. Zhu, A.X., et al., *Phase II study of gemcitabine and oxaliplatin in combination with bevacizumab in patients with advanced hepatocellular carcinoma.* J Clin Oncol, 2006. **24**(12): p. 1898-903.
34. Hsu, C., et al., *Modified-dose capecitabine + bevacizumab for the treatment of advanced/metastatic hepatocellular carcinoma (HCC): a phase II, single-arm study.* Journal of Clinical Oncology, 2007. **25**(18S): p. 15190.
35. Sun, W., DG Haller, K Mykulowycz, M. Rosen, M. Soulem, M. Capparo, T Faust, B. Giantoniao, K. Olthoff. *Combination of capecitabine and oxaliplatin with bevacizumab in treatment of advanced hepatocelular carcinoma: A Phase II study*. in *American Society of Clinical Oncology Annual Meeting*. 2007. Chicago Il.
36. Siegel, A.B., et al., *Phase II trial evaluating the clinical and biologic effects of bevacizumab in unresectable hepatocellular carcinoma.* J Clin Oncol, 2008. **26**(18): p. 2992-8.
37. Thomas, M.B., et al., *Phase II trial of the combination of bevacizumab and erlotinib in patients who have advanced hepatocellular carcinoma.* J Clin Oncol, 2009. **27**(6): p. 843-50.
38. Okano, H., et al., *Functional expression of a proliferation-related ligand in hepatocellular carcinoma and its implications for neovascularization.* World J Gastroenterol, 2005. **11**(30): p. 4650-4.
39. Zhang, Q., et al., *Resveratrol inhibits hypoxia-induced accumulation of hypoxia-inducible factor-1alpha and VEGF expression in human tongue squamous cell carcinoma and hepatoma cells.* Mol Cancer Ther, 2005. **4**(10): p. 1465-74.
40. Sun, W., et al., *Combination of capecitabine, oxaliplatin with bevacizumab in treatment of advanced hepatocellular carcinoma (HCC): A phase II study.* Journal of Clinical Oncology, 2007 ASCO Annual Meeting Proceedings Part I. **25**(No18S): p. Abstract 4574.
41. Malka, D., et al., *Bevacizumab in patients (pts) with advanced hepatocellular carcinoma (HCC): Preliminary results of a phase II study with circulating endothelial cell (CEC) monitoring.* Journal of Clinical Oncology, 2007 ASCO Annual Proceedings Part I. **25**(No18S): p. Abstract 4570.

42. Hsu, C., et al., *Modified-dose capecitabine + bevacizumab for the treatment of advanced/metastatic hepatocellular carcinoma (HCC): A phase II, single-arm study.* Journal of Clinical Oncology, 2007 ASCO Annual Meeting Proceedings Part I. **25**(No18S): p. Abstract 15190.
43. Thomas, M.B., et al., *Phase 2 study of erlotinib in patients with unresectable hepatocellular carcinoma.* Cancer, 2007. **110**(5): p. 1059-67.
44. Llovet, J.M., et al., *Sorafenib in advanced hepatocellular carcinoma.* N Engl J Med, 2008. **359**(4): p. 378-90.
45. Llovet, J.M., et al., *Design and endpoints of clinical trials in hepatocellular carcinoma.* J Natl Cancer Inst, 2008. **100**(10): p. 698-711.
46. Kim, H.T., *Cumulative incidence in competing risks data and competing risks regression analysis.* Clin Cancer Res, 2007. **13**(2 Pt 1): p. 559-65.
47. Miller, A.B., et al., *Reporting results of cancer treatment.* Cancer, 1981. **47**(1): p. 207-14.
48. Bruix, J., et al., *Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of the Liver.* J Hepatol, 2001. **35**(3): p. 421-30.

APPENDIX A: NEW YORK HEART ASSOCIATION (NYHA) GUIDELINES

Class I	People whose physical activity is not limited. Ordinary physical activity does not cause undue fatigue, heart palpitations, trouble breathing, or chest pain.
Class II	People who have some limitation on physical activity. They are comfortable at rest, but ordinary physical activity causes fatigue, heart palpitations, trouble breathing, or chest pain.
Class III	People who have a marked limitation on physical activity. They are comfortable at rest, but less-than-ordinary physical activity causes fatigue, heart palpitations, trouble breathing, or chest pain.
Class IV	People who are unable to carry on any physical activity without discomfort. Symptoms may be present even at rest. If any physical activity is undertaken, discomfort is increased.

