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S0635
Activation Date July 15, 2007
Version Date 12/02/2011

SWOG

A PHASE II TRIAL OF THE COMBINATION OF OSI-774 (ERLOTINIB; NSC-718781) AND BEVACIZUMAB (RHUMAB VEGF; NSC-704865) IN STAGE IIIB AND IV BRONCHIOLOALVEOLAR CARCINOMA (BAC) AND ADENOCARCINOMA WITH BAC FEATURES (ADENOBAC)

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AGENTS:

Bevacizumab for injection (Avastin®)
(NSC-704865, IND-100426);
OSI-774 (Erlotinib, Tarceva®)
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1.0 OBJECTIVES

The primary objective of this Phase II study is:

1.1 To assess overall survival in patients with BAC/adenoBAC who receive daily oral OSI-774 (erlotinib) in combination with intravenous bevacizumab every 3 weeks.

The secondary objectives are:

1.2 To assess progression-free survival in this group of patients treated with this regimen.

1.3 To investigate in a preliminary manner the level of agreement between response outcomes determined by RECIST and response outcomes as determined by a central, computer assisted image analysis system (CAIA) in the subset of patients with measurable disease.

1.4 To evaluate the frequency and severity of toxicities associated with this regimen.

1.5 To assess tissue collected from BAC/adenoBAC for EGFR and ras mutations as well as EGFR expression, plasma markers of angiogenesis, angiogenesis-related polymorphisms, and to perform exploratory analysis of the relationships between these features and the clinical outcomes of the present trial.

2.0 BACKGROUND

BAC has a distinct clinical presentation, radiologic appearance and natural history compared to other types of non-small cell lung cancer (NSCLC). (*1*) Nodal involvement and distant metastatic disease occur much less commonly than in other forms of NSCLC. Instead, it generally follows a much more localized growth pattern and may be spread aerogenously. *(2,3)* Even for the subset of patients with advanced BAC, death is most typically from respiratory failure secondary to diffuse pulmonary involvement or intercurrent pulmonary infection rather than from disease spread to other organ sites. Importantly, recent clinical trials targeting this population have included patients with both "pure" BAC and adenoBAC. *(4,5)*

While patients may be cured after resection of focal BAC, there is no optimal established therapy for multilobar or recurrent disease. Conventional chemotherapy is widely perceived to have a minimal impact on clinical course. The largest prospective trial of chemotherapy in BAC, Southwest Oncology Group protocol **S9714**, administered 96-hour paclitaxel infusion and was associated with a modest objective response rate of 14%, a median survival of 12 months and considerable toxicity that precluded the further study of this regimen for advanced BAC. *(6)* In contrast, the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) ZD1839 (gefitinib) and OSI-774 (erlotinib) have each been studied as single-agent therapy for first-line or previously treated BAC and have been associated with overall more favorable results, most notably in women, never-smokers and those who develop a rash. *(4, 5)* Each of the EGFR TKIs has been associated with a response rate in the 15-25% range in this setting, with a subset of patients demonstrating prolonged survival on ZD1839 (gefitinib), with a three-year OS of 23% for untreated patients, compared with an OS of 13% for prolonged-infusion paclitaxel on **S9714**; data with prolonged follow-up are not yet available for OSI-774 (erlotinib). *(4,6)* Significantly, in subset analyses of these trials, the beneficial effects of EGFR-based therapies have not been restricted to pure BAC but are comparable, if not superior, in patients with adenoBAC. Franklin and colleagues reported that results on **S0126** were similar among patients with invasive adenocarcinoma with BAC features compared to those with pure BAC, while Kris and colleagues noted that the response rate to erlotinib was 29% for adenoBAC compared with 11% for pure BAC. *(5,7)*

Bevacizumab is an antibody to the vascular endothelial growth factor (VEGF) ligand and has antiangiogenic activity in multiple preclinical models and clinical settings. *(reviewed in 8)* It has been approved in metastatic colon cancer, in which a highly statistically significant survival benefit has been seen when bevacizumab was combined with standard chemotherapy. There has also been considerable interest in the integration of bevacizumab with treatment of advanced NSCLC. A randomized Phase II trial demonstrated a very encouraging potential survival benefit, particularly for the dose of 15 mg/kg IV q 3 weeks when combined with standard carboplatin and paclitaxel. *(9)* This approach has been tested further in a randomized Phase III trial of standard chemotherapy with or without bevacizumab, in which a significant survival benefit has been shown to be conferred by the addition of bevacizumab in patients with nonsquamous histology in whom the median overall survival of the bevacizumab/chemotherapy combination was 12.5 months compared to 10.2 months for chemotherapy alone. *(10)*

While the treatment of advanced BAC/adenoBAC may potentially include chemotherapy, single-agent EGFR TKI therapy is very widely practiced as an early intervention, based on the two studies described above with ZD1839 (gefitinib) and OSI-774 (erlotinib) in this population. Moreover, with the highly positive results from the BR.21 trial, there is now greater focus on OSI-774 (erlotinib) in this setting. The combination of bevacizumab and OSI-774 (erlotinib), targeting both the tumor itself and its blood supply, provides the potential advantage of integrating the survival benefit conferred by anti-angiogenic therapy with an existing early (and potentially first-line) treatment strategy. A recent Phase I/II trial tested the combination of OSI-774 (erlotinib) with bevacizumab in the salvage setting. *(11)* This trial demonstrated a 20% response rate and a non-progression rate of 85%, a promising 12.6 month median survival, and a modest toxicity profile at the established Phase II dose. Specifically, the most common adverse events (any grade) were rash (85%), diarrhea (65%), infection (29%), hematuria (32%), proteinuria (9%), and epistaxis (6%). The only serious adverse events were pneumonia, and there were no treatment-related deaths. Based on these promising results, a larger randomized Phase III trial is being undertaken in the second-line NSCLC setting, comparing the combination of OSI-774 (erlotinib) and bevacizumab to OSI-774 (erlotinib) alone. Of note, all of the bevacizumab trials in NSCLC currently exclude patients with squamous cell histology and those with brain metastases, exclusion criteria that will be applied in the current trial as well.

Taken together, these data demonstrate that EGFR TKI therapy is a current standard of care for patients with advanced BAC/adenoBAC, that OSI-774 (erlotinib) has an established survival benefit in NSCLC overall, and that bevacizumab in combination with first-line chemotherapy is associated with improved survival compared to chemotherapy alone. While the combination of OSI-774 (erlotinib) and bevacizumab has not been tested in these patient populations specifically, the combination has demonstrated safety and encouraging efficacy in early trials in the salvage setting.

The current proposal is to examine in a Phase II multicenter trial the clinical benefit and the long-term tolerability of daily OSI-774 (erlotinib) along with intravenous q3week bevacizumab at 15 mg/kg in patients with advanced BAC or adenoBAC who have not previously received an EGFR TKI or bevacizumab. This would integrate the potential benefit of bevacizumab, which has provided a survival benefit in combination with chemotherapy, with the FDA-approved agent erlotinib in the particular subsets of patients in whom erlotinib has demonstrated the greatest likelihood of clinical benefit. For the subset of patients with BAC/adenoBAC, the endpoints of this study may potentially be compared with the historical results of **S9714** and **S0126**. If the results from this study are promising, a subsequent Phase III trial comparing OSI-774 (erlotinib) to OSI-774 (erlotinib)/bevacizumab in BAC/adenoBAC would be considered.

Inclusion of Women and Minorities:

This study was designed to include women and minorities, but was not designed to measure differences of intervention effects.

3.0 DRUG INFORMATION

3.1 Bevacizumab (rhuMAb VEGF) (Avastin) (NSC-704865) (IND-100426)

a. DESCRIPTION

Bevacizumab is a recombinant humanized monoclonal antibody that inhibits vascular endothelial growth factor (VEGF) resulting in inhibition of angiogenesis. Of the identified angiogenic factors, vascular endothelial growth factor (VEGF; also known as vascular permeability factor) is the most potent and specific and has been identified as a crucial regulator of both normal and pathologic angiogenesis. VEGF produces a number of biologic effects, including endothelial cell mitogenesis and migration, induction of proteinases leading to remodeling of the extracellular matrix, increased vascular permeability, maintenance of survival for newly formed blood vessels, and, possibly, suppression of dendritic cell antigen presentation. The biologic effects of VEGF are mediated through binding and stimulation of two receptors on the surface of endothelial cells: Flt-1 (fms-like tyrosine kinase)/VEGFR-1 and KDR (kinase domain region)/VEGFR-2.

Increased levels of VEGF expression have been found in most human tumors examined to date, including tumors of the lung, breast, thyroid, gastrointestinal tract, kidney, bladder, ovary, and cervix, angiosarcomas, glioblastomas, as well as multiple myeloma, lymphoma, and AML. Inhibition of VEGF using an anti-VEGF monoclonal antibody blocks the growth of a number of human cancer cell lines in nude mice. The human cancers represented by these cell lines that are growth-inhibited by anti-VEGF antibody include non–small cell lung cancer (Calu-6), colorectal cancer (LS174T, HM-7, LSLiM6), breast cancer (MCF-7), prostate cancer (D-145), head and neck cancer (KB), ovarian cancer (SK-OV-3), and others.

b. TOXICOLOGY

Comprehensive Adverse Events and Potential Risks List (CAEPR) *for* Bevacizumab (NSC #704865)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with ***bold*** and ***italicized*** text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI via AdEERS (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification.

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

Version 2.2, October 21, 2011[1]

Adverse Events with Possible Relationship to Bevacizumab (rhuMAb VEGF) (CTCAE 4.0 Term)			Specific Protocol Exceptions to Expedited Reporting (SPEER) (formerly known as ASAEL)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr. 3)***
		Blood and lymphatic system disorders - Other (renal thrombotic microangiopathy)	
	Febrile neutropenia		***Febrile neutropenia (Gr. 3)***
CARDIAC DISORDERS			
		Acute coronary syndrome	
		Heart failure	
		Left ventricular systolic dysfunction	
CARDIAC DISORDERS (contd.)			
		Myocardial infarction	
	Supraventricular tachycardia		***Supraventricular tachycardia (Gr. 3)***
		Ventricular arrhythmia	
		Ventricular fibrillation	
EAR AND LABYRINTH DISORDERS			
	Vertigo		
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr. 3)***
	Colitis		***Colitis (Gr. 3)***
	Constipation		***Constipation (Gr. 3)***
	Diarrhea		***Diarrhea (Gr. 3)***
	Dyspepsia		***Dyspepsia (Gr. 2)***
		Gastrointestinal fistula[2]	
	Gastrointestinal hemorrhage[3]		***Gastrointestinal hemorrhage[3] (Gr. 2)***
	Gastrointestinal obstruction[4]		
		Gastrointestinal perforation[5]	
		Gastrointestinal ulcer[6]	

	Ileus		
	Mucositis oral		***Mucositis oral (Gr. 3)***
	Nausea		***Nausea (Gr. 3)***
	Vomiting		***Vomiting (Gr. 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Fatigue		***Fatigue (Gr. 3)***
	Infusion related reaction		***Infusion related reaction (Gr. 2)***
	Non-cardiac chest pain		***Non-cardiac chest pain (Gr. 3)***
	Pain		***Pain (Gr. 3)***
IMMUNE SYSTEM DISORDERS			
	Allergic reaction		***Allergic reaction (Gr. 2)***
		Anaphylaxis	
INFECTIONS AND INFESTATIONS			
	Infection[7]		***Infection[7] (Gr. 3)***
	Infections and infestations - Other (peri-rectal abscess)		
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
		Gastrointestinal anastomotic leak	
	Wound dehiscence		***Wound dehiscence (Gr. 2)***
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr. 3)***
	Alkaline phosphatase increased		***Alkaline phosphatase increased (Gr. 3)***
INVESTIGATIONS			
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr. 3)***
	Blood bilirubin increased		***Blood bilirubin increased (Gr. 2)***
	Cardiac troponin I increased		
	Neutrophil count decreased		***Neutrophil count decreased (Gr. 3)***
	Weight loss		***Weight loss (Gr. 3)***
	White blood cell decreased		***White blood cell decreased (Gr. 3)***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr. 3)***

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		***Arthralgia (Gr. 3)***
	Musculoskeletal and connective tissue disorder - Other (bone metaphyseal dysplasia)[8]		
	Myalgia		***Myalgia (Gr. 3)***
	Osteonecrosis of jaw[9]		
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness (Gr. 2)***
	Headache		***Headache (Gr. 3)***
		Intracranial hemorrhage	
		Ischemia cerebrovascular	
	Peripheral sensory neuropathy[10]		
		Reversible posterior leukoencepha-lopathy syndrome	
	Syncope		
RENAL AND URINARY DISORDERS			
		Acute kidney injury	
	Hematuria		***Hematuria (Gr. 3)***
	Proteinuria		***Proteinuria (Gr. 2)***
		Renal and urinary disorders - Other (Nephrotic Syndrome)	
		Urinary fistula	
REPRODUCTIVE SYSTEM AND BREAST DISORDERS			
Reproductive system and breast disorders - Other (ovarian failure)[11]			
		Vaginal fistula	
	Vaginal hemorrhage		***Vaginal hemorrhage (Gr. 3)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Allergic rhinitis		***Allergic rhinitis (Gr. 3)***
		Bronchopleural fistula	
		Bronchopulmonary hemorrhage	
	Cough		***Cough (Gr. 3)***

	Dyspnea		***Dyspnea (Gr. 2)***
	Epistaxis		***Epistaxis (Gr. 3)***
	Hoarseness		***Hoarseness (Gr. 3)***
		Respiratory, thoracic and mediastinal disorders - Other (nasal-septal perforation)	
		Respiratory, thoracic and mediastinal disorders - Other (tracheo-esophageal fistula)	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Pruritus		***Pruritus (Gr. 2)***
	Rash maculo-papular		***Rash maculo-papular (Gr. 2)***
	Urticaria		***Urticaria (Gr. 2)***
VASCULAR DISORDERS			
Hypertension			***Hypertension (Gr. 3)***
	Thromboembolic event		***Thromboembolic event (Gr. 3)***
		Vascular disorders - Other (arterial thromboembolic event)[12]	

[1] This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2] Gastrointestinal fistula may include: Anal fistula, Colonic fistula, Duodenal fistula, Esophageal fistula, Gastric fistula, Gastrointestinal fistula, Rectal fistula, and other sites under the GASTROINTESTINAL DISORDERS SOC

[3] Gastrointestinal hemorrhage may include: Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Intra-abdominal hemorrhage, Oral hemorrhage, Rectal hemorrhage, and other sites under the GASTROINTESTINAL DISORDERS SOC.

[4] Gastrointestinal obstruction may include: Colonic obstruction, Duodenal obstruction, Esophageal obstruction, Ileal obstruction, Jejunal obstruction, Rectal obstruction, Small intestinal obstruction, and other sites under the GASTROINTESTINAL DISORDERS SOC.

[5] Gastrointestinal perforation may include: Colonic perforation, Duodenal perforation, Esophageal perforation, Gastric perforation, Jejunal perforation, Rectal perforation, Small intestinal perforation, and other sites under the GASTROINTESTINAL DISORDERS SOC.

[6] Gastrointestinal ulcer may include: Duodenal ulcer, Esophageal ulcer, Gastric ulcer, and other sites under the GASTROINTESTINAL DISORDERS SOC.

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

[8] Metaphyseal dysplasia was observed in young patients who still have active epiphyseal growth plates.

[9] Cases of osteonecrosis of the jaw (ONJ) have been reported in cancer patients in association with bevacizumab treatment, the majority of whom had received prior or concomitant treatment with i.v. bisphosphonates.

[10] Increased rate of peripheral sensory neuropathy has been observed in trials combining bevacizumab and chemotherapy compared to chemotherapy alone.

[11] Ovarian failure, defined as amenorrhea lasting 3 or more months with follicle-stimulating hormone (FSH) elevation (≥30 mIU/mL), was increased in patients receiving adjuvant bevacizumab plus mFOLFOX compared to mFOLFOX alone (34% vs. 2%). After discontinuation of bevacizumab, resumption of menses and an FSH level <30 mIU/mL was demonstrated in 22% (7/32) of these women. Long term effects of bevacizumab exposure on fertility are unknown.

[12] Arterial thromboembolic event includes visceral arterial ischemia, peripheral arterial ischemia, heart attack, and stroke.

Also reported on Bevacizumab (rhuMAb VEGF) trials but with the relationship to Bevacizumab (rhuMAb VEGF) still undetermined:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (idiopathic thrombocytopenia purpura); Disseminated intravascular coagulation
CARDIAC DISORDERS - Pericardial effusion
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Gait disturbance; Sudden death NOS
HEPATOBILIARY DISORDERS - Hepatic failure
INFECTIONS AND INFESTATIONS - Infections and infestations - Other (aseptic meningitis)
INVESTIGATIONS - Platelet count decreased
METABOLISM AND NUTRITION DISORDERS - Hyponatremia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Musculoskeletal and connective tissue disorder - Other (aseptic necrotic bone); Musculoskeletal and connective tissue disorder - Other (myasthenia gravis)
NERVOUS SYSTEM DISORDERS - Dysgeusia; Peripheral motor neuropathy; Seizure
PSYCHIATRIC DISORDERS – Confusion
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Pneumonitis; Pneumothorax; Pulmonary hypertension
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Palmar-plantar erythrodysesthesia syndrome; Skin ulceration

Note: Bevacizumab (rhuMAb VEGF) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

Based on clinical trials with bevacizumab as monotherapy or in combination with chemotherapy, the most common adverse events of any severity include asthenia, pain, headache, hypertension, diarrhea, stomatitis, constipation, epistaxis, dyspnea, dermatitis and proteinuria. The most common Grade 3-4 adverse events were asthenia, pain, hypertension, diarrhea and leukopenia. The most serious AEs include life-threatening or fatal hemorrhage, arterial thromboembolic events, gastrointestinal perforation and wound dehiscence; these events were uncommon but occurred at an increased frequency compared to placebo or chemotherapy controls in randomized studies.

The following is a description of major adverse events associated with bevacizumab therapy. Reference may also be made to the Investigators' Brochure and the FDA package insert (www.fda.gov/cder/foi/label/2004/125085lbl.pdf).

Infusion-Related Reactions: Infusion reactions with bevacizumab were uncommon (< 3%) and rarely severe (0.2%). Infusion reactions may include rash, urticaria, fever, rigors, hypertension, hypotension, wheezing, or hypoxia. Currently, there is no adequate information on the safety of retreatment with bevacizumab in patients who have experienced severe infusion-related reactions.

Hypertension: Hypertension is common in patients treated with bevacizumab, with an incidence of 20-30% across trials. Initiation or increase of anti-hypertensive medications may be required, but in most cases, blood pressure (BP) can be controlled with routine oral drugs. However, incidents of hypertensive crisis with encephalopathy or cardiovascular sequelae have been rarely reported. BP should be closely monitored during bevacizumab therapy and the goal of BP control should be consistent with general medical practice. Bevacizumab therapy should be suspended in the event of uncontrolled hypertension.

Proteinuria: Proteinuria has been seen in all bevacizumab studies to date, ranging in severity from an asymptomatic increase in urine protein (incidence of about 20%) to rare instances of nephrotic syndrome (0.5% incidence). Pathologic findings on renal biopsies in two patients showed proliferative glomerulonephritis. NCI-CTCAE Grade 3 proteinuria (> 3.5 gm/24 hour urine) is uncommon, but the risk may be higher in patients with advanced RCC. In the Phase II randomized study in RCC, 24-hour urine was collected in a subset of patients enrolled, and Grade 3 proteinuria was found in 4 patients in the 10 mg/kg-arm (n=37), 2 patients in the 3mg/kg arm (n=35) and none in the placebo arm (n=38). The safety of continuing bevacizumab in patients with moderate or severe proteinuria has not been adequately tested.

Hemorrhage: The incidence of hemorrhage is increased with bevacizumab therapy. Epistaxis is common, occurring in 20-40% of patients, but it is generally mild and rarely requires medical intervention. Life-threatening and fatal hemorrhagic events have been observed in bevacizumab studies and included pulmonary hemorrhage, CNS bleeding and gastrointestinal (GI) bleeding. In a Phase II study in non-small cell lung cancer, 6 cases of life-threatening hemoptysis or hematemesis were reported among 66 patients treated with bevacizumab and chemotherapy; 4 of these events were fatal (Novotny et al., 2001). In the pivotal Phase III trial in advanced colorectal cancer, the rate of GI hemorrhage (all grades) was 24% in the IFL/bevacizumab arm compared to 6% in the IFL arm; Grade 3-4 hemorrhage was 3.1% for IFL/bevacizumab and 2.5% for IFL. Serious GI hemorrhage has also been observed in clinical trials with bevacizumab in patients with pancreatic cancer or varices treated with bevacizumab.

Arterial Thromboembolic Events: The risk of arterial thromboembolic events is increased with bevacizumab therapy, and such events included cerebral infarction, transient ischemic attack (TIA), myocardial infarction and other peripheral or visceral arterial thrombosis. In the pivotal trial in CRC (AVF2107), the incidence of arterial thromboembolic events was 1% in the IFL/placebo arm compared to 3% in the IFL/ bevacizumab arm. A pooled analysis of five randomized studies showed a two-fold increase in these events (4.4% vs 1.9%). Certain baseline characteristics, such as age and prior arterial ischemic events, appear to confer additional risk (Schilling et al, ASCO 2005). In patients ≥ 65 years treated with bevacizumab and chemotherapy, the rate of arterial thromboembolic events was approximately 8.5%.

Gastrointestinal Perforation/Fistula: GI perforations/fistula were rare but occurred at an increased rate in bevacizumab-containing therapies. The majority of such events required surgical intervention and some were associated with a fatal outcome. In the pivotal Phase III trial in CRC (AVF2107), the incidence of bowel perforation was 2% in patients receiving IFL/bevacizumab and 4% in patients receiving 5-FU/bevacizumab compared to 0.3% in patients receiving IFL alone. GI perforation has also been reported in patients with gastric/esophageal cancer, pancreatic cancer, ovarian cancer or comorbid GI conditions such as diverticulitis and gastric ulcer. GI perforation should be included in the differential diagnosis of patients on bevacizumab therapy presenting with abdominal pain or rectal/abdominal abscess.

Tracheoesophageal (TE) fistula: In a Phase II trial of concurrent chemoradiation and bevacizumab in limited SCLC (concurrent irinotecan, carboplatin, radiotherapy, and bevacizumab, followed by maintenance bevacizumab), among the first 25 patients enrolled, there have been two confirmed cases of tracheoesophageal (TE) fistula (one fatal) and a third case of fatal upper aerodigestive tract hemorrhage, with TE fistula suspected but not confirmed. All three events occurred during the bevacizumab maintenance phase (1.5 to 4 months after completion of concurrent bevacizumab and chemoradiation). The TE fistula rate in this trial was higher than expected with chemoradiation alone. While pulmonary fistula (including TE fistula) has also been observed in advanced NSCLC or SCLC patients receiving bevacizumab and chemotherapy (without radiation), the incidence was extremely low (<< 1%), and the relationships to treatment vs. tumor in those cases were unclear. Experience is limited for bevacizumab administered sequentially after chemoradiation for either NSCLC or SCLC; in a study for chemoradiation followed by bevacizumab in SCLC, one of the 60 patients enrolled developed TE fistula.

Wound Healing Complications: Bevacizumab delays wound healing in rabbits, and it may also compromise or delay wound healing in patients. Bowel anastomotic dehiscence and skin wound dehiscence have been reported in clinical trials with bevacizumab. The appropriate interval between surgery and initiation of bevacizumab required to avoid the risk of impaired wound healing has not been determined. However, all clinical trials with bevacizumab have required a minimum of 28 days from prior major surgery; experience in the pivotal trial in advanced CRC suggests that initiation of bevacizumab 29-50 days following surgery should be associated with a very low incidence of wound dehiscence. The optimal interval between termination of bevacizumab and subsequent elective surgery has not been determined either. In the pivotal study in CRC, 40 patients on the IFL/bevacizumab arm and 25 patients on the ILF/placebo arm underwent major surgery while on study; among them, significant post-operative bleeding or wound healing complications occurred in 4 of the 40 patients from the IFL/bevacizumab arm and none of the 25 patients

from the IFL alone arm. Decisions on the timing of elective surgery should take into consideration the half-life of bevacizumab (average 21 days, with a range of 11-50 days).

Congestive Heart Failure: The risk of left ventricular dysfunction may be increased in patients with prior or concurrent anthracycline treatment. In Phase III controlled clinical trial in metastatic breast cancer (AVF 2119g) in which all patients had received prior anthracyclines, congestive heart failure (CHF) or cardiomyopathy were reported in 7 patients (3%) in the bevacizumab/capecitabine arm compared to 2 (1%) in the capecitabine-only arm. No increase in CHF was observed in CRC trials with bevacizumab in combination with IFL or 5-FU.

Venous Thrombosis: Venous thromboembolic events reported in bevacizumab trials included lower extremity deep vein thrombosis (DVT), pulmonary embolism and rarely, mesenteric or portal vein thrombosis. In the pivotal Phase III trial of IFL ± bevacizumab (given at 5 mg/kg q 2 weeks), the overall incidences of G3-4 venous thromboembolic events were comparable in the two arms (15.1 vs 13.6%).

Fertility and Pregnancy: Clinical data are lacking regarding the immediate or long-term effect of bevacizumab on fertility and pregnancy. However, bevacizumab is known to be teratogenic and detrimental to fetal development in animal models. In addition, bevacizumab may alter corpus luteum development and endometrial proliferation, thereby having a negative effect on fertility. As an IgG1, it may also be secreted in human milk. Therefore, fertile men and women on bevacizumab studies must use adequate contraceptive measures and women should avoid breast feeding. The duration of such precautions after discontinuation of bevacizumab should take into consideration the half-life of the agent (average 21 days, with a range of 11 to 50 days).

Immunogenicity: As a therapeutic protein, there is a potential for immunogenicity with bevacizumab. With the currently available assay with limited sensitivity, high titer human anti-bevacizumab antibodies have not been detected in approximately 500 patients treated with bevacizumab.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS) or similar leukoencephalopathy syndrome: RPLS or clinical syndromes related to vasogenic edema of the white matter have been rarely reported in association with bevacizumab therapy (< 1%). Clinical presentations are variable and may include altered mental status, seizure and cortical visual deficit. HTN is a common risk factor and was present in most (though not all) patients on bevacizumab who developed RPLS. MRI scans are key to diagnosis and typically demonstrate vasogenic edema (hyperintensity in T2 and FLAIR images and hyposensitivity in T1 images) predominantly in the white matter of the posterior parietal and occipital lobes; less frequently, the anterior distributions and the gray matter may also be involved. RPLS is potential reversible, but timely correction of the underlying causes, including control of BP and interruption of the offending drug, is important in order to prevent progression to irreversible tissue damage.

Neutropenia: When combined with chemotherapy, bevacizumab increased the risk of neutropenia compared to chemotherapy alone. In a Phase III trial with IFL ± bevacizumab in colorectal cancer, Grade 3-4 neutropenia was 21% in the bevacizumab + IFL arm vs. 14% in the IFL arm (Grade 4 neutropenia was 3 vs. 2%). In the Phase III trial with carboplatin and paclitaxel ± bevacizumab in metastatic NSCLC, the bevacizumab-containing arm was associated with

increased rates of Grade 4 neutropenia (26% vs. 17%), febrile neutropenia (5.4% vs. 1.8%) and an increased rate of infection with neutropenia (4.5 vs. 1.8%) with 3 cases with fatal outcome in the bevacizumab + chemotherapy arm vs. 0 in the chemotherapy only control.

c. PHARMACOLOGY

Kinetics: In Study AVF0737g, the pharmacokinetics of bevacizumab appeared to be linear for doses of ≥ 1 mg/kg, with a half-life of ~15 days. A consistent profile was seen in Study AVF0761g. Co-administration of bevacizumab with cytotoxic chemotherapy did not appear to result in a change in the systemic concentrations of the cytotoxic agents.

How Supplied: Bevacizumab is supplied as a clear to slightly opalescent, sterile liquid ready for parenteral administration. For Bevacizumab, each 400 mg (25 mg/mL – 16 mL fill) glass vial contains bevacizumab with phosphate, trehalose, polysorbate 20, and Sterile Water for Injection, USP.

Preparation: Vials contain no preservatives and are intended for single use only. **Place the calculated dose in 100 mL of 0.9% sodium chloride for injection.** Once the bevacizumab has been added to the bag with 0.9% Sodium Chloride for Injection, the solution must be administered within 8 hours. When the bevacizumab IV bag is empty, an additional 50 ml of 0.9% Sodium Chloride for Injection should be added to the IV bag and the infusion continued for a volume equal to that of the tubing to insure complete delivery of the bevacizumab. An alternative method of flushing the infusion line would be to replace the empty bevacizumab infusion bag with a 50 mL bag of 0.9% Sodium Chloride for Injection and infuse a volume equal to that of the tubing to insure complete delivery of the bevacizumab. Note that this flush is not included in the infusion times.

Storage and Stability: Bevacizumab is shipped on blue ice for next day delivery. On receipt, bevacizumab should be stored in the refrigerator (2^{o} to 8^{o}C) and should remain refrigerated until just prior to use. Do not freeze. Do not shake. Shelf-life studies of bevacizumab are continuing. Investigators will be notified of any dating extensions, when lots have expired, and how to handle disposition of the agent. The sterile single use vials contain no antibacterial preservatives. Therefore, vials should be discarded 8 hours after initial entry. Once diluted in 0.9% Sodium Chloride for Injection, solution of bevacizumab must be administered within 8 hours.

Administration: The route of administration is intravenous as a continuous infusion. The initial dose should be administered over a minimum of 90 minutes. If no adverse reactions occur after the initial dose, the second dose should be administered over a minimum of 60 minutes. If no adverse reactions occur after the second dose, all subsequent doses should be administered over a minimum of 30 minutes. If infusion-related adverse reactions occur, all subsequent infusions should be administered over the shortest period that was well tolerated.

d. SUPPLIER

Bevacizumab is investigational for this study and will be supplied free of charge to patients by Genentech for distribution by Biologics**. Allow 7 business days for shipment of drug from receipt of the Biologics Drug Request Form (see S0635 abstract page on the SWOG website [https://swog.org/Members/ClinicalTrials/ViewProtocolDetails.asp?ProtocolID=2065]). Forms should be faxed to the number on the form.** Orders received before 4 p.m. E.S.T Monday through Thursday will be processed and shipped for same day delivery. Orders received after 4 pm E.S.T. Monday through Thursday or anytime on Friday will be processed and shipped the next business morning. Shipments will be sent via Federal Express for Priority Overnight delivery. Biologics will be closed the following holidays:

New Years Eve, New Years Day, Memorial Day, Independence Day, Labor Day, Thanksgiving, Thanksgiving Friday, Christmas Eve and Christmas Day. The bevacizumab to be supplied for this protocol is intended for clinical trial use only and is not the commercially available Avastin®. Investigational bevacizumab and commercially available Avastin® may be produced at separate facilities and some difference may exist between the two products, although both are required to meet similar product testing criteria and are expected to be very similar in safety and activity. For further details and molecule characterization, see the updated bevacizumab Investigator Brochure.

3.2 OSI-774 (Tarceva®) (NSC-718781, IND-100426)

a. DESCRIPTION

Chemical Name: N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine, monohydrochloride

Other Names*:* CP-358, 774, USAN: erlotinib hydrochloride, Tarceva®

Classification: Tyrosine kinase Inhibitor (EGFR)

Molecular Formula: $C_{22}H_{23}N_3O_4$ **M.W.:** 393.4 (free base)
429.9 (hydrochloride salt)

Mode of Action: Direct inhibition of EGFR tyrosine kinase

b. TOXICOLOGY

Reported Adverse Events and Potential Risks:

Animal Data:

On chronic administration studies the following toxicities were observed:

Rat: increased ovarian atrophy (females)

Dog: salivation, ocular changes (tapedal fundus pigmentation not considered an adverse finding), corneal ulceration

At the highest doses administered to dogs the following toxicities were observed: bloody stools, ocular changes (palpebral and bulbar conjunctiva redness, partially-closed eyes, lacrimation, purulent discharge, protruding nictitating membranes, corneal opacities, edema, ulceration & corneal perforation), discoloration of anterior chamber and/or cornea, abnormal corneal surface, increased fibrinogen, increased cholesterol and triglycerides, decreased Na, Cl, albumin, and Ca, dilatation and/or abnormal contents of gall bladder, enlarged & pale cervical lymph nodes (1 female), microscopic findings: diffuse corneal atrophy, corneal ulcers, degeneration of skeletal muscle, sinusal histiocytosis in cervical lymph nodes

Genetic toxicology studies demonstrate that OSI-774 does not induce microbial or mammalian cell gene mutations in vitro, and does not produce chromosomal aberrations in vitro or in vivo.

Comprehensive Adverse Events and Potential Risks list (CAEPR) for Erlotinib (OSI-774, NSC 718781)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Agent Specific Adverse Event List (ASAEL), appears in a separate column and is identified with ***bold*** and ***italicized*** text. This subset of AEs (ASAEL) contains events that are considered 'expected' for expedited reporting purposes only. Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.info.nih.gov/protocolDevelopment/default.htm#adverse_events_adeers for further clarification. *Frequency is provided based on 3622 patients.* Below is the CAEPR for Erlotinib (OSI-774).

Version 2.3, March 29, 2010[1]

Adverse Events with Possible Relationship to Erlotinib (OSI-774) (CTCAE 4.0 Term) [n= 3622]			**EXPECTED AEs FOR ADEERS REPORTING** **Agent Specific Adverse Event List (ASAEL)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	***Expected***
EYE DISORDERS			
	Conjunctivitis		***Conjunctivitis***
	Dry eye		***Dry eye***
	Eye disorders - Other (eyelash in-growth and/or thickening)		
		Eye disorders - Other (corneal perforation)	
		Keratitis	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain***
Diarrhea			***Diarrhea***
	Dry mouth		***Dry mouth***
	Dyspepsia		***Dyspepsia***
	Gastrointestinal hemorrhage[2]		
		Gastrointestinal perforation[3]	
	Mucositis oral		***Mucositis oral***
	Nausea		***Nausea***
Vomiting			***Vomiting***

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			***Fatigue***
HEPATOBILIARY DISORDERS			
		Hepatic failure	
INFECTIONS AND INFESTATIONS			
	Skin infection[4]		***Skin infection[4]***
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased***
	Alkaline phosphatase increased		
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased***
	Blood bilirubin increased		***Blood bilirubin increased***
METABOLISM AND NUTRITION DISORDERS			
Anorexia			***Anorexia***
	Dehydration		***Dehydration***
NERVOUS SYSTEM DISORDERS			
	Dysgeusia		***Dysgeusia***
	Headache		***Headache***
		Intracranial hemorrhage	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough***
	Dyspnea		***Dyspnea***
	Epistaxis		
	Pneumonitis		***Pneumonitis***
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		***Alopecia***
	Dry skin		***Dry skin***
		Erythema multiforme	
	Nail loss		***Nail loss***
		Palmar-plantar erythrodysesthesia syndrome	
	Pruritus		***Pruritus***
	Rash acneiform		***Rash acneiform***
Rash maculo-papular			***Rash maculo-papular***

[1] This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2] Gastrointestinal hemorrhage could include Colonic hemorrhage, Duodenal hemorrhage, Gastric hemorrhage or hemorrhage of other sites under the GASTROINTESTINAL DISORDERS SOC.

[3] Gastrointestinal perforation includes Duodenal perforation, Gastric perforation, or perforation in other sites under the GASTROINTESTINAL DISORDERS SOC.

[4] Includes infection of the skin (folliculitis or cellulitis) as complications of rash.

Also reported on erlotinib (OSI-774) trials but with the relationship to erlotinib (OSI-774) still undetermined:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Disseminated intravascular coagulation
EYE DISORDERS - Blurred vision; Eye disorders - Other (orbital cellulitis); Uveitis; Watering eyes
GASTROINTESTINAL DISORDERS - Colitis; Constipation; Duodenal ulcer; Dysphagia; Esophagitis; Gastric ulcer; Gastritis; Gastrointestinal disorders - Other (pneumatosis intestinalis); Pancreatitis
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema limbs
HEPATOBILIARY DISORDERS - Cholecystitis
INVESTIGATIONS - Creatinine increased; INR increased (in patients taking Coumadin); Lymphocyte count decreased; Platelet count decreased
METABOLISM AND NUTRITION DISORDERS - Hyperglycemia; Hyperkalemia; Hypocalcemia; Hypokalemia; Hypomagnesemia; Hyponatremia; Hypophosphatemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Generalized muscle weakness
NERVOUS SYSTEM DISORDERS - Dizziness; Ischemia cerebrovascular; Peripheral sensory neuropathy
PSYCHIATRIC DISORDERS - Confusion
RENAL AND URINARY DISORDERS - Acute kidney injury
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Pharyngolaryngeal pain
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Urticaria
VASCULAR DISORDERS - Thromboembolic event

Note: Erlotinib (OSI-774) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

Note: Erlotinib (OSI-774)-induced diarrhea and/or vomiting has been associated with dehydration, hyperkalemia; hypocalcemia; hypokalemia; hypomagnesemia; hyponatremia; hypophosphatemia, increased creatinine, and renal failure.

Note: Cases of hepatic failure and hepatorenal syndrome (including fatalities) have been reported during use of erlotinib (OSI-774) in patients with baseline hepatic impairment.

Gastrointestinal Perforation: Patients receiving erlotinib are at increased risk of developing gastrointestinal perforation, which was observed uncommonly. Some cases had a fatal outcome. Patients receiving concomitant anti-angiogenic agents, corticosteroids, NSAIDs, and/or taxane based chemotherapy, or who have prior history of peptic ulceration or diverticular disease, are at increased risk. Erlotinib should be permanently discontinued in patients who develop gastrointestinal perforation.

Bullous and Exfoliative Skin Disorders: Bullous, blistering and exfoliative skin conditions have been reported, including very rare cases suggestive of Stevens-Johnson syndrome/Toxic epidermal necrolysis, which in some cases were fatal. Erlotinib treatment should be interrupted or discontinued if the patient develops severe bullous, blistering, or exfoliating conditions.

Ocular Disorders: Very rare cases of corneal perforation or ulceration have been reported during use of erlotinib. Other ocular disorders including abnormal eyelash growth, keratoconjunctivitis sicca or keratitis have been observed with erlotinib treatment and are known risk factors for corneal perforation/ulceration. Erlotinib therapy should be interrupted or discontinued if patients present with acute/worsening ocular disorders such as eye pain.

Potential Drug Interactions: OSI-774 is both protein bound (92% to 95%) and metabolized by CYP3A4. Therefore, a potential for drug-drug interactions exists when OSI-774 is co-administered with drugs that are highly protein-bound or CYP3A4 inhibitors or inducers.

There is a potential interaction between OSI-774 and warfarin. Patients have experienced elevated INRs and bleeding with this combination of drugs. Patients on warfarin and OSI-774 should have more frequent INR/PT determinations (e.g., weekly for the first month and weekly for a minimum of 2 weeks following discontinuation of OSI-774).

Proton Pump Inhibitor: OSI-774's solubility decreases as the pH increases. Co-administration of omeprazole with OSI-774 will decrease the AUC and C_{max} by 46% and 61%, respectively.

H_2-antagonist: Avoid concomitant use of OSI-774 with gastric acid reducing agents if possible. When ranitidine 300 mg is given with OSI-774, OSI-774 AUC and C_{max} decrease by 33% and 54%, respectively. Increasing the dose of OSI-774 will not compensate the loss of exposure. However, if an H_2-antagonist receptor is needed, **take OSI-774 at least 2 hours before or 10 hours following the H_2-antagonist administration.** Dosing such, OSI-774 loss of exposure is minimized to AUC of 15% and C_{max} of 17%.

Patient Care Implications: If the patient vomits after taking the tablets, the dose is replaced only if the tablets can actually be seen and counted.

Patients should wear sun screen protection, hat, and long sleeves to avoid sun as it can exacerbate skin rash.

Pregnancy and Lactation: No information on pregnancy and lactation in humans is available yet.

c. PHARMACOLOGY

Total clearance of OSI-774 is similar to hepatic blood flow in dogs and rats. At intravenous doses > 1 mg/kg the clearance decreases and the plasma drug exposure increases supra-proportionately in rats and dogs. In vitro, the agent is slowly oxidized by liver microsomes. OSI-774 is extensively metabolized in rats and dogs with only a small amount excreted unchanged in urine, bile and feces. In a rat model designed to study pulmonary first pass extraction, OSI-774 had a pulmonary extraction of approximately 48%. In vitro studies have shown that the agent is metabolized by CYP1A1, which is expressed in lung tissue. Several circulating metabolites have been identified in mouse, rat and dog and subsequently synthesized and demonstrated to be potent as EGFR inhibitors. Only one, OSI-420, a hydroxylated metabolite, was a major metabolite in systemic circulation with a metabolite: parent ratio of 1:4 in plasma from rats or dogs given oral doses. This compound is as potent as OSI-774 in the in vivo tumor xenograft model.

The enzymes responsible for formation of the major metabolite in humans were identified as cytochromes P450 3A4 and 3A5 (expressed in liver) and 1A1 (expressed in lung). Studies on the inhibition potential of OSI-774 and its major metabolite, OSI-420, on the main human cytochrome P450 isoenzymes revealed a relatively strong inhibition of CYP 3A4 by OSI-774 (Ki 8 μM) and a weak inhibition of CYPs 1A2 and 3A4 by OSI-420 (Ki 20 μM). Further studies to evaluate the mechanism of inhibition are ongoing.

Oral bio-availability was found to be 77% in rats and 88% in dogs. Plasma protein binding is 92 - 95% in humans, rats, monkeys and mice, and was 85% in dogs.

How Supplied: OSI-774 is supplied as 25 mg, 100 mg, and 150 mg white film-coated tablets. In addition to the active ingredient, OSI-774, the tablets contain lactose, microcrystalline cellulose, sodium starch glycolate, sodium lauryl sulfate, and magnesium stearate. Tablets are unmarked and unscored. The 25 mg tablets [1/4 inch diameter, 3 mm deep (formerly non-film coated)], 100 mg tablets (11/32 inch diameter, 5 mm deep), and 150 mg tablets (13/32 inch diameter, 5.1 mm deep) are supplied 30 tablets/bottle.

Storage and Stability: The intact bottles should be stored at controlled room temperature (15°C-30°C). Shelf life surveillance studies of the intact bottle are on-going. Current data indicates OSI-774 is stable for at least 3 years at room temperature.

Administration: OSI-774 is administered orally. Tablets should be taken once daily preferably in the morning with up to 200 mL of water one hour before or two hours after food.

Administration through G-tube: The tablets required for the dose should be dissolved in 100 mL of sterile water. The dissolved tablets should be shaken vigorously to form a uniform suspension. The suspension should be drawn up into a syringe and administered through the G-tube port. Repeat the syringe transfer until the entire volume has been administered. A small volume (40 mL) of sterile water should be added to the container used to dissolve the tablets and the residual suspension should be shaken, aspirated into syringe, and administered. This last step should be repeated to ensure the entire dose is administered. The total volume of delivery/rinse (as per procedure submitted to IND) is ~180 ml.

d. SUPPLIER

OSI-774 is investigational for this study and will be supplied free of charge to patients by Genentech for distribution by Biologics. **Allow 7 business days for shipment of drug from receipt of the Biologics Drug Request Form (see S0635 abstract page on the SWOG website [https://swog.org/Members/ClinicalTrials/ViewProtocolDetails.asp?ProtocolID=2065]). Forms should be faxed to the number on the form.** Orders received before 4 p.m. E.S.T Monday through Thursday will be processed and shipped for same day delivery. Orders received after 4 pm E.S.T. Monday through Thursday or anytime on Friday will be processed and shipped the next business morning. Shipments will be sent via Federal Express for Priority Overnight delivery. Biologics will be closed the following holidays: New Years Eve, New Years Day, Memorial Day, Independence Day, Labor Day, Thanksgiving, Thanksgiving Friday, Christmas Eve and Christmas Day. For further details and molecule characterization, see the updated Tarceva Package insert.

4.0 STAGING CRITERIA

Patients must have **selected** Stage IIIB disease or Stage IV disease as outlined below (AJCC Cancer Staging Manual, 6th Edition, 2002):

4.1 **Selected** Stage IIIB

- T4 (cytology confirmed malignant pleural effusion, OR pleural tumor foci that are separate from direct pleural invasion by the primary tumor)
- Any N
- M0

4.2 Stage IV

- Any T
- Any N
- M1 (distant metastases present)

NOTE: Any disease that is recurrent after surgery or radiation is classified as Stage IV.

5.0 ELIGIBILITY CRITERIA

Each of the criteria in the following section must be met in order for a patient to be considered eligible for registration. Use the spaces provided to confirm a patient's eligibility. For each criterion requiring test results and dates, please record this information on the **S0635** Prestudy Form (Form #11652) and submit to the Data Operations Center in Seattle (see Section 14.0). Any potential eligibility issues should be addressed to the Data Operations Center in Seattle at 206/652-2267 prior to registration.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday four weeks later would be considered Day 28. This allows for efficient patient scheduling without exceeding the guidelines. **If Day 7, 14, 28 or 42 falls on a weekend or holiday, the limit may be extended to the next working day.**

SWOG Patient No. _____

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

_____ 5.1 Patients must have biopsy-proven, incompletely resected or unresectable bronchioloalveolar carcinoma or BAC variants (adenocarcinoma with BAC features, BAC with invasive adenocarcinoma). No component of squamous carcinoma can be present in any histologic sample.

NOTE: Cytology specimens, such as bronchial brushings, washings, or fine needle aspiration specimens alone are **not** acceptable for diagnosis of BAC or its subtypes.

_____ 5.2 Patients must be willing to provide prior smoking history as requested on the **S0635** Prestudy Form (Form #11652). Patients with BAC who are designated as "Never-Smokers" by their smoking history should be preferentially placed on trial **S0636**, which shares an identical plan, provided that this protocol is available for enrollment at the same institution.

_____ 5.3 Patients must have **selected** Stage IIIB (cytology-confirmed malignant pleural effusion) or Stage IV disease as defined in Section 4.0. Tumors may be multi-focal or diffuse. Recurrences of BAC in a separate lobe after prior resection within the preceding five years or multifocal lesions in more than one lobe are considered Stage IV disease.

_____ 5.4 Patients must have measurable and/or non-measurable disease (see Section 10.1) documented by chest CT. Measurable disease must be assessed within 28 days prior to registration. Pleural effusions, ascites and laboratory parameters are not acceptable as the only evidence of disease. Non-measurable disease must be assessed within 42 days prior to registration. All disease must be assessed and documented on the Baseline Tumor Assessment Form (Form #848).

_____ 5.5 Patients must have no symptomatic brain metastases. Patients may have treated, asymptomatic brain metastases as long as they do not require steroids for symptomatic management. Patients must have EITHER a negative CT/MRI scan of the brain, OR (for patients with treated brain metastases) a stable or improved scan. These scans must be performed within 42 days prior to registration. The timeframe for having completed any radiation and/or surgery for brain metastases must conform to the 28-day rule as outlined in Sections 5.6 and 5.7.

_____ 5.6 Prior radiation is allowed provided that at least 28 days have elapsed since the completion of prior radiation therapy and patients have recovered from all associated toxicities at the time of registration. Measurable or non-measurable disease must be present outside the previous radiation field or a new lesion inside the port must be present. If the patient received palliative radiation, at least 14 days must have elapsed since completion and patients must have recovered from all associated toxicities at the time of registration.

SWOG Patient No. _____

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

_____ 5.7 Prior surgery is allowed, provided that at least 28 days have elapsed since surgery (thoracic or other major surgeries) and patients have recovered from all associated toxicities at the time of registration.

_____ 5.8 Patients must not have had a fine needle aspiration or core biopsy within 7 days prior to registration.

_____ 5.9 Patients may have received prior systemic chemotherapy or biologic therapy. Prior systemic therapy must have been discontinued at least 28 days prior to registration. Patients must not have received prior treatment with ZD1839 (gefitinib), OSI-774 (erlotinib), or bevacizumab. In addition, patients must not have received other targeted therapies against the EGFR or VEGF axes.

_____ 5.10 Patients must not have had hemoptysis ≥ ½ teaspoon within 28 days prior to registration. Patients with clinical history of pulmonary/upper respiratory hemorrhage ≥ Grade 2 (per CTCAE 3.0) within 6 months or Grade 1 within 28 days prior to registration are not eligible. Patients must have no history of either thromboses or hemorrhage, including hemorrhagic or thrombotic stroke or other CNS bleeding.

NOTE: The treating physician is responsible for documenting the amount of blood at hemoptysis.

_____ 5.11 Patients may be on stable therapeutic anticoagulation, including warfarin or low molecular weight heparin, as needed, except for those with a history of bleeding complications on anticoagulation or an inability to establish a stable therapeutic regimen for anticoagulation.

_____ 5.12 Patients must have adequate hepatic function, as determined by the following tests measured within 28 days prior to registration: serum bilirubin ≤ 1.0 x the institutional upper limit of normal (IULN) and a SGOT or SGPT ≤ 2.5 x IULN

_____ 5.13 Patients must have adequate renal function, as determined by the following tests measured within 28 days prior to registration: serum creatinine ≤ 1.5 x IULN or a calculated or measured creatinine clearance ≥ 50 ml/min using the following formula:

$$\text{Calculated Creatinine Clearance} = \frac{(140 - \text{age}) \times \text{wt (kg)} \times 0.85 \text{ (if female)}}{72 \times \text{serum creatinine (mg/dl)}}$$

_____ 5.14 Urine protein must be screened by urine analysis for Urine Protein Creatinine (UPC) ratio. For UPC ratio > 0.5, 24-hour urine protein must be obtained and the level must be < 1,000 mg for patient enrollment. The urine protein used to calculate the UPC ratio must be obtained within 28 days prior to registration.

NOTE: UPC ratio of spot urine is an estimation of the 24-hour urine protein excretion – a UPC ratio of 1 is roughly equivalent to a 24-hour urine protein of 1 gm. UPC ratio is calculated using one of the following formulas:

[urine protein]/[urine creatinine] – if both protein and creatinine are reported in mg/dL
[(urine protein) x0.088]/[urine creatinine] – if urine creatinine is reported in mmol/L

_____ 5.15 Patients must have an ANC ≥ 1,500/mcl and a platelet count ≥ 100,000/mcl obtained within 28 days prior to registration.

SWOG Patient No. _____

Patient's Initials (L, F, M)

_____ 5.16 Patients with hypertension must have hypertension controlled on medication prior to enrollment.

_____ 5.17 Patients must have a Zubrod Performance Status of 0 - 2 (see Section 10.5).

_____ 5.18 All patients must be 18 years of age or older.

_____ 5.19 Institutions must offer patient participation in correlative science studies as outlined in Section 15.0.

_____ 5.20 Patients must not be currently receiving or planning to receive surgery or any other non-protocol treatment (including chemotherapy, hormonal, biologic or radiation therapy) directed at the BAC.

_____ 5.21 Patients must not have a serious non-healing wound, ulcer, or bone fracture.

_____ 5.22 No other prior malignancy is allowed except for the following: adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, adequately treated Stage I or II cancer from which the patient is currently in complete remission, or any other cancer from which the patient has been disease-free for five years.

_____ 5.23 Pregnant or nursing women are not eligible to participate in this trial due to the potential teratogenic or abortifacient effects of the study drug on the fetus or nursing infant. Women and men of reproductive potential must have agreed to use an effective contraceptive method.

_____ 5.24 Patients must be informed of the investigational nature of this study and must sign and give written informed consent in accordance with institutional and federal guidelines.

_____ 5.25 At the time of patient registration, the treating institution's name and ID number must be provided to the Data Operations Center in Seattle in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered into the data base.

6.0 STRATIFICATION FACTORS

There will be no stratification in this protocol.

7.0 TREATMENT PLAN

For treatment or dose modification questions, please contact Dr. West at 206/386-2424 or Dr. Antoinette Wozniak at 313/576-8752. For dosing principles or questions, please consult the Southwest Oncology Group Policy #38 "Dosing Principles for Patients on Clinical Trials" at http://swog.org (then click on "Policies and Manuals" under the "Visitors" menu and choose Policy 38).

7.1 Good Medical Practice

The following tests (and/or assessments) are recommended within 28 days prior to registration in accordance with Good Medical Practice. Results of these tests do not determine eligibility and minor deviations from normal limits would be acceptable if they do not affect patient safety in the clinical judgment of the treating physician. If there are significant deviations in these tests/assessments that could impact patient safety, it is highly recommended that the registering investigator discuss the patient with the Study Coordinator prior to registering.

a. HGB ≥ 9 g/dl

b. Albumin and LDH

c. Alkaline phosphatase

d. Bone scan, if clinically indicated

e. PET scan, if clinically indicated

f. Patients should not have psychological, familial, sociological or geographical conditions that do not permit medical follow-up and compliance with the study protocol.

g. Except for cancer-related abnormalities, patients should not have unstable or pre-existing major medical conditions.

h. Patients should not have any immediate life-threatening complications of their malignancies.

7.2 Treatment

AGENT	DOSE	ROUTE	DAYS	INTERVAL**
OSI-774	*150 mg/day	PO	1 - 21	Daily
Bevacizumab	15 mg/kg	IV infusion over 90 ± 15 minutes***	1	q 21 days

* OSI-774 tablets are supplied as 25 mg, 100 mg, and 150 mg tablets. Tablets should be taken in the morning with up to 200 mL of water 1 hour before or 2 hours after food.

** A cycle of therapy is 21 days.

*** If no adverse reactions occur, the second dose of bevacizumab should be given over a minimum of 60 minutes. If no adverse event occurs, third and subsequent doses should be administered over a minimum of 30 minutes. Infusions should be run in a volumetric infusion device. Infusions should be run over the shortest period that is well-tolerated.

NOTE: Patients will be given a 30-day supply of OSI-774. Patients receiving full dose therapy will be supplied with 150 mg tablets and those reduced to a dose of 100 mg/day will be supplied with 100 mg tablets. Patients dose reduced to 50 mg/day will be instructed to take two 25 mg tablets once a day.

Administration through G-tube: The tablets required for the dose should be dissolved in 100 mL of sterile water. The dissolved tablets should be shaken vigorously to form a uniform suspension. The suspension should be drawn up into a syringe and administered through the G-tube port. Repeat the syringe transfer until the entire volume has been administered. A small volume (40 mL) of sterile water should be added to the container used to dissolve the tablets and the residual suspension should be shaken, aspirated into a syringe, and administered. This last step should be repeated to ensure the entire dose is administered. The total volume of delivery/rinse is about 180 mL.

7.3 Protocol treatment and parameters will continue on the same schedule until the patient has met any of the criteria listed in Section 7.6.

7.4 Drug compliance will be recorded by patients in the Intake Calendar (see Appendix 19.2). Institutional CRAs will review and ascertain patient adherence with protocol therapy at the end of treatment for each cycle. Calendar should be kept in the patient's clinic chart. Note that the Intake Calendar is provided only as a tool for tracking patient compliance. Sites may utilize institutional pill diaries or other source documentation in place of the Intake Calendar at the discretion of the treating physician.

7.5 Supportive Treatment

Patients should receive full supportive care including transfusions of blood products, antibiotics, antiemetics, antidiarrheals, growth factor support, bisphosphonates, etc., when appropriate. Use of G-CSF for patients being treated on this study is not anticipated to be necessary due to the low likelihood of significant hematologic toxicity for this combination. Use of G-CSF for myelosuppression, per the ASCO guidelines (http://www.jco.org/cgi/content/full/18/20/3558), is at the discretion of the treating physician. If used, it must be documented on the **S0635** Treatment Form (Form #37277). The use of erythropoietin is also at the discretion of the treating physician. If used, it must be documented on the **S0635** Treatment Form (Form #37277).

7.6 **Criteria for Removal from Protocol Treatment:**

a. Progression of disease or symptomatic deterioration (as defined in Sections 10.2d and 10.2e)

b. Unacceptable toxicity

c. Development of any gross hemoptysis

d. Treatment delay for both agents > 35 days, for any reason

e. The patient may withdraw from the study at any time for any reason

f. Physician's discretion

7.7 All reasons for discontinuation of treatment must be documented on the Off Treatment Notice (Form #28829).

7.8 All patients will be followed for a maximum of 3 years.

8.0 TOXICITIES TO BE MONITORED AND DOSAGE MODIFICATIONS

8.1 **Two different versions of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be used on this study.**

a. Serious Adverse Event (SAE) reporting

The CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 4.0 will be utilized **for SAE reporting only**. The CTCAE Version 4.0 is identified and located at the CTEP website at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTCAE Version 4.0.

b. Routine toxicity reporting

This study will utilize the CTCAE Version 3.0 for routine toxicity reporting. A copy of the CTCAE Version 3.0 can be downloaded from the CTEP home page (http://ctep.cancer.gov). All appropriate treatment areas should have access to a copy of the CTCAE Version 3.0.

8.2 General Considerations

a. Dose modifications will be based on toxicities experienced during the previous cycle of treatment.

b. Once a dose is reduced, it will remain reduced for all subsequent administrations. There are no dose re-escalations.

c. If multiple toxicities are experienced, dose modifications will be based on the toxicity requiring the largest dose reduction.

d. Patients who must discontinue erlotinib or bevacizumab may continue on the other agent and continue on study.

e. **Patient must be removed from protocol treatment if dose of both agents is delayed > 21 days.**

f. NOTE: In the event that treatment is held, therapy for that week cannot be made up (i.e., the calendar is not stopped).

8.3 If patients require radiation therapy for palliation in the absence of progressive disease, please contact Dr. West at 206/386-2424 to clarify the purpose of treatment.

8.4 **Dosage Modification Criteria and Guidelines for Management of OSI-774-Related Toxicities**

a. OSI-774 Dose Level Reductions

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

NOTE: If a third dose level reduction is required, discontinue OSI-774. The patient may continue on protocol treatment with single agent bevacizumab.

b. Diarrhea

Grade	OSI-774 Dosage Modification	Guideline for Management
Grade 2 that is unacceptable to the patient	Hold until resolution to ≤ Grade 1, and subsequently re-start at the same dose. If Grade 2 diarrhea recurs after re-instituting treatment at the same dose, treatment should be held until resolution to ≤ Grade 1 and re-instituted at a one level dose reduction.	Loperamide (4 mg at first onset, followed by 2 mg q 2 - 4 hr until diarrhea free for 12 hr with a maximum of 16 mg/day).
≥ 3	Hold until resolution to ≤ Grade 1, then re-institute at a one level dose reduction.	Loperamide (4 mg at first onset, followed by 2 mg q 2 - 4 hr until diarrhea free for 12 hr with a maximum of 16 mg/day).

c. Rash

Grade	OSI-774 Dosage Modification	Guideline for Management
Grade 2 that is unacceptable to the patient	Hold until resolution to ≤ Grade 1, and subsequently re-start at the same dose. If Grade 2 skin rash recurs after re-instituting treatment at the same dose, treatment should be held until resolution to ≤ Grade 1 and re-instituted at a one level dose reduction.	Administer any of the following: minocycline,[1] topical tetracycline, topical clindamycin, topical silver sulfadiazine, diphenhydramine, oral prednisone (short course), topical steroids.
≥ 3	Hold until resolution to ≤ Grade 1, then re-institute at a one level dose reduction.	Administer any of the following: minocycline,[1] topical tetracycline, topical clindamycin, topical silver sulfadiazine, diphenhydramine, oral prednisone (short course), topical steroids.

[1] Recommended dose of minocycline: 200 mg po initially (loading dose) followed by 100 mg po bid x 7 - 10 days.

d. Pulmonary Toxicity/Pneumonitis

Pneumonitis and pulmonary toxicity have been reported with oral EGFR inhibitors such as ZD1839 and OSI-774. Patients who continue to smoke tobacco products should be encouraged to discontinue their use due to a possible association between tobacco smoking and pulmonary toxicity. All patients with new onset or worsening symptoms/signs of pneumonitis (i.e.,

cough, dyspnea, fever) should have their treatment held pending investigation into the cause of their symptoms. Patients found to have pneumonitis thought to be related to OSI-774 should be removed from treatment with OSI-774. Patients with alternative explanations for their pulmonary symptoms may restart OSI-774 without a dose reduction once symptoms return to Grade 1 or less.

e. Liver Function Abnormalities

Grade	OSI-774 Dose Modification
SGOT or SGPT ≥ Grade 3 OR Bilirubin ≥ Grade 3	Hold OSI-774. Check weekly. Upon resolution to ≤ Grade 2, re-start OSI-774 at one level dose reduction.

f. GI Perforation

In the event of bowel perforation, permanently discontinue erlotinib.

g. Ocular Toxicities

If patient experiences acute/worsening eye pain, hold erlotinib until recovery and then re-start at same dose. If inflammation persists or if severe eye surface damage occurs, permanently discontinue erlotinib.

h. Other medically concerning toxicities

No dose reduction will be considered for any grade of alopecia.

For any other Grade 3 or greater toxicity, hold treatment until the toxicity resolves to Grade 1 or less, then resume treatment at a reduced dose of 100 mg/day. If toxicity has not resolved to Grade 1 or less after 14 days off of treatment, call the Study Coordinator to reconsider further therapy on this study. If Grade 3 or greater toxicity recurs after the patient has been already reduced to 100 mg/day, hold treatment until the toxicity resolves to Grade 1, then resume treatment at a dose of 50 mg/day.

8.5 Treatment Modification Criteria and Guidelines for Management of Bevacizumab-Related Toxicities

There are no dose reductions for bevacizumab, only dose delays. If adverse events occur that require holding bevacizumab, the dose will remain the same once treatment resumes. Adverse events requiring delays or permanent discontinuation of bevacizumab are outlined below.

Patients who require discontinuation of bevacizumab for toxicity may continue to receive OSI-774.

a. Infusion-Related Adverse Events

If a patient experiences a Grade 1 or 2 bevacizumab infusion-related adverse event, he or she may be premedicated for the next bevacizumab 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 patient continues to be premedicated. If the patient experiences an infusion-associated adverse event with the 60-minute infusion, all subsequent doses should be given over 90 ± 15 minutes. Similarly, if the patient experiences an infusion-associated adverse event with the 30 minute infusion, all subsequent bevacizumab doses should be given over 60 ± 10 minutes.

In the event of Grade 3 or 4 infusion reaction, discontinue bevacizumab.*

b. For platelet counts < 50,000/mcl, hold bevacizumab. If platelet count does not recover within 21 days after discontinuation, the patient should be removed from bevacizumab treatment.*

c. Hemorrhage

Any CNS hemorrhage	Discontinue bevacizumab*
Grade 2 hemoptysis	Discontinue bevacizumab*
Grade 2 other than hemoptysis	Hold bevacizumab until both of the following criteria are met: • The bleeding has resolved and hemoglobin is stable • There is no anatomic or pathologic condition that would significantly increase the risk of hemorrhage recurrence
Grade 3 or 4	Discontinue bevacizumab*

d. Venous Thrombosis

Grade 3 or 4	Discontinue bevacizumab and initiate therapeutic anti-coagulation*

e. Proteinuria

UPC ratio to be performed prior to every other bevacizumab treatment. If UPC ratio > 1 then a 24 hour urine protein must be obtained. If at any point a patient has a UPC ratio > 1 (including patients who have had UPC > 1 prior to Revision #9) they do not need to undergo any further UPC ratio testing, but may proceed directly to 24 hour urine protein test for all future timepoints.

Grade 3 (> 3.5 g/24 hr)	Hold bevacizumab until proteinuria improves to ≤ Grade 2
Grade 4 (nephrotic syndrome)	Discontinue bevacizumab*

f. Hypertension

Grade 3	If not controlled with medication, discontinue bevacizumab
Grade 4	Discontinue bevacizumab

g. Gastrointestinal perforation or dehiscence

If a patient experiences a GI perforation or wound dehiscence requiring medical or surgical therapy, discontinue bevacizumab.*

h. Bevacizumab should be held in patients with symptoms/signs suggestive of reversible posterior leukoencephalopathy syndrome (RPLS), pending work-up and management, including control of blood pressure. Bevacizumab should be discontinued upon diagnosis of RPLS.*

i. Arterial thromboembolic events (including angina, myocardial infarction, transient ischemic attack, cerebrovascular accident, or any other arterial thromboembolic event)

Grade	Dose Modification
Any Grade	Discontinue bevacizumab*

j. Other non-hematological Grade 3 or 4 adverse events: If a patient develops any other Grade 3 toxicity (except for controllable nausea/vomiting) thought to be related to bevacizumab or that would increase the risk of bevacizumab toxicity, bevacizumab should be held until symptoms resolve to Grade 1 or less. If Grade 3 toxicity persists for > 21 days or recurs after resumption of the therapy, discontinue bevacizumab.* For Grade 4 toxicities (except for controllable nausea/vomiting), discontinue bevacizumab.*

*Patients are to continue on protocol treatment with single agent OSI-774 (per Section 8.2d).

8.6 For treatment or dose modification questions, please contact Dr. West at 206/386-2424 or Dr. Antoinette Wozniak at 313/576-8752.

8.7 Toxicities (including suspected reactions) that meet the expedited reporting criteria as outlined in section 16.0 of the protocol must be reported to the Operations Office, Study Coordinator and NCI via AdEERS, and to the IRB per local IRB requirements.

9.0 STUDY CALENDAR

		Cycle 1			Cycle 2			Cycle 3			Cycle 4 ∑				√
REQUIRED STUDIES	PRE	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Follow-Up Prior	Follow-Up After
	STUDY	1	2	3	4	5	6	7	8	9	10	11	12	To Progression	Progression
PHYSICAL															
History and Physical Exam, including Blood Pressure	X				X			X			X			X Δ	
Review Intake Calendar					X			X			X				
Weight and Performance Status	X	X			X			X			X				
Disease Assessment %	X							X						X%	
Toxicity Notation		X			X			X			X			X#	X#
LABORATORY															
CBC/Differential/Platelets	X	X			X			X			X				
Bilirubin	X				X			X			X				
SGOT or SGPT	X				X			X			X				
Serum Creatinine Φ	X	X			X			X			X				
Calculated or Measured Creatinine Clearance	X	X			X			X			X				
Urine Protein Creatinine (UPC) Ratio*	X				X						X				
SUGGESTED LABORATORY															
Albumin and LDH ß	X				X			X			X				
Alkaline phosphatase ◊ ß	X				X			X			X				
SPECIMEN SUBMISSION															
Tissue per Section 15.2	X														
Blood specimens and plasma per Section 15.2	X				X			X						X¥	
X-RAYS & SCANS															
Chest CT %	X							X						X%	
Correlative Imaging Study ‡	X														
Brain CT/MRI	X														
Bone scan £	X														
PET £	X														
TREATMENT (see Section 7.0 for details)															
OSI-774		X	X	X	X	X	X	X	X	X	X	X	X		
Bevacizumab		X			X			X			X				

Note: Forms are found in Section 18.0. Forms submission guidelines are found in Section 14.0.

% To be performed every 6 weeks for 18 weeks, then every 9-12 weeks until progression up to 2 years. For patients who have not progressed by the two-year point, chest CT must be performed once every 6 months until progression. Disease must be assessed using the same technique as baseline and must be documented on the Follow-Up Tumor Assessment form. A response must be confirmed by a second determination at least 4 weeks after a CR or PR has been noted.

‡ If patient is removed from protocol treatment before Week 13, perform scan after discontinuation of treatment. Prestudy and follow-up CT scans should be performed with the same CT scanner (or identical brand and model) and techniques to allow for reliable comparison of response to be determined by central computer-assisted image analysis. See Section 15.1 for Radiology Review Requirements.

Δ To be performed every 9 weeks until progression.

Φ Not necessary if measured creatinine clearance is used.

◊ Abnormalities in alkaline phosphatase levels should be appropriately followed to document the possibility of bone or hepatic metastases.

* UPC ratio to be performed prior to every other bevacizumab treatment. If UPC ratio > 1 then a 24 hour urine protein must be obtained. If at any point a patient has a UPC ratio > 1 (including patients who have had UPC > 1 prior to Revision #9) they do not need to undergo any further UPC ratio testing, but may proceed directly to 24 hour urine protein test for all future timepoints.

ß Results of these tests do not determine eligibilty but are recommended prior to registration in accordance with Good Medical Practice (see Section 7.1) and are required during treatment and throughout follow-up.

£ PET and/or bone scan is to be performed only if clinically indicated (per GMP).

∑ Protocol treatment and parameters will continue on the same schedule until patient has met any of the criteria in Section 7.6.

√ After disease progression, patients must be followed every 3 months for 1 year and then every 6 months for a maximum of 3 years from initial registration.

Toxicity should be evaluated until resolution to ≤ Grade 1 of any adverse events.

¥ It is very important to obtain a blood specimen (approximately 10 ml) from any patient that is being removed from protocol treatment, regardless of the timepoint.

10.0 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS

10.1 Measurability of lesions

a. **Measurable disease**: Lesions that can be accurately measured in at least one dimension by 1) medical photograph (skin or oral lesion), palpation, plain x-ray, CT, MRI or other conventional technique with longest diameter 2 cm or greater in the axial plane (bone lesions not included), or 2) spiral CT with longest diameter 1 cm or greater. Ultrasound is suitable only for superficial disease (superficial palpable nodes, subcutaneous lesions, thyroid nodules).

CT imaging is the preferred radiographic method for measuring response. Conventional CT or MRI slices are recommended to be 5 mm or smaller; spiral CT should be performed using a 5 mm contiguous reconstruction algorithm.

b. **Non-measurable disease**: All other lesions including lesions too small to be considered measurable, pleural or pericardial effusions, ascites, bone disease, inflammatory breast disease, leptomeningeal disease, lymphangitis, pulmonitis, abdominal masses not confirmed and followed by imaging techniques, cystic lesions or disease documented by indirect evidence only (e.g., by lab values), previously radiated lesions that have not progressed.

10.2 **Objective status at each evaluation**: Objective Status is to be recorded at each evaluation. All measurable lesions up to a maximum of 5 lesions per organ and 10 lesions in total, representative of all involved organs, should be identified as target lesions at baseline. All measurable lesions not identified as target lesions are non-target lesions and are included as non-measurable disease. Measurements must be provided for target measurable lesions, while presence or absence must be noted for non-target measurable and non-measurable disease.

a. **Complete Response (CR)**: Complete disappearance of all measurable and non-measurable disease. No new lesions. No disease related symptoms. Normalization of markers and other abnormal lab values. All disease must be assessed using the same technique as baseline.

b. **Partial Response (PR)**: Applies only to patients with at least one measurable lesion. Greater than or equal to 30% decrease under baseline of the sum of longest diameters of all target measurable lesions. No unequivocal progression of non-measurable disease. No new lesions. All target measurable lesions must be assessed using the same techniques as baseline.

c. **Stable**: Does not qualify for CR, PR, Progression or Symptomatic Deterioration. All target measurable lesions must be assessed using the same techniques as baseline.

d. **Progression**: One or more of the following must occur: 20% increase in the sum of longest diameters of target measurable lesions over smallest sum observed (over baseline if no decrease during therapy) using the same techniques as baseline. Unequivocal progression of non-measurable disease in the opinion of the treating physician (an explanation must be provided). Appearance of any new lesion/site. Death due to disease without prior documentation of progression and without symptomatic deterioration (see Section 10.2e).

e. **Symptomatic deterioration**: Global deterioration of health status requiring discontinuation of treatment without objective evidence of progression. Efforts should be made to obtain objective evidence of progression after discontinuation.

f. **Assessment inadequate, objective status unknown**: Progression or symptomatic deterioration has not been documented, and one or more target measurable lesions have not been assessed or inconsistent assessment methods were used.

g. Objective status notes:

1. Non-measurable and non-target measurable disease do not affect objective status except in determination of CR (must be absent--a patient who otherwise has a CR, but who has non-measurable or non-target measurable disease present or not assessed, will be classified as having a PR), and in determination of progression (if new sites of disease develop or if unequivocal progression occurs in the opinion of the treating physician).

2. An objective status of PR or stable cannot follow one of CR. Stable can follow PR only in the rare case that tumor increases too little to qualify as progression, but enough that a previously documented 30% decrease no longer holds.

3. In cases for which initial flare reaction is possible (hypercalcemia, increased bone pain, erythema of skin lesions), objective status is not progression unless either symptoms persist beyond 4 weeks or there is additional evidence of progression.

4. Lesions that appear to increase in size due to presence of necrotic tissue will not be considered to have progressed.

5. For bone disease documented on bone scan only, increased uptake does not constitute unequivocal progression.

6. Appearance or worsening of pleural effusions does not constitute unequivocal progression unless cytologically proven of neoplastic origin.

7. If CR determination depends on a lesion for which the status is unclear by the required tests, it is recommended the residual lesion be investigated with biopsy or fine needle aspirate.

10.3 **Best Response**: This is calculated from the sequence of objective statuses.

a. CR: Two or more objective statuses of CR a minimum of four weeks apart documented before progression or symptomatic deterioration.

b. PR: Two or more objective statuses of PR or better a minimum of four weeks apart documented before progression or symptomatic deterioration, but not qualifying as CR.

c. Unconfirmed CR: One objective status of CR documented before progression or symptomatic deterioration but not qualifying as CR or PR.

d. Unconfirmed PR: One objective status of PR documented before progression or symptomatic deterioration but not qualifying as CR, PR or unconfirmed CR.

e. Stable/no response: At least one objective status of stable/no response documented at least 6 weeks after registration and before progression or symptomatic deterioration, but not qualifying as anything else above.

f. Increasing disease: Objective status of progression within 12 weeks of registration, not qualifying as anything else above.

g. Symptomatic deterioration: Objective status of symptomatic deterioration within 12 weeks of registration, not qualifying as anything else above.

h. Inadequate assessment, response unknown: Progression or symptomatic deterioration greater than 12 weeks after registration and no other response category applies.

10.4 Computer-Assisted Image Analysis

a. A pre-study chest CT must show evidence of disease, and repeat CT scans must be performed with the same CT scanner and techniques (e.g., slice width, the use of contrast) used for subsequent evaluation of two follow-up CT scans to assess response to therapy by computerized image analysis. Chest CT scans must be downloaded in DICOM format to CDs.

b. For the purposes of computer-assisted image analysis, the following alternate response definitions will be employed.

1. **Measurable disease**: Any lesion on CT measurable by computer-assisted image analysis.

2. **Complete Response (CR)**: Complete disappearance of all measurable disease. No new lesions. All measurable lesions and sites must be assessed using the same techniques as baseline.

3. **Partial Response (PR)**: Greater than or equal to a 50% decrease in the volume of lesions compared to baseline measured by computer-assisted image analysis.

4. **Stable Disease (SD)**: Does not qualify as CR, PR, or PD (below).

5. **Progressive Disease (PD)**: 30% increase in the volume of disease over baseline, OR reappearance of any lesion that had disappeared, OR appearance of any new lesion, OR failure to return for evaluation due to death or deteriorating condition unless clearly unrelated to the underlying cancer.

Exceptions: (1) In cases for which initial tumor flare reaction is possible (hypercalcemia, increased bone pain, erythema of skin lesions), either symptom must persist beyond four weeks or there must be additional evidence of progression. (2) Lesions, which appear to increase in size due to presence of necrotic tissue, will not be considered to have progressed.

6. **Unknown**: Progression has not been documented and one or more measurable sites have not been assessed.

10.5 **Performance Status**: Patients will be graded according to the Zubrod Performance Status scale.

POINT	DESCRIPTION
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
2	Ambulatory and capable of self-care but unable to carry out any work activities; up and about more than 50% of waking hours.
3	Capable of limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair.

10.6 **Progression-Free Survival**: From date of registration to date of first documentation of progression or symptomatic deterioration (as defined in Sections 10.2d - 10.2e), or death due to any cause. Patients last known to be alive and progression-free are censored at date of last contact.

10.7 **Time to Death:** From date of registration to date of death due to any cause. Patients last known to be alive are censored at date of last contact.

11.0 STATISTICAL CONSIDERATIONS

11.1 The accrual rate is expected to be 6-10 per month (conservatively) based on **S0126** accrual. With emerging positive data for bevacizumab in NSCLC and the fact that this costly agent is being provided free-of-charge for this study, interest in this trial may lead to higher accrual rates.

11.2 The main objective of this study is to assess the overall survival of patients with BAC/adenoBAC who receive daily oral OSI-774 (erlotinib) in combination with intravenous bevacizumab every 3 weeks. It is assumed that the regimen would not be promising if the true median survival were ≤ 12 months, but would be of considerable interest if the true median survival were ≥ 19 months. Eighty eligible patients will be accrued over an estimated eight months. With an additional 18 months of follow-up, we will have 86% power to rule out the null hypothesis of a 12-month median survival at a .05 level (indicating no further interest in the regimen) versus an alternative of a 19-month median survival. An observed median survival of 16 months or longer will be considered evidence that this regimen warrants further testing in a Phase III setting providing other factors such as toxicity appear favorable.

11.3 The rate of Grade 4 or 5 hemorrhage will be closely monitored throughout this trial. Once adverse event data becomes available on the first 30 eligible patients who receive protocol treatment, if the rate of Grade 4 or 5 hemorrhage exceeds or equals 10% of all eligible patients who have received protocol treatment, the trial will be stopped. Eighty patients will be sufficient to estimate the probability of a particular toxicity to within ± 11% (95% confidence interval). Any toxicity with at least 5% probability is likely to be seen at least once (98% chance).

11.4 Eighty patients are sufficient to estimate the progression-free survival rate at any time point (e.g. 12 months) to within ± 11% (95% confidence interval). Assuming that 70% of patients will have measurable disease, then response will be assessed in approximately 56 patients. Fifty-six patients are sufficient to estimate the RECIST response rate (confirmed plus unconfirmed, complete plus partial) to within ± 13% (95% confidence interval).

The level of agreement between response outcomes via CAIA versus response by RECIST will be preliminarily assessed among the subset of patients who have both measurable disease (as defined by RECIST) and CT images available for central review.

11.5 Molecular Correlative Statistical Considerations

The relationship between clinical outcomes and EGFR and ras mutations, as well as EGFR and VEGF expression in tissue collected from patients with bronchioloalveolar carcinoma or BAC variants will be investigated. Due to the limited sample size provided in a Phase II setting, these correlative studies will be considered exploratory in nature and will help generate hypotheses for future studies. Assuming an 80% submission rate for specimens, we expect to have specimens from approximately 64 patients.

11.6 There is no formal data and safety monitoring committee for Phase II studies. Toxicity and accrual monitoring are done routinely by the Study Coordinator, study Statistician and the Disease Committee Chair. Response monitoring is done by the study Statistician and Study Coordinator. Accrual reports are generated weekly, and formal toxicity reports are generated every 6 months. In addition, the Statistical Center, Adverse Event Coordinator at the Operations Office, SAE Physician Reviewer, and Study Coordinator monitor toxicities on an ongoing basis.

12.0 DISCIPLINE REVIEW

No formal discipline review will be performed in conjunction with this study.

13.0 REGISTRATION GUIDELINES

13.1 Patients must be registered prior to initiation of treatment (no more than seven working days prior to planned start of treatment).

13.2 For either phone or web registration, the individual registering the patient must have completed the appropriate Southwest Oncology Group Registration Form. The completed form must be referred to during the registration but should not be submitted as part of the patient data.

The individual registering the patient must also be prepared to provide the treating institution's name and ID number in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered into the data base. Patients will not be registered if the IRB approval date has not been provided or is > 365 days prior to the date of registration.

13.3 Registration Procedures

a. You may register patients from Member, CCOP and approved Affiliate institutions to a therapeutics study using the SWOG Registration program. To access the Registration program go to the SWOG Web site (http://swog.org) and click on the *Logon* link to go to the SWOG Members Area logon page

(https://swog.org/visitors/logon.asp). This Web program is available at any time except for periods listed **under *Down Times*.** Log on as an Individual User using your SWOG Roster ID Number and individual web user password. Help for the logon process may be found at https://swog.org/visitors/logonhelp.asp. After you have logged on, click on the *Clinical Trials* link and then the *Patient Reg* link to go to the Entry Page for the Patient Registration program. If you are a Registrar at an institution with Internet access you are encouraged to register this way. For new users, the link to a "Starter Kit" of help files may be found by clicking on **Starter Kit link at the logon page.**

To register a patient the following must be done (in order):

1. You are entered into the Southwest Oncology Group Roster and issued a SWOG Roster ID Number,

2. You are associated as an investigator or CRA/RN to the institution where a registration is occurring, and

3. You are granted permission to use the Patient Registration program at that institution.

For assistance with points 1 and 2 call the SWOG Operations Office at 210/614-8808. For point 3 you must contact your Web User Administrator. Each SWOG institution has one or more Web User Administrators who may set up Web Users at their institution and assign permissions and passwords to these users. For other password problems or problems with the Patient Registration program, please e-mail webreghelp@crab.org. Include your name, Roster ID Number, and telephone number, when the problem occurred, and exactly what you were doing.

b. If the Web Reg program is not used, the registration must be done by phone.

Member, Affiliate and CCOP Institutions

Registration by phone of patients from member, affiliate and CCOP institutions must be done through the Southwest Oncology Group Data Operations Center in Seattle by telephoning 206/652-2267, 6:30 a.m. to 4:00 p.m. Pacific Time, Monday through Friday, excluding holidays.

13.4 For either method of registration, exceptions to Southwest Oncology Group registration policies will not be permitted.

a. Patients must meet all eligibility requirements.

b. Institutions must be identified as approved for registration.

c. Registrations may not be cancelled.

d. Late registrations (after initiation of treatment) will not be accepted.

14.0 DATA SUBMISSION SCHEDULE

14.1 Data must be submitted according to the protocol requirements for **ALL** patients registered, whether or not assigned treatment is administered, including patients deemed to be ineligible. Patients for whom documentation is inadequate to determine eligibility will generally be deemed ineligible.

14.2 Master forms are included in Section 18.0 and (with the exception of the sample consent form and the Registration Form) must be photocopied for data submission to the Data Operations Center in Seattle. Data from approved SWOG institutions must be submitted on-line via the Web; see Section 14.3a for details. Exceptions to online data submission are patient-completed (e.g. Quality of Life) forms and source documents (e.g. pathology/operative/lab reports).

14.3 Data Submission Procedures.

a. Southwest Oncology Group institutions must submit data electronically via the Web by using the SWOG CRA Workbench. To access the CRA Workbench, go to the SWOG Web site (http://swog.org) and logon to the Members Area. After you have logged on, click on the *CRA Workbench* link to access the home page for CRA Workbench website. Next, click on the *Data Submission* link and follow the instructions. For new users, the link to a "Starter Kit" of help files may be found by clicking on the **Starter Kit** link at the Members' logon page.

To submit data via the web the following must be done (in order):

1. You are entered into the Southwest Oncology Group Roster and issued a SWOG Roster ID Number,
2. You are associated as an investigator or CRA/RN at the institution where the patient is being treated or followed, and
3. Your Web User Administrator has added you as a web user and has given you the appropriate system permissions to submit data for that institution.

For assistance with points 1 and 2 call the Operations Office at 210/614-8808. For point 3, contact your local Web User Administrator (refer to the "Who is my Web User Administrator?" function on the swog.org Members logon page). For other difficulties with the CRA Workbench, please email *technicalquestion@crab.org*.

b. If you need to submit data that are not available for online data submission, the only alternative is via facsimile. Should the need for this occur, institutions may submit data via facsimile to 800/892-4007 or 206/342-1680 locally. Please do not use cover sheet for faxed data.

14.4 WITHIN 14 DAYS OF REGISTRATION:

Submit a copy of the following:

a. **S0635** Prestudy Form (Form #11652).

b. Baseline Tumor Assessment Form (#848).

c. Pathology Report (for confirmation of histological diagnosis of bronchioloalveolar carcinoma) must be faxed.

14.5 SPECIMEN SUBMISSION:

Submit specimens for correlative testing as outlined in Section 15.0.

14.6 WITHIN 7 DAYS AFTER COMPLETION OF EACH CYCLE OF TREATMENT:

Submit a copy of the following:

a. **S0635** Treatment Form (Form #37277).

b. **S0635** Adverse Event Form (Form #34254).

NOTE: One cycle = 21 days.

14.7 AFTER EVERY DISEASE ASSESSMENT WHILE ON PROTOCOL TREATMENT:

Submit a copy of the Follow-Up Tumor Assessment Form (Form #38305).

14.8 WITHIN 14 DAYS OF DISCONTINUATION OF TREATMENT:

Submit a copy of the following:

a. Off Treatment Notice (Form #28829) documenting date of progression/relapse/other reason and summarizing inclusive dates of treatment and patient status.

b. Final **S0635** Treatment Form (Form #37277).

c. **S0635** Adverse Event Form (Form #34254). If acute adverse events are not resolved within 14 days of discontinuation of treatment, submit a final **S0635** Adverse Event Form (Form #34254) after the date of the first visit or contact after their resolution.

14.9 WITHIN 30 DAYS AFTER THE WEEK 13 CT SCAN OR WITHIN 30 DAYS OF DISCONTINUATION OF TREATMENT:

Submit a copy of the following:

a. Materials for Radiology Analysis per Section 15.1.

b. A copy of the CAIA Radiology Submission Form (Form #58117) to the Data Operations Center in Seattle.

14.10 WITHIN 14 DAYS OF PROGRESSION OR RELAPSE:

Submit a copy of the following:

a. Lung Carcinoma First Site(s) of Progression or Relapse Form (Form #9469).

b. Follow-Up Tumor Assessment Form (Form #38305).

c. If the patient is off protocol treatment, also submit the Lung Carcinoma Follow-Up Form (Form #32426).

14.11 ONCE OFF ALL PROTOCOL TREATMENT, EVERY 3 MONTHS FOR 1 YEAR AND THEN EVERY 6 MONTHS FOR A MAXIMUM OF 3 YEARS FROM REGISTRATION:

Submit a copy of the following:

a. Copies of the Follow-Up Tumor Assessment Form (Form #38305) corresponding to every disease assessment performed every 9 weeks until disease progression.

b. Lung Carcinoma Follow-Up Form (Form #32426).

14.12 WITHIN 4 WEEKS OF KNOWLEDGE OF DEATH:

Submit a copy of the following:

a. Lung Carcinoma Follow-Up Form (Form #32426).

b. Notice of Death (Form #49467).

15.0 SPECIAL INSTRUCTIONS

15.1 Radiology Analysis

a. The prestudy chest CT and first two follow-up scans (Week 7 and Week 13, or end of treatment scan if off treatment prior to Week 13) must be performed using the same scanner (or identical brand and model) and techniques to allow for comparison by image analysis. These scans will be submitted for central review and analysis.

b. **Submit the chest CT scans in 16-bit images in DICOM format on CD** with accompanying radiology report and a copy of the CAIA Radiology Submission Form (Form #58117) within 30 days after the Week 13 assessment or within 30 days of removal from protocol treatment to:

Dr. Derick H. M. Lau
Division of Hematology/Oncology
Department of Medicine
UC Davis Cancer Center
4501 X Street, Room 3019
Sacramento, CA 95817-2229
Phone: 916/734-3772

It is strongly recommended that the pre-treatment and post-treatment CT scans be sent together rather than separately.

An additional copy of the CAIA Radiology Submission Form (Form #58117) must be submitted to the Data Operations Center in Seattle each time submissions are made to Dr. Lau.

c. Image analysis of CT scans to assess responses will be performed with a previously published method. *(17)*

d. Centralized testing will be performed only after study funding for these analyses is obtained.

15.2 Specimens for correlative studies and banking (submitted to the SWOG Specimen Repository – Solid Tissue, Myeloma and Lymphoma Division, Lab #201)(optional):

a. With patient's consent, specimens must be collected at the following times and submitted (see Section 9.0):

1. Submit 1 - 2 paraffin-embedded tissue blocks or slides at time of diagnosis (or subsequent, but prior to any previous treatment). If a tissue block is unavailable or unable to be sent, 12 – 15 unstained slides are acceptable as an alternative. Paraffin-embedded tissue blocks or slides will be evaluated for expression of molecular targets relevant to the activity of bevacizumab and OSI-774 (see Section 15.2d). Results will be correlated with patient clinical data.

2. Collect blood and plasma specimens in a 10 cc purple-top EDTA tube at:

   a. Prior to treatment

   b. Cycle 2 prior to treatment

   c. Cycle 3 prior to treatment

   d. It is very important to obtain a blood specimen (approximately 10 ml) from any patient that is being removed from protocol treatment, regardless of the timepoint.

   The tube of blood should be immediately centrifuged at approximately 1,000 rpm for 10 minutes. Buffy coat cells should be removed and placed in labeled cryo tubes. Plasma should be separately removed and placed in two labeled cryo tubes. All tubes are then to be frozen. Store frozen at -70°C until shipped on **dry ice** as detailed on the specimen submission webpage (see Section 15.2b). These specimens will be used for protein and DNA assays. Blood Specimens will be examined for the presence of shed mutant tumor DNA (see Section 15.2d). Results will be correlated with patient clinical data.

b. Specimen collection and submission instructions can be accessed on the SWOG Specimen Submission webpage (http://swog.org/Members/ClinicalTrials/Specimens/STSpecimens.asp), or via the link on the **S0635** protocol abstract page on the SWOG website (www.swog.org).

c. Specimen collection kits are not being provided for this submission; sites will use institutional supplies.

d. **Molecular Markers, Background, Hypotheses, Preliminary Studies and Methods**

   1. **Expression of EGFR and HER-2/neu**

   Hypothesis: EGFR and/or HER-2/neu expression levels and/or activation of signal pathway molecules will correlate with patient responses and/or survival.

This proposed trial provides an opportunity to prospectively re-examine this hypothesis, recently put into question by the poor predictive value of EGFR expression status in ZD1839 (gefitinib) trials. For example, our data from **S0126** showed that EGFR expression levels did not correlate with survival; instead it was phospho-MAPK (p-MAPK) and HER2 that significantly correlated with overall survival following treatment with ZD1839 (gefitinib). *(12)* Determining the status of these receptors will be part of a comprehensive analysis in delineating the contribution of signal transduction pathway elements in bronchioloalveolar carcinoma (BAC) patients treated with OSI-774 (erlotinib) plus bevacizumab.

An objective and reproducible method for staining and scoring of immunohistochemical results developed by Dr. Franklin (University of Colorado) will be used for this trial and this aspect of the correlative science will be conducted under his direct supervision. This is the same method used for analysis of BAC specimens from **S9714** and **S0126**, providing continuity. *(7, 12)* The method consists of microscopically estimating the dominant intensity of staining of tumor cells on a scale of

0 to 4 with 0 being negative (no staining) and 4 intense staining. The intensity of staining is then multiplied by the estimated percentage of tumor cells that stain positively. The labeling scores thus range from 0-400. This grading scheme has the advantage that it does not depend on predetermined cut points, but is an objective estimation of the intensity of staining in the tissue section. Similar grading scales have been used in Leukocyte CD clustering workshops and were recently used to evaluate EGFR expression in the Iressa® Dose Evaluation in Advanced Lung cancer (IDEAL) trials for which Dr. Franklin was one of two reference pathologists. *(13, 15)* We have tested several series of NSCLC tumors using a monoclonal antibody from Zymed anti-EGFR monoclonal antibody 31G7. From our studies, we estimate that approximately 60% of NSCLC patient tumors can be expected to exhibit staining levels of 200 or more (IHC positive). *(24, 25)* In several studies with gefitnib, we have demonstrated a significant correlation between EGFR IHC levels and clinical outcome, both in terms of response and survival. *(24, 25)* Likewise, in the Canadian BR-21 study with erlotinib an association was found between EGFR IHC and clinical outcome. *(26)*

Because of concerns regarding cellular phosphatase activity and tissue fixation, scoring of the phospho-specific antibody stains will be done only at the tissue periphery, where formalin (a known phosphatase inhibitor) is able to penetrate the tissue quickly and render the phosphatases inactive. (NOTE: Detailed methods for these correlative studies can be found below.)