Appendix B:

EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG)
PERFORMANCE STATUS CRITERIA

Grade	Scale
0	Fully active, able to carry on all pre-disease performance without restriction (Karnofsky 90-100)
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, i.e., light housework, office work (Karnofsky 70-80)
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours (Karnofsky 50-60)
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours (Karnofsky 30-40)
4	Completely disabled. Cannot carry out any self-care. Totally confined to bed or chair (Karnofsky 10-20)
5	Dead

APPENDIX C: PROCEDURE FOR OBTAINING A URINE PROTEIN: CREATININE RATIO

1) Obtain at least 4 ml of a random urine sample (does not have to be a 24 hour urine)
2) Determine protein concentration (mg/dL)
3) Determine creatinine concentration (mg/dL)
4) Divide #2 by #3 above: urine protein / creatinine ratio = protein concentration (mg /dL) / creatinine concentration (mg /dL)

The UPC directly correlates with the amount of protein excreted in the urine per 24 hrs (i.e. a UPC of 1 should be equivalent to 1g protein in a 24hr urine collection)

Protein and creatinine concentrations should be available on standard reports of urinalyses, not dipsticks. If protein and creatinine concentrations are not routinely reported at an Institution, their measurements and reports may need to be requested.

APPENDIX D - Childs-Pugh Scale

Chemical and Biochemical Parameters	Scores (Points) for Increasing Abnormality		
	1	2	3
Encephalopathy	None	1-2	3-4
Ascites	None	Slight	Moderate
Albumin (g/dL)	>3.5	2.8-3.5	<2.8
Prothrombin time prolonged (sec)	1-4	4-6	>6
Bilirubin (mg/dL)	1-2	2-3	>3
For primary biliary cirrhosis	1-4	4-10	>10

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

Appendix E: **Guide to Using Modified RECIST For Assessment of Disease Response**

The RECIST Criteria were developed and published by Therasse et al (2000) and will be employed in this study with modifications based on current practices of the medical community.

Eligibility

To be eligible, subjects must have at least 1 uni-dimensionally measurable lesion measuring ≥20 mm using conventional techniques (CT scan or MRI) or ≥10 mm using spiral CT scan.

Measurable Lesions

Measurable target lesions are defined at baseline as lesions that can be accurately measured in at least one dimension (longest diameter to be recorded) ≥ 20 mm using conventional techniques (CT or MRI) or ≥10 mm using spiral CT scan. All sites of disease must be evaluated.

Target lesions must not be chosen from a previously irradiated field, unless there has been documented disease progression in that field after irradiation and prior to enrollment.

The distribution of the target lesions should be representative of the subject's overall disease.

Non-Measurable Lesions

All other lesions (longest diameter < 20 mm), including small lesions and other truly non-measurable lesions are considered non-measurable and characterized as non-target lesions.

This will include any measurable lesions beyond the maximum number of 10 that were not chosen as target lesions.

Other examples of non-measurable lesions include bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, lymphangitis cutis/pulmonis, cystic lesions and groups of lesions that are small and numerous.

Lesions clinically measured by the investigator, and not imaged by radiographic methods (ie, skin nodules and palpable lymph nodes) will automatically be considered non-target lesions.

Method

CT or MR scans will be performed at screening and during the study to evaluate tumor response. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at screening and during the study. All measurements should be taken and recorded in metric notation (mm), using a ruler or

calipers.

CT and MRI are the best currently available and reproducible methods to measure target lesions and qualitatively assess non-target lesions selected for response assessment. Conventional CT (non-spiral or non-helical) and conventional MRI (MRI performed without fast scanning techniques) should produce images contiguously reconstructed at 10 mm or less. Spiral (helical or multidetector CT) should product images contiguously reconstructed between 5 and 8 mm.

Lesions on chest X-ray should be imaged by CT or MRI scan.

A switch from CT to MRI (or visa versa) of the liver is considered the only acceptable change in modality and should not preclude response assessment if, in the judgment of the site radiologist, there is no significant difference in the assessment by changing modalities. This may occur if a subject has developed a medical contraindication to IV contrast for CT scan while on study.