2. **Status of Downstream Signal Transduction Pathway Molecules**

Hypothesis: Activated downstream components of the signal transduction cascade initiated by HER family receptor dimerization will allow identification of patient subsets responsive to treatment with OSI-774 (erlotinib).

Pertinent here will be examination of activated downstream molecules including p-MAPK (aka, ERK1/2), indicating activation of the proliferation associated *RAS* pathway, and p-AKT, indicating activated PI3-K/AKT survival associated pathway. Similarly, low or absent basal levels of the cyclin-dependent kinase inhibitor p27 indicate activation of the EGFR pathways.

As noted above, BAC patients with p-MAPK had significantly worse outcome following ZD1839 (gefitinib) therapy. *(7, 12)* However, the underlying mechanism for this observation remains unclear, particularly in other tumor types. Because OSI-774 (erlotinib) has activity against EGFR, it is important to determine the status of multiple HER1/2-RAS-MAPK-AKT pathway members in order to determine the relative contribution of each to clinical outcome.

HER family signals induce cell proliferation through the RAS-MAPK (ERK) pathway. These downstream markers can potentially serve as predictors for patient outcome following treatment with HER pathway inhibitors. As mentioned above, p-MAPKn and pMAPKc significantly correlated with overall survival following treatment with ZD1839 (gefitinib) in BAC. Furthermore, inhibition of the EGFR and HER-2 by antibodies and small molecules, such as OSI-774 (erlotinib), has been shown to induce G1 phase cell-cycle arrest. Inhibition of EGFR by OSI-774 (erlotinib) is not only associated with cell-cycle arrest, but also the

induction of apoptosis. The particular mechanism and pathway(s) utilized are not established, but there is evidence implicating activation of the PI3K-AKT pathway and RhoB in reduced apoptosis associated with tumors overexpressing tyrosine kinase oncogenes such as EGFR. One role ascribed to RhoB is in the increased ubiquitin-mediated degradation of the p27. In in vitro models, increased levels of p27 are associated with both cell-cycle arrest and induction of apoptosis. Loss of p27 has been shown to be a negative prognostic factor for lung and other tumor types, with loss of the protein found in approximately 70%. Basal levels of p27, p-MAPK, and p-AKT will be assessed by immunohistochemistry (IHC) in pre-treatment tumor tissues or tumor aspirates.

3. **EGFR Gene Mutations**

Hypothesis: Mutations in the ATP-binding site/kinase domain of EGFR will correlate with response in patients treated with the small molecule EGFR inhibitor OSI-774 (erlotinib). Further, we expect that this correlation will extend to overall patient survival and/or progression-free survival.

One of the most recent exciting developments in cancer research is the finding that mutations in the EGFR gene are associated with response in NSCLC to a molecularly targeted small molecule inhibitor of EGFR. Two groups have simultaneously reported similar results that responders to ZD1839 (gefitinib) have either missense point mutations or in-frame deletions in their tumors. *(14, 16)* The relevant mutations are now known to cluster within exons 19 and 21, and when one of both types of mutations were tested in vitro, they conferred gain-of-function or oncogenic activation to EGFR. *(14)*

Recently, analogous mutations in HER2 have been identified in lung cancers. *(18, 19)* In the latter study, HER2 mutations were found in 1.6% of NSCLC but were absent in other types of cancers. All HER2 mutations were in-frame insertions in exon 20 and are in the identical corresponding region as for EGFR insertions (exon 19). HER2 mutations were found to be significantly more frequent in never smokers (3.2%, 8 of 248; P=0.02) and adenocarcinoma histology (2.8%, 11 of 394; P=0.003). We will conduct an exploratory study of HER2 mutations in BAC from the specimens on this trial.

Procedures to isolate tumor DNA and analyze it for mutations by PCR and sequencing have been established for many years in the laboratory of Dr. Gumerlock at UC Davis. *(21)* The specific primer sets needed to amplify EGFR exons 19 and 21, and the conditions for amplification will be as described in the recent publications. These products will be directly sequenced using an automated DNA sequencing approach. Results will be correlated with patient clinical data. (NOTE: Methods are summarized below.)

Recently, acquired resistance to ZD1839 (gefitinib) has been shown to be associated with an additional mutation in EGFR exon 20. *(20)* Our group has recently identified a BAC patient from the **S0126** trial that had this mutation de novo, prior to exposure to ZD1839 (gefitinib). *(21)* Thus, it appears important to also examine pre-treatment specimens for this potential resistance factor to EGFR small molecule inhibitors.

4. **EGFR Gene Copy Number and/or Amplification**

Hypothesis: That copy number and/or amplification of the EGFR gene will correlate with patients outcomes to OSI-774 (erlotinib) treatment.

Hirsch et al from our group, have evaluated gene copy number and protein status of EGFR in micro-arrayed tumors from 183 NSCLC patients, including squamous cell carcinoma (89 patients). *(22)* Protein expression was assessed by immunohistochemistry on a scale from 0 to 400 (percentage of positive cells x staining intensity). Gene and chromosome 7 copy numbers were identified by fluorescent in situ hybridization (FISH). Table 1 outlines the definitions used to interpret FISH results.

Table 1: FISH definitions

Group Definition:

FISH Negative
No or low level of genomic gain for the EGFR gene (≤ 4 copies of the gene in > 40% of cells)

FISH Positive
High level of polysomy (≥ 4 copies of the gene in ≥ 40% of cells) or gene amplification, defined by presence of tight gene clusters, a ratio gene/chromosome per cell ≥ 2, or ≥ 15 copies of the genes per cell in ≥ 10% of analyzed cells.

Patients with high polysomy and gene amplification were deemed to be FISH-positive: EGFR protein over-expression was observed in 62% of the NSCLC (25% scored 201 to 300; 37% scored 301 to 400), more frequently in squamous histology than non-squamous (82% *v* 44%; $P < 0.001$), and in 80% of the bronchioloalveolar carcinomas. The prevalent FISH patterns were balanced disomy (40%) and trisomy (38%) for *EGFR* gene and chromosome 7 (40%), whereas balanced polysomy was seen in 13% and gene amplification was seen in 9% of the patients. Gene copy number correlated with protein expression ($r = 0.4$; $P < 0.001$).

Building on these results, these same investigators then proceeded to compare the relationship between EGFR gene copy number, EGFR protein expression, EGFR mutations, and Akt activation status as predictive markers for ZD1839 (gefitinib) therapy in advanced NSCLC. *(24)* Tumors from 102 NSCLC patients (from an Italian study) treated daily with 250 mg of ZD1839 (gefitinib) were evaluated for EGFR status by FISH, DNA sequencing, and IHC and for Akt activation status (phospho-Akt [P-Akt]) by IHC. Amplification or high polysomy of the EGFR gene (seen in 33 of 102 patients) and high protein expression (seen in 58 of 98 patients) were statistically significantly associated with better response (36% versus 3%, mean difference = 34%, 95% CI = 16.6 to 50.3; P< 0.001), disease control rate (67% versus 26%, mean difference = 40.6%, 95% CI = 21.5 to 59.7; P< 0.001), time to progression (9.0 versus 2.5 months, mean difference = 6.5 months, 95% CI = 2.8 to 10.3; P< 0.001), and survival (18.7 versus 7.0 months, mean difference = 11.7 months, 95% CI = 2.1 to 21.4; P = 0.03). EGFR mutations (seen in 15 of 89 patients) were also statistically significantly related to response and time to progression, but the association with

survival was not statistically significant, and 40% of the patients with mutation had progressive disease. In multivariable analysis, only high EGFR gene copy number remained statistically significantly associated with better survival (hazard ratio = 0.44, 95% CI = 0.23 to 0.82). Independent of EGFR assessment method, EGFR+/P-Akt+ patients had a statistically significantly better outcome than EGFR-, P-Akt-, or EGFR+/P-Akt- patients. These investigators concluded that high EGFR gene copy number identified by FISH may be an effective molecular predictor for efficacy of an oral EGFR tyrosine kinase inhibitor in advanced NSCLC. Hirsch and colleagues have also reported from the prospective placebo-controlled ISEL trial that increased EGFR gene copy number detected by FISH was a strong predictor for clinical outcome on gefitinib therapy, with a hazard ratio (HR) for survival of 0.61 in the FISH-positive group, compared with no reduction in HR in the FISH-negative group. *(9, 23)*

Similar results were observed when tumor tissue from 81 patients with advanced stage BAC treated with ZD1839 (gefitinib) 500 mg/day in the Southwest Oncology Group protocol **S0126** were analyzed by FISH and classified in two main categories: *FISH positive* (high polysomy/gene amplification) and *FISH negative* (disomy, trisomy and low polysomy). *(25)* Among 19 FISH positive patients, 12 (63%) had disease control (response or stable disease) versus 14/36 pts (39%) in the FISH negative group (exact p-value=0.099). Eighty-one patients were evaluable for survival, and the median survival time for the FISH negative patients was 8 (95%CI 6-15) months. While the median survival for the FISH positive pts has not yet been reached, it is approaching 18 months, with a hazard ratio of 2.02 (95%CI 1.03- 3.99; p = 0.042). The median progression-free survival time for FISH negative patients was 4 (95%CI 2- 5) months versus 9 (3-20) months for FISH positive patients with a hazard ratio of 1.67 (95%CI 0.96- 2.91; p=0.072). EGFR copy number by FISH remained a significant predictive factor after accounting for smoking status, sex, histology and performance status. This study again demonstrated a strong association between increased EGFR gene copy number detected by FISH and sensitivity for ZD1839 (gefitinib) treatment in patients with advanced NSCLC. The results suggested that FISH methodology can be used to select patients for treatment with EGFR tyrosine kinase inhibitors.

5. **Polymorphisms of the EGFR Gene**

Hypothesis: Polymorphisms within the EGFR gene will correlate with response and/or patient outcome to OSI-774 (erlotinib).

We hypothesize that either or both of two specific polymorphisms within the EGFR gene will correlate with response and/or patient outcome. Analyses will be done in tumor tissue initially, with analyses in a subset of patient PBMCs if interesting data on specific polymorphisms are found in the tumor tissues. Blood will be collected from all consenting patients for the analysis of genomic DNA in peripheral blood mononuclear cells (PBMCs) for the EGFR polymorphisms that have been shown to correlate with prognosis or drug activity.

EGFR polymorphisms of potential interest for activity of EGFR inhibitors will be evaluated as follows, with results compared to the predecessor study **S0126**. One known EGFR polymorphism, positioned within exon sequences at codon 497, was shown to be easily detected using PCR-

SSCP. *(27)* This G to A transition results in a substitution of a lysine for an arginine (HER1-497K) and appears to be fairly common in the human population. By comparison with the wild-type receptor, the HER1-497K exhibited a reduced induction of cell growth and downstream gene activation when stimulated by EGF or TGF-alpha. *(28)* Another polymorphism is an A to T change at position 2073 that is silent and does not change the encoded amino acid, but does generate a unique *BsrI* restriction site which provides an assay for its rapid detection. *(29, 30)* Both the T and A alleles appear to be relatively common in the population, although the exact frequencies have not been established. Both alleles have also been found in normal and tumor tissues, although there may be an increased association of the T allele with malignant oral keratinocytes. No specific biological differences have yet been found for these alleles.

Further, several new polymorphisms were recently reported in or near the ATP binding site by the two groups who were sequencing for mutations. *(14, 16)* Because these data will also be obtained during the sequencing here, any associations with patient clinical data will be evaluated.

6. Plasma Markers of Angiogenesis

Hypotheses: The distribution of pro-angiogenic factors in patient plasma will be predictive of patient outcome in response to bevacizumab-containing regimens. Specifically, patients with higher levels of tumor or plasma PDGF and lower levels of sICAM and OPN will have comparatively superior outcomes.

We will focus our investigations on plasma levels of three markers that we hypothesize will correlate with patient outcome: PDGF, sICAM and OPN. Platelet-derived growth factor (PDGF) and its receptors (PDGFR-alpha and beta) are variably expressed in NSCLCs. In a study by Shikada *et al*, PDGF-AA correlated with VEGF expression and was a negative prognostic factor (Shikada CR 65:7241, 2005). Further, their cell line modeling indicated that PDGF, a critical angiogenic switch, regulated expression of VEGF. PDGF, while a negative prognostic indicator, may be a positive predictive factor for bevacizumab activity. Although VEGF is the sole target of bevacizumab, PDGF may be a superior marker as it may better reflect tumor-mediated angiogenesis without the inter-patient variability that VEGF is subject to. Furthermore, post-treatment changes in PDGF levels may serve as an early indicator of therapeutic activity; whereas post-treatment VEGF levels may be obfuscated by bevacizumab binding. Using ELISA or Luminex, we will measure the major isoforms of PDGF (AA, AB and BB). Pre-treatment plasma levels of VEGF will also be measured, and we hypothesize that PDGF levels will roughly correlate with VEGF levels, such that patients high in PDGF will also show elevated VEGF (although some patients low in PDGF may still have elevated plasma VEGF). Tumor levels of PDGF and VEGF will be assessed by IHC in archival tumor material.

We hypothesize that patients with lower baseline levels of soluble intercellular adhesion molecule-1 (sICAM) will have superior outcomes. Serum levels of sICAM are elevated in patients with NSCLC compared with healthy volunteers, and further correlate with the presence of metastatic disease (Grothrey et al, Br. J Cancer, 77:801,

1998). Dowlati *et al.*, reported at the 2006 ASCO Annual Meeting the correlative biomarkers assessed for the E4599 randomized phase II/III trial of carboplatin and paclitaxel with or without bevacizumab in patients with advanced NSCLC. From these studies, sICAM emerged as a strong prognostic marker of patient outcome. When stratified at the median, patients with lower levels of sICAM had significantly improved response rates and overall survival, regardless of treatment arm. Further investigation revealed a potential correlation between lower baseline sICAM and improved progression-free survival due to the inclusion of bevacizumab. The currently proposed trial provides an opportunity to validate these findings. In serial blood draws, sICAM will be measured by ELISA in all patients, with results correlated to patient response, overall survival and progression-free survival.

Tumor expression of osteopontin (OPN) was found to be associated with more aggressive phenotypes in advanced NSCLC patients (Hu et al CCR 11:4646, 2005). We have found that OPN plasma levels showed substantial intra-patient variability and were highly prognostic for NSCLC patient response to therapy and overall survival (Mack ASCO 2006, manuscript in preparation). However, the role of this factor has not been defined in the context of an anti-angiogenic therapy, and this study affords that opportunity. OPN, a highly pleiotropic factor involved in metastasis and tissue remodeling, is produced under hypoxic conditions. We hypothesize that patients with elevated OPN will be less responsive to bevacizumab as OPN may enhance tumor cell survival in low oxygen conditions and serve as an alternative to VEGF as a pro-angiogenic stimulus, mediating against the effects of bevacizumab.

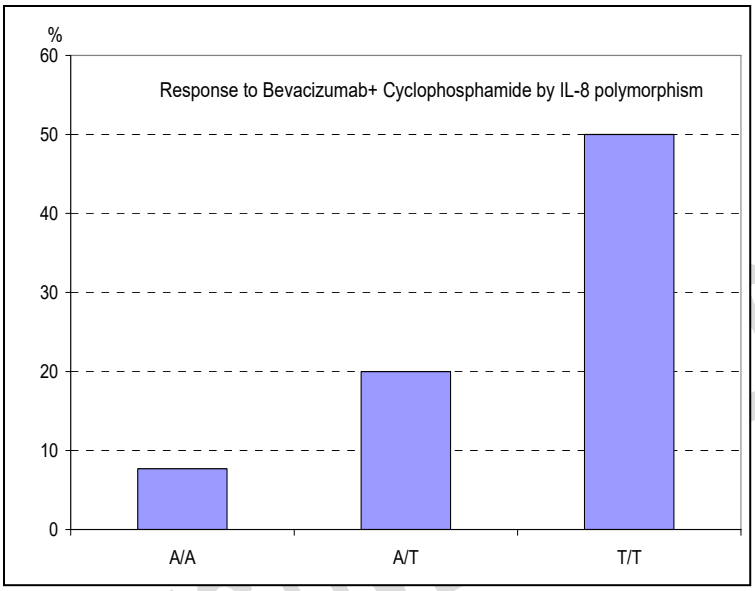
Exploratory analysis of angiogenesis-associated plasma proteins. As no biomarkers have been fully established to date as predictive for patient response and survival following treatment with anti-angiogenic agents, the work proposed in this section is by its nature exploratory. Furthermore, it is unlikely that any single marker will be completely informative in isolation. At UC Davis we have established a panel of angiogenesis-related factors, measurable in patient plasma, which can be assessed simultaneously by multiplex analysis (Luminex). This exploratory work is necessitated by the need to identify marker profiles predictive of response to anti-angiogenic agents. A blinded comparison of VEGF plasma levels as measured by conventional ELISA vs Luminex showed a highly significant correlation between these assays (r^2=0.9359; p <0.0001), providing validation for this high-throughput technique.

7. Angiogenesis-related polymorphisms

Hypothesis: Polymorphisms in IL-8 (locus -251) and VEGF (locus 936) will be predictive of response to therapy.

Work conducted in the laboratory of Dr. Heinz-Josef Lenz (University of Southern California) has identified associations between germline polymorphisms in the IL-8 and VEGF genes with response to bevacizumab plus cyclophosphamide in patients with recurrent or metastatic ovarian cancer (California Cancer Consortium trial phase II-45, manuscript in preparation). Specifically, analysis of -251 T→A polymorphisms in IL-8 showed that patients homozygous T/T had a favorable response rate compared to heterozygous patients or those homozygous A/A (see adjacent figure; Fisher's exact test: P=0.047; HJ

Lenz, personal communication). Furthermore, patients with any T allele at the 936 locus of the VEGF gene had a median PFS of 17 months compared to 6.4 months for patients with the C/C genotype (log-rank test: P=0.041). Patients with the C/C genotype comprised 73% of the population. We will determine whether these markers retain their predictive value in lung cancer patients enrolled on this trial. PBMCs will be collected from each patient and snap frozen for DNA extraction and polymorphism identification in collaboration with Dr. Lenz. Circulating plasma levels of the pro-angiogenic cytokine IL-8 will also be measured and correlated with patient outcome, genotype and other plasma markers.



8. **K-RAS Mutations and Resistance to EGFR Inhibition**

Hypothesis: Tumors harboring K-RAS mutations will be less sensitive to treatment with OSI-774 (erlotinib) than those with wild-type K-RAS.

One potential cause for activation of the MAPK pathway, high levels of p-MAPK, and failure of response to EGFR inhibitors is the presence of a K-RAS oncogene. The RAS family of G proteins function as signal transduction switches located downstream of receptor tyrosine kinases, but upstream of MAPK. Mutations in RAS at codon 12 result in constitutive activation of this protein resulting in sustained signaling, regardless of the status of upstream receptors. Our examination of the **S0126** specimens has demonstrated this K-RAS mutation in 30% of BAC tumors, more frequent association with smoking, and that the mutation is a potential resistance marker to ZD1839 (gefitinib), as only 1/19 patients (6%) with a K-RAS mutation responded. *(31)* Thus, we hypothesize that tumors harboring K-RAS mutations will be less sensitive to treatment with OSI-774 (erlotinib). We have used highly sensitive PCR assays to detect K-RAS 12th codon mutations, and will use those here to examine pre-treatment, paraffin-embedded tumor tissues, and in exploratory studies, DNA shed in patient plasma. *(32)* Results will be correlated with patient outcomes.

9. **Proteomics and Other Pharmacogenomics**

With the patient's consent, blood specimens will be banked for future proteomic and pharmacogenomic analyses.

10. **Molecular Correlative Statistical Considerations**

Due to the limited sample size provided in this setting, the correlative studies will help generate hypotheses for future studies.

16.0 ETHICAL AND REGULATORY CONSIDERATIONS

The following must be observed to comply with Food and Drug Administration regulations for the conduct and monitoring of clinical investigations; they also represent sound research practice:

Informed Consent

The principles of informed consent are described by Federal Regulatory Guidelines (Federal Register Vol. 46, No. 17, January 27, 1981, part 50) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46). They must be followed to comply with FDA regulations for the conduct and monitoring of clinical investigations.

Institutional Review

This study must be approved by an appropriate institutional review committee as defined by Federal Regulatory Guidelines (Ref. Federal Register Vol. 46, No. 17, January 27, 1981, part 56) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46).

Drug Accountability

An investigator is required to maintain adequate records of the disposition of investigational drugs according to procedures and requirements governing the use of investigational new drugs as described in the Code of Federal Regulations 21 CFR 312.

Monitoring

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31.

16.1 Adverse Event Reporting Requirements

a. Purpose

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse

(Directions for routine reporting are provided in Section 14.0.) Additionally, certain adverse events must be reported in an expedited manner to allow for more timely monitoring of patient safety and care. The following guidelines prescribe expedited adverse event reporting for this protocol. See also Appendix 19.1 for general and background information about expedited reporting.

b. Reporting methods

This study requires that expedited adverse event reporting use the NCI's Adverse Event Expedited Reporting System (AdEERS). The NCI's guidelines for AdEERS can be found at http://ctep.cancer.gov. An AdEERS report must be submitted to the SWOG Operations Office electronically via the AdEERS Web-based application located at http://ctep.cancer.gov.

c. When to report an event in an expedited manner

Some adverse events require 24-hour notification (refer to Table 16.1) via AdEERS. When Internet connectivity is disrupted, a 24-hour notification is to be made to the Operations Office by telephone at 210/614-8808. Once Internet connectivity is restored, a 24-hour notification that was phoned in must be entered electronically into AdEERS by the original submitter at the site.

When the adverse event requires expedited reporting, submit the report within the number of calendar days of learning of the event specified in Table 16.1.

d. Other recipients of adverse event reports

The Operations Office will forward reports and documentation to the appropriate regulatory agencies and drug companies as required.

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

e. **Expedited reporting for investigational agents**

Expedited reporting is required if the patient has received at least one dose of the investigational agent(s) as part of the trial. Reporting requirements are provided in Table 16.1. The investigational agents used in this study are bevacizumab and OSI-774. If there is any question about the reportability of an adverse event or if on-line AdEERS cannot be used, please telephone or email the SAE Specialist at the Operations Office, 210/614-8808 or adr@swog.org, before preparing the report.

Table 16.1:

Phase II and III Trials Utilizing an Agent under a CTEP IND or Non-CTEP IND: AdEERS Expedited Reporting Requirements for Adverse Events that Occur within 30 Days[1] of the Last Dose of the Investigational Agents Bevacizumab and/or OSI-774 in this Study

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

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

AdEERS 24-hour notification (**via AdEERS for CTEP IND agents; via email to *adr@swog.org* for agents in non-CTEP IND studies**) followed by complete report within 5 calendar days for:

- Grade 4 and Grade 5 unexpected events

AdEERS 10 calendar day report:

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

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

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

- Expedited AE reporting timelines defined:
  - "24 hours; 5 calendar days" – The investigator must initially report the AE via AdEERS within 24 hours of learning of the event followed by a complete AdEERS report within 5 calendar days of the initial 24-hour report.
  - "10 calendar days" - A complete AdEERS report on the AE must be submitted within 10 calendar days of the investigator learning of the event.

- Any medical event equivalent to CTCAE Grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.

- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via AdEERS if the event occurs following treatment with an agent under a CTEP IND.

- Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

f. **Additional Instructions or Exceptions to AdEERS Expedited Reporting Requirements for Phase II and III Trials Utilizing an Agent under a CTEP-IND or Non-CTEP IND:**

1) **Group-specific instructions.**

Within 10 calendar days, submit the following to the Operations Office (mail address below, FAX: 210/614-0006):

- Printed copy of the AdEERS report
- Copies of clinical source documentation of the event
- Copy of IRB notification of the event
- If applicable, copies of Off Treatment Notice (Form #28829) and Notice of Death (Form #49467).

g. Reporting secondary AML/ALL/MDS

1. All cases of acute myeloid leukemia (AML), acute lymphocytic leukemia (ALL), and myelodysplastic syndrome (MDS) that occur in patients on NCI-sponsored trials following chemotherapy for cancer must be reported in AdEERS.

i. In protocols using CTCAE Version 4.0 for SAE reporting, three options are available to describe treatment-related events:

- Leukemia secondary to oncology chemotherapy
- Myelodysplastic syndrome. NOTE: The only grading option for "Myelodysplastic syndrome" is Grade 4, life-threatening. If reporting MDS that is other than Grade 4, use “Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other, (specify,__)” and insert MDS as the specify term.
- Treatment related secondary malignancy

ii. In protocols using CTCAE Version 3.0 for SAE reporting, the event(s) can be reported as “Secondary malignancy-Other (specify, ___)”. Report MDS as “Myelodysplasia,” in the BLOOD/BONE MARROW category.

iii. Secondary malignancies <u>other than</u> AML/ALL/MDS that are related to protocol treatment must also be reported in AdEERS.

iv. <u>Non</u>-treatment related cases of AML/ALL/MDS must be reported as follows:

In protocols using CTCAE Version 4.0 for SAE reporting, report as “Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other, specify”

In protocols using CTCAE Version 3.0 for SAE reporting, report MDS as “Myelodysplasia” and Leukemias as “Blood/Bone Marrow - Other (Specify, __)”

For more information see:
<u>http://ctep.cancer.gov/protocolDevelopment/default.htm#adverse_events_adeers</u>

2. The following supporting documentation must also be submitted within 30 days:

   - a copy of the pathology report confirming the AML/ALL /MDS diagnosis
   - (if available) a copy of the cytogenetics report

   Submit the Report and documentation to:

   SWOG
   ATTN: SAE Program
   4201 Medical Drive, Suite 250
   San Antonio, TX 78229

   NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the report must be submitted for the most recent trial.

17.0 BIBLIOGRAPHY

1. Detterbeck FC, Rivera MP, Socinski MS, et al (Eds). Diagnosis and treatment of lung cancer: an evidence-based guide for the practicing clinician, pp. 394-407, 2000.

2. Donovan WD, Yankelevitz DF, Henechke CI, et al. Endobronchial spread of bronchioloalveolar carcinoma. Chest 104(3):951-3, 1993.

3. Hidaka N, Hidaka Y, Tajima Y, et al. Bronchioloalveolar carcinoma presenting aerogenous metastasis to the upper airway. Eur J Cancer 32A(7):1261-2, 1996.

4. West H, Franklin WA, McCoy J, Gumerlock PH, Vance R, Lau DHM, Chansky K, Crowley JJ, Gandara DR. Gefitinib in bronchioloalveolar carcinoma (BAC): Southwest Oncology Group study S0126. Clinical Oncol 24:1807-1813, 2006.

5. Kris MG, Sandler A, Miller V, et al. Cigarette smoking history predicts sensitivity to erlotinib: Results of a phase II trial in patients with bronchioloalveolar carcinoma (BAC). J of Clinical Oncology ASCO Annual Meeting Proceedings (Post-Meeting Edition) Vol. 22, No 14S (July 15 Supplement) A#7062, 2004.

6. West HL, Crowley JJ, Vance RB, et al. Advanced bronchioloalveolar carcinoma: A phase II trial of paclitaxel by 96-hour infusion (SWOG 9714). Annals of Oncology 16:1076-1080, 2005.

7. Franklin WA, Gumerlock PH, Crowley JJ, et al. EGFR, HER2 and ERB-B Pathway Activation in Bronchioloalveolar Carcinoma (BAC): Analysis of SWOG 9417 and Lung SPORE tissue samples. Proceedings of the American Society of Clinical Oncology 22:620 (Abstract #2493), 2003.

8. Herbst RS, Sandler AB. Non-small cell lung cancer and antiangiogenic therapy: what can be expected of bevacizumab? Oncologist 9 (suppl 1):19-26, 2004.

9. Johnson DH, Fehrenbacher L, Novotny WF, et al. Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small-cell lung cancer. J of Clin Onc Jun 1;22(11):2184-91, 2004.

10. Sandler AB, Gray R, Brahmer J, et al. Randomized phase II/III trial of paclitaxel (P) plus carboplatin (C) with or without bevacizumab (NSC#704865) in patients with advanced non-squamous non-small cell lung cancer (NSCLC): An Eastern Cooperative Oncology Group (ECOG) Trial – E4599. Journal of Clinical Oncology ASCO Annual Meeting Proceedings Vol. 23, No 16S (June 1 Supplement) A# LBA4, 2005.

11. Herbst RS, Johnson DH, Mininberg E, et al. Phase I/II trial evaluating the anti-VEGF MAb bevacizumab in combination with erlotinib, a HER1/EGFR-TK inhibitor, for patients with recurrent non-small cell lung cancer. J of Clin Onc Apr 10: 23 (11), 2544-2555, 2005.

12. Gandara DR, West H, Chansky K, et al. Bronchioloalveolar carcinoma: A model for investigating the biology of EGFR inhibition. Clinical Canc Res 10:4205s-4209s, 2004.

13. Gilks WR, Oldfield L, Rutherford A. Statistical Analysis. In: Knapp W, Dorken B, Gilks WR, Rieber EP, Schmidt RE, Stein H, von dem Borne AEG Kr. (eds.), Leucocyte Typing IV, pp. 6-12. Oxford: Oxford University Press, 1989.

14. Lynch TJ, Bell DW, Sordella R, et al. Activating Mutations in the Epidermal Growth Factor Receptor Underlying Responsiveness of Non-Small-Cell Lung Cancer to Gefitinib. NEJM 350:online Apr 29, 2004.

15. Bailey R, Kris M, Wolff M, et al Gefitinib monotherapy for pretreated advanced non-small cell lung cancer in IDEAL 1 and 2: tumor response is not clinically relevantly predictable from tumor EGFR membrane staining alone. Lung Cancer 41:571, 2003 (abstract 0-242).

16. Paez JG, Janne PA, Lee JC, et al. EGFR Mutations in Lung Cancer: Correlation with Clinical Response to Gefitinib Therapy. Science (Express online) Apr 29, 2004.

17. Lau D, Seibert A, Gandara D, Laptalo L, Geraghty E, Coulon C. Computer-assisted image analysis of bronchioalveolar carcinoma. Clin Lung Cancer 6:281-286, 2005.

18 Stephens P, Hunter C, Bignell G, et al. Lung cancer: intragenic ERBB2 kinase mutations in tumours. Nature Sep 30;431(7008):525-6, 2004.

19. Shigematsu H, Takahashi T, Nomura M, et al. Somatic mutations of the HER2 kinase domain in lung adenocarcinomas. Cancer Res Mar 1;65(5):1642-6, 2005.

20. Pao W, Miller VA, Politi KA, et al. Acquired resistance of lung adenocarcinomas to gefitinib or erlotinib is associated with a second mutation in the EGFR kinase domain. PLoS Med. Mar;2(3):e73. Epub 2005 Feb 22.

21. Gumerlock PH. Personal communication.

22. Hirsch FR, Varella-Garcia M, Bunn P, et al. Epidermal Growth Factor Receptor in Non–Small-Cell Lung Carcinomas: Correlation Between Gene Copy Number and Protein Expression and Impact on Prognosis. J of Clin Onc Vol 21, Issue 20: 3798-3807, 2003.

23. Hirsch FR, Varella-Garcia M, McCoy J, et al. Molecular analysis of EGFR gene copy number, EGFR expressing and AK+ activation status in advanced non-small cell lung cancer treated with gefitinib or placebo (ISEL trial). J of Clin Onc: in press.

24. Capuzzo F, Hirsch FR, Rossi E, et al. Epidermal growth factor receptor gene and protein and gefitinib sensitivity in non-small-cell lung cancer. JNCI 4;97(9):643-55, 2005.

25. Hirsch FR, Varella-Garcia M, McCoy J, West H, Xavier AC, Gumerlock P, Bunn PA, Franklin WA, Crowley JJ, Gandara DR. Increased EGFR gene copy number detected by FISH is associated with increased sensitivity to gefitinib in patients with bronchioloalveolar cardinoma (BAC) (S0126). J Clin Oncol 23:6838-6845, 2005.

26. Tsao MS, Sakurada A, Cutz JC, et al. Erlotimib in lung cancer-molecular and clinical predictors of outcome. NEJM 23:6838-45, 2005.

27. Lopez ME, Kobrin MS, Moriai T, et al. Single-strand conformation polymorphism analysis of the epidermal growth factor receptor at codon 497. Pancreas 12:216-220, 1996.

28. Moriai T, Kobrin MS, Hope C, Speck L, Korc M. A variant epidermal growth factor receptor exhibits altered type alpha transforming growth factor binding and transmembrane signaling. Proceedings of the National Academy of Sciences USA 91:10217-10221, 1994.

29. Shintani S, Matsuo K, Crohin CC, et al. Intragenic mutation analysis of the human epidermal growth factor receptor (EGFR) gene in malignant human oral keratinocytes. Cancer Research 59:4142-4147, 1999.

30. Reiter JL, Eley G, James CD, et al. Correspondence re: Shintani et al. Intragenic mutation analysis of the human epidermal growth factor receptor (EGFR) gene in malignant human oral keratinocytes. (Cancer Res., 59:4142-4147, 1999.) Cancer Research 60:766-767, 2000.

31. Gumerlock PH, Holland WS, Chen HL, et al. Mutational analysis of K-RAS and EGFR implicates K-RAS as a resistance marker in the Southwest Oncology Group (SWOG) trial S0126 of bronchioalveolar carcinoma (BAC) patients treated with gefitinib. Proceedings of the American Society of Clinical Oncology 24: Abstract #, 2005.

32. Levi S, Urbano-Ispizua A, Gill R, et al. Multiple K-ras codon 12 mutations in cholangiocarcinomas demonstrated with a sensitive polymerase chain reaction technique. Cancer Research 51:3497-502, 1991.

18.0 MASTER FORMS SET

This section includes copies of all data forms that must be completed for this study. These include:

18.1 Model Informed Consent Form. This is preceded by "Notes for Local Institution Consent Form Authors" and "Notes for Local Investigators." The study - as well as the local consent form meeting the guidelines noted in these documents - must be reviewed and approved by the Institutional Review Board prior to registration and treatment of patients on this study.

18.2 **S0635** Registration Form (Form #47242) (10/1/07) and Coding Guidelines.

18.3 **S0635** Prestudy Form (Form #11652) (3/1/09)

18.4 Baseline Tumor Assessment Form (Form #848). (9/1/03)

18.5 **0635** Treatment Form (Form # 37277) (10/1/07)

18.6 **0635** Adverse Event Form (Form #34254). (7/15/07)

18.7 Follow-Up Tumor Assessment Form (Form #38305). (9/1/03)

18.8 Off Treatment Notice (Form #28829). (6/15/06)

18.9 CAIA Radiology Submission Form (Form #58117) (7/15/07)

18.10 Lung Carcinoma First Site(s) of Progression or Relapse Form (Form #9469). (3/15/01)

18.11 Lung Carcinoma Follow Up Form (Form #32426). (9/1/02)

18.12 Notice of Death (Form #49467). (9/1/03)

Informed Consent Model for **S0635**

*NOTES FOR LOCAL INSTITUTION INFORMED CONSENT AUTHORS:

This model informed consent form has been reviewed by the DCT/NCI and is the official consent document for this study. Local IRB changes to this document are allowed. (Institutions should attempt to use sections of this document that are in bold type in their entirety.) Editorial changes to these sections may be made as long as they do not change information or intent. If the institutional IRB insists on making deletions or more substantive modifications to the risks or alternatives sections, they may be justified in writing by the investigator and approved by the IRB. Under these circumstances, the revised language, justification and a copy of the IRB minutes must be forwarded to the Southwest Oncology Group Operations Office for approval before a patient may be registered to this study.

Please particularly note that the questions related to banking of specimens for future study are in bolded type and may not be changed in any way without prior approval from the Southwest Oncology Group Operations Office.

Readability Statistics:	
Flesch Reading Ease	61.2 (targeted above 55)
Flesch-Kincaid Grade Level	8.6 (targeted below 8.5)

- Instructions and examples for informed consent authors are in *[italics]*.
- A blank line, _____, indicates that the local investigator should provide the appropriate information before the document is reviewed with the prospective research participant.
- The term "study doctor" has been used throughout the model because the local investigator for a cancer treatment trial is a physician. If this model is used for a trial in which the local investigator is not a physician, another appropriate term should be used instead of "study doctor".
- The dates of protocol updates in the header and in the text of the consent is for reference to this model only and should not be included in the informed consent form given to the prospective research participant.
- The local informed consent must state which parties may inspect the research records. This includes the NCI, the drug manufacturer for investigational studies, any companies or grantors that are providing study support (these will be listed in the protocol's model informed consent form) and the Southwest Oncology Group.

  The "Southwest Oncology Group" must be listed as one of the parties that may inspect the research records in all protocol consent forms for which patient registration is being credited to the Southwest Oncology Group. This includes consent forms for studies where all patients are registered directly through the Southwest Oncology Group Data Operations Office, all intergroup studies for which the registration is being credited to the Southwest Oncology Group (whether the registration is through the SWOG Data Operations Office or directly through

the other group), as well as consent forms for studies where patients are registered via CTSU and the registration is credited to the Southwest Oncology Group.

- When changes to the protocol require revision of the informed consent document, the IRB should have a system that identifies the revised consent document, in order to preclude continued use of the older version and to identify file copies. An appropriate method to identify the current version of the consent is for the IRB to stamp the final copy of the consent document with the approval date. The stamped consent document is then photocopied for use. Other systems of identifying the current version of the consent such as adding a version or approval date are allowed as long as it is possible to determine during an audit that the patient signed the most current version of the consent form.

*NOTES FOR LOCAL INVESTIGATORS:

- The goal of the informed consent process is to provide people with sufficient information for making informed choices. The informed consent form provides a summary of the clinical study and the individual's rights as a research participant. It serves as a starting point for the necessary exchange of information between the investigator and potential research participant. This model for the informed consent form is only one part of the larger process of informed consent. For more information about informed consent, review the "Recommendations for the Development of Informed Consent Documents for Cancer Clinical Trials" prepared by the Comprehensive Working Group on Informed Consent in Cancer Clinical Trials for the National Cancer Institute. The Web site address for this document is http://cancer.gov/clinicaltrials/understanding/simplification-of-informed-consent-docs/
- A blank line, _____, indicates that the local investigator should provide the appropriate information before the document is reviewed with the prospective research participant.
- Suggestion for Local Investigators: An NCI pamphlet explaining clinical trials is available for your patients. The pamphlet is entitled: "If You Have Cancer…What You Should Know about Clinical Trials". This pamphlet may be ordered on the NCI Web site at *http://cissecure.nci.nih.gov/ncipubs/details.asp?pid=1035* or call 1-800-4- CANCER (1-800-422-6237) to request a free copy.
- Optional feature for Local Investigators: Reference and attach drug sheets, pharmaceutical information for the public, or other material on risks. Check with your local IRB regarding review of additional materials.

*These notes for authors and investigators are instructional and should not be included in the informed consent form given to the prospective research participant.

S0635, "A PHASE II TRIAL OF THE COMBINATION OF OSI-774 (ERLOTINIB; NSC-718781) AND BEVACIZUMAB (RHUMAB VEGF; NSC-704865) IN STAGE IIIB AND IV BRONCHIOLOALVEOLAR CARCINOMA (BAC) AND ADENOCARCINOMA WITH BAC FEATURES (ADENOBAC)"

This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.

You are being asked to take part in this study because you have a specific type of non-small cell lung cancer called bronchioloalveolar carcinoma, or "BAC", and your cancer is present in multiple areas of the lungs and cannot be surgically removed.

Who is doing this study?

The Southwest Oncology Group (SWOG) is sponsoring this trial. SWOG is an adult cancer clinical trials organization. SWOG is funded through the National Cancer Institute, and its network consists of almost four thousand physicians at almost three hundred institutions throughout the United States. Your study doctor has met all requirements to be a member of SWOG and to perform National Cancer Institute-funded research through this Group.

Why is this study being done?

The purpose of this study is to find out what effects (good and bad) the combination of OSI-774 and bevacizumab has on you and your lung cancer.

OSI-774 is an oral drug approved by the FDA to treat lung cancer in patients who have already received chemotherapy. OSI-774 is investigational for this study.

Bevacizumab is the common name for the commercial drug, Avastin®. It is approved for use in colon cancer and as a first-line treatment for patients with locally advanced metastatic or recurrent non-small cell lung cancer in combination with platinum-based chemotherapy. Bevacizumab is considered investigational for this study. The bevacizumab used in this trial may be made at locations different from those where Avastin® is made. Although some differences may exist, bevacizumab for research use and the commercial drug Avastin® are manufactured by a similar process, meet similar standards for final product testing, and are expected to be very similar in safety and effectiveness.

It works against a protein that helps form new blood vessels in tumors. As tumors grow bigger, they need their own blood supply. Blocking the formation of these tumor blood vessels, which is what bevacizumab can do, may limit or even shrink the tumor.

As part of this study, your tumor tissue samples and blood samples may be sent to a special laboratory. They may be evaluated for various molecules that can help researchers to predict, in the future, which patients can best benefit from treatment with OSI-774. You will not have to undergo any further biopsies, as the biopsy already used to diagnose your lung cancer will be used.

This research is being done because we are still trying to find the most effective treatment for this type of cancer (BAC).

How many people will take part in the study?

About 80 people will take part in this study.

What will happen if I take part in this research study?

Before you begin the study …

You will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

- Medical history and physical examination
- Blood tests for blood counts, blood chemicals and to test your kidney and liver
- Urine tests to check your kidneys if blood test is not done
- X-rays/scans to assess disease
- Brain CT/MRI
- Bone scan (if clinically indicated)
- PET scan (if clinically indicated)

During the study….

If the exams, tests and procedures show that you can be in the study, and you choose to take part, then you will receive the following treatment:

If you take part in this study, you will receive two drugs. Bevacizumab will be given to you through an IV and may take 30 to 90 minutes depending on how you tolerate the treatment. It will be given once every 21 days. This 21-day period is called a "cycle". In addition, you will

take OSI-774 once a day by mouth. You should take this drug daily (preferably in the morning) with up to 8 ounces of water, one hour before or two hours after food. You will continue on these drugs until you have dangerous side-effects, your disease gets worse, or you and your doctor decide that you should stop taking the drug for other reasons.

You will record the number of pills you take each day and any side effects you experience on a calendar. You should bring your calendar with you each time you have an appointment. During your visits, your calendar will be reviewed.

You will also need the following tests and procedures. They are part of regular cancer care. These tests will all be done in an outpatient setting.

• Medical history	Prestudy
• Physical exam	Prestudy and at the start of every cycle
• Complete blood counts	Prestudy and at the start of every cycle
• Blood chemistry (including tests to check your liver and kidneys)	Prestudy and at the start of every cycle
• Urine tests (if kidney blood test not done)	Prestudy and at the start of every cycle
• X-rays/scans to assess disease	Prestudy and after every 2 cycles for first 6 cycles, then after every 3-4 cycles up to 2 years, then every 6 months *(1/9/09)*

How long will I be in the study?

You will be asked to take bevacizumab and OSI-774 until your disease gets worse or your side effects become too great. After you are finished with the study treatment, you will need to come to the clinic for doctor visits and blood tests every three months for one year and then every six months for a maximum of three years from the time you started the study. If your disease did not get worse on the treatment, you will also need CT scans and/or x-rays. These will be done every 6 weeks for 18 weeks, then every 9-12 weeks for 2 years, then every 6 months until your disease gets worse. *(paragraph updated 1/9/09)*

Can I stop being in the study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from the drugs can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest, if you do not follow the study rules, or if the study is stopped.

What side effects or risks can I expect from being in the study?

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop taking the OSI-774 and bevacizumab. In some cases, side effects can be serious, long lasting, or may never go away. There also is a risk of death.

You should talk to your study doctor about any side effects that you have while taking part in the study.

OSI-774 can interact with many medications. Please tell your study doctor or nurse about all medications that you are currently taking including any over the counter or herbal products. OSI-774 potentially reacts with drugs that are dependent on the P450 cytochrome isoenzyme.

The side effects of the bevacizumab and OSI-774 include the following:

***Likely*:**

- *(items moved to Less Likely 10/15/08)*
- **Skin rash with the presence of macules (flat discolored area) and papules (raised bump)** *(updated 5/31/10)*
- **Diarrhea**
- *(moved to Less Likely 12/2/11)*
- *(moved to Less Likely 8/2/10)*
- *(moved to Less Likely 8/2/10)*
- *(item moved to Less Likely 10/15/08)*
- *(moved to Less Likely 8/2/10)*
- *(item moved to Less Likely 10/15/08)*
- *(item moved to Less Likely 9/17/07)*
- *(item moved to Less Likely 5/11/09)*
- *(items moved to Less Likely 9/17/07)*
- *(moved to Less Likely 8/2/10)*
- *deleted 8/2/10)*
- **High blood pressure**
- *(moved to Less Likely 8/2/10)*
- *(moved to Less Likely 8/2/10)*
- **Fatigue or tiredness** *(updated 5/31/10)*
- *(item moved to Less Likely 10/15/08)*
- *(item moved from Less Likely 9/17/07) (deleted 5/31/10)*
- *(moved to Less Likely 8/2/10)*
- *(moved to Less Likely 8/2/10)*
- *(moved to Less Likely 8/2/10).*
- *(moved to Less Likely 8/2/10)*
- **Loss of appetite** *(item moved from Likely 9/17/07) (item moved from Less Likely 10/15/08*

- **Vomiting** *(item moved from Likely 9/17/07) (item moved from Less Likely 10/15/08)*
- *(moved to Less Likely 12/2/11)*
- **Loss of the normal functioning of the ovaries in a woman that can result in temporary or permanent menopause; the impact on fertility (temporary or permanent) is unknown.** *(added 12/2/11)*

***Less Likely*:**

- **Hair loss**
- **Acne***(updated 5/31/10)*
- **Dry mouth**
- **Taste changes**
- **Dry eyes**
- *(deleted 8/2/10)*
- *(Item moved to likely 9/17/07)*
- **Irritation or sores in the lining of the mouth** *(12/11/07) (updated 5/31/10)*
- **Increased blood level of a liver or bone enzyme (alkaline phosphatase)** *(12/11/07) (updated 5/31/10) (updated 8/2/10)*
- **Increased blood level of a liver enzyme (ALT/SGPT)** *(added 5/31/10)*
- **Increased blood level of a liver enzyme (AST/SGOT)** *(added 5/31/10)*
- **Increased blood level of a liver pigment (bilirubin) often a sign of liver problems** *(updated 5/31/10)*
- *(Item moved to likely 9/17/07)*
- *(deleted 12/11/07)*
- *(deleted 12/11/07)*
- *(deleted 9/17/07)*
- **Bleeding in the vagina** *(added 9/17/07) (updated 8/2/10)*
- *(deleted 12/11/07)*
- *(deleted 9/17/07)*
- *(deleted 9/17/07)*
- *(Item moved to likely 9/17/07)*
- **Formation of a blood clot that plugs the blood vessel; blood clots may break loose and travel to another place, such as the lung** *(updated 8/2/10)*
- **Reaction that can occur during or following infusion of the drug. The reaction may include fever, chills, rash, low blood pressure, and difficulty breathing** *(updated 8/2/10)*
- **Infection** *(item moved from Likely 9/17/07) (updated 8/2/10)*
- *(deleted 10/15/08)*
- *(item moved to Likely 10/15/08)*
- **Heartburn** *(item moved from Likely 9/17/07)*
- *(item moved to Likely 10/15/08)*
- **Cough** *(item moved from Likely 9/17/07)*
- *(deleted 8/2/10)*
- **Lack of enough red blood cells (anemia)** *(added 9/17/07) (updated 8/2/10)*

- **Dry skin** *(item moved from Likely 10/15/08)*
- **Itching** *(item moved from Likely 10/15/08)*
- **Belly pain** *(item moved from Likely 10/15/08)*
- **Nose bleed** *(item moved from Likely 10/15/08)*
- *(item deleted 5/11/09)*
- *(item moved to Likely 10/15/08)*
- **Headache or head pain** *(Moved from Likely 12/2/11)*
- **Nausea or the urge to vomit** *(moved from Likely 12/2/11)*
- **Fever associated with dangerously low levels of a type of white blood cell (neutrophils)** *(added 12/2/11)*
- **Blockage in an organ(s)/part(s) of the digestive tract** *(added 12/2/11)*
- **Infection of the skin** *(added 10/15/08) (updated 5/31/10)*
- **Loss of some or all of the finger or toenails** *(added 10/15/08) (updated 5/31/10)*
- **Dehydration (when your body does not have as much water and fluid as it should)** *(added 5/11/09)) (updated 5/31/10)*
- *(moved to Likely 8/2/10)*
- **Eyelash in-growth and/or thickening** *(added 5/11/09) (updated 5/31/10)*
- **Inflammation (swelling and redness) of the lungs** *(moved from Rare but Serious 5/11/09) (updated 5/31/10)*
- **Bleeding in some organ(s) of the digestive tract** *(added 5/31/10)*
- **Shortness of breath** *(moved from Likely 5/31/10)*
- **Inflammation (swelling and redness) of the conjunctiva (the outermost layer of the eye and the inner surface of the eyelids). Commonly called "pink eye"** *(added 5/31/10) (updated 7/1/10)*
- **Fast heartbeat usually originating in an area located above the ventricles** *(added 8/2/10)*
- **Feeling of spinning or whirling** *(added 8/2/10)*
- **Inflammation (swelling and redness) of the large bowel (colon)** *(added 8/2/10)*
- **Constipation** *(moved from Likely 8/2/10)*
- **Partial or complete blockage of the small and/or large bowel. Ileus is a functional rather than actual blockage of the bowel.** *(added 8/2/10)*
- **Chest pain not heart-related** *(updated and moved from Likely 8/2/10)*
- **Pain** *(added 8/2/10)*
- **Allergic reaction by your body to the drug product that can occur immediately or may be delayed. The reaction may include hives, low blood pressure, wheezing, swelling of the throat, and difficulty breathing.** *(updated and moved from Likely 8/2/10)*
- **Infection (collection of pus) around the rectum** *(added 8/2/10)*
- **Premature opening of a wound along surgical stitches after surgery** *(updated and moved from Rare But Serious 8/2/10)*
- **Increased blood level of a heart muscle protein (troponin I) indicating damage to the heart muscle** *(updated and moved from Rare but Serious 8/2/10)*
- **Decreased number of a type of white blood cell (neutrophil/granulocyte)** *(updated 8/2/10)*
- **Weight loss** *(moved from Rare but Serious 8/2/10)*

- **Decrease in total number of white blood cells (leukocytes)** *(updated and moved from Likely 8/2/10)*
- **Joint pain (***moved from Likely 8/2/10)*
- **Muscle Pain** *(moved from Rare but serious 8/2/10)*
- **Dizziness (or sensation of lightheadedness, unsteadiness, or giddiness)** *(updated and moved from Likely 8/2/10)*
- **Fainting** *(added 8/2/10)*
- *(moved to Rare but Serious 12/2/11)*
- **Blood in the urine** *(added 8/2/10)*
- **More protein leaking into the urine than usual, often a sign of kidney disease** *(updated and moved from Likely 8/2/10)*
- **Destruction or death of jaw bone** *(added 12/2/11)*
- **Inflammation (swelling and redness) or degeneration of the peripheral nerves (those nerves outside of brain and spinal cord) causing numbness, tingling, burning** *(added 12/2/11)*
- **Stuffy or runny nose, sneezing** *(updated and moved from Likely 8/2/10)* (updated 12/2/11)
- **Hives** *(moved from Likely 8/2/10)*
- *(deleted 12/2/11)*
- **Hoarseness** *(updated and moved from Likely 8/2/10)*

***Rare but Serious*:**

- *(moved to Less Likely 5/11/09)*
- *(deleted 8/2/10)*
- *(moved to less Likely 8/2/10)*
- *(deleted 12/11/07)*
- *(deleted 8/2/10)*
- *(moved to likely 9/17/07)*
- **Abnormal changes in the brain that can cause a collection of symptoms including headache, confusion, seizures, and vision loss associated with MRI findings (RPLS)** *(updated 8/2/10)***.**
- *(deleted 8/2/10)*
- *(deleted 12/11/07)*
- *(item moved to Likely 9/17/07)*
- *(item moved to Likely 9/17/07)*
- *(deleted 12/11/07)*
- *(deleted 8/2/10)*
- *(moved to Less likely 8/2/10)*
- **Leakage from the stomach due to breakdown of anastomosis (surgical connection of two separate body structures)** *(12/11/07) (updated 8/2/10) (updated 12/2/11)*
- **Heart failure: inability of the heart to adequately pump blood to supply oxygen to the body** *(updated 8/2/10)*

- **Heart attack caused by a blockage or decreased blood supply to the heart** *(updated 8/2/10)*
- **Irregular heartbeat resulting from an abnormality in the one of the lower chambers of the heart (ventricle)** *(updated 8/2/10)*
- **Ventricular fibrillation: irregular heartbeat that involves the lower chambers of the heart (ventricles) that results in uncoordinated contraction of the heart; life threatening and potentially fatal, needing immediate attention** *(updated 8/2/10)*
- **Decrease in heart's ability to pump blood during the "active" phase of the heartbeat (systole)** *(updated 8/2/10)*
- *(deleted 8/2/10)*
- *(deleted 8/2/10)*
- *(deleted 8/2/10)*
- *(moved to Less Likely 8/2/10)*
- *(deleted 9/17/07)*
- *(deleted 8/2/10)*
- *(moved to Less Likely 8/2/10)*
- *(deleted 12/11/07)*
- **Gastrointestinal fistula: Abnormal hole between an organ of the digestive tract and another organ or tissue** *(updated 8/2/10)*
- **Hole in a part(s) of the digestive tract** *(updated 5/31/10)*
- *(deleted 12/2/10)*
- **Abnormal hole between part of the urinary system and another organ or tissue** *(added 9/17/07) (updated 8/2/10)*
- **Severe reaction of the skin and gut lining that may include rash and shedding or death of tissue** *(added 10/15/08) (updated 5/31/10)*
- **Swelling and redness of the skin on the palms of the hands and soles of the feet** *(added 10/15/08) (updated 5/31/10)*
- **Liver failure** *(added 10/5/08) (updated 5/31/10)*
- **Bleeding in the brain