Ultrasound should not be used for assessment of visceral index lesions for the pre-study documentation of progressive disease in order to meet the eligibility criteria, or the on-study assessment of response. Ultrasound can be used during the study to assess superficial lesions such as skin lesions, lymph nodes or masses. However, ultrasound is a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules, or to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

Positron Emission Tomography (PET) with fluoro-2-deoxy-D-glucose (FDG) [FDG-PET] is occasionally used to assess subjects with colon cancer. However, for this study, a response of CR, PR, or SD will be determined by cross sectional imaging techniques (CR or MRI). PET will not be used or contribute to the assessment of response (CR, PR, or SD).

If a combined FDG-PET/CT scan is performed at the discretion of the investigator, the CT portion of that exam should not necessarily be substituted for the dedicated CT exams required by this protocol. RECIST still applies.

Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a subject to be considered in complete clinical response (ie, CR) when all lesions have disappeared.

Baseline Documentation of “Target” and “Non-Target” Lesions

Screening (baseline) images will be used to prospectively identify all sites of disease present at the start of treatment. Sites of disease will be characterized as either target or non-target lesions.

Up to 10 target lesions (a maximum of 5 per organ) will be chosen to measure over the course of therapy. The distribution of these target lesions should be representative of the subject’s overall disease status.

Target lesions should be selected on the basis of their size (≥ 20 mm in the longest dimension using CT or MRI) and suitability for accurate repeated measurements by

imaging techniques.

A sum of the longest diameter (LD) for all *target lesions* will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

All other lesions (or sites of disease), including any measurable lesions that were not chosen as target lesions, should be identified as *non-target lesions* and should also be recorded and assessed qualitatively over the course of therapy.

Evaluation of Overall Response:

The subject response will be assessed based on the response of the target lesions, the response of the non-target lesions and the presence or absence of new lesions. The convention will be used that if a lesion being measured decreases in size to ≤ 5 mm in the LD, a value of 5 mm will be assigned. If the lesion subsequently increases in size to ≥ 5 mm in one dimension, its true size will be recorded.

The following criteria as outlined in Table 1 and 2 will be used to assess tumor response in the target and non-target lesions, respectively

Table 1. Evaluation of Target Lesions at Each Assessment Point

Response	Criteria
Complete Response (CR):	Disappearance of all target lesions
Partial Response (PR):	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum of the longest diameters (SLD)
Progressive Disease (PD):	At least a 20% increase in the sum of the LD of target lesions, taking as reference the nadir SLD recorded since the treatment started or the appearance of one or more new lesions
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the nadir LD since the treatment started
Unable to Evaluate (UE):	A target lesion(s) was not measured or was unable to be evaluated leading to an inability to determine the status of that particular tumor for that time point.
Not Applicable (NA)	No target lesions were identified at baseline
Not Done (ND)	Scans were not performed at this time point to evaluate the target lesions

Table 2. Evaluation of Non-target Lesions at Each Assessment Point

Response	Criteria
Complete Response (CR):	Disappearance of all non-target lesions
Stable Disease (SD):	Persistence of one or more non-target lesion(s) not qualifying for either CR or PD
Progressive Disease (PD):	Unequivocal progression of existing non-target lesions. If the visit response of the target lesions is not PD and there are no new lesions, progressive disease of non-target lesions will be assessed when: 1) the SLD of the non-target lesion(s) has increased by 20% or greater, taking as reference the nadir SLD of the non-target lesion(s), and each lesion(s) measures ≥ 10 mm in one dimension at the time of progression, or 2) there is a significant increase in pleural effusions, ascites, or other fluid collections with cytologic proof of malignancy
Unable to Evaluate (UE)	Any non-target lesion present at baseline which was not assessed or was unable to be evaluated leading to an inability to determine the status of that particular tumor for that time point
Not Applicable (NA)	No non-target lesions identified at baseline
Not Done (ND)	Scans were not performed at this time point to evaluate non-target lesions

The following criteria as outlined in Table 3 will be used to assess the subject's overall disease status based on target and non-target lesions and the presentation of a new lesion(s) since the last assessment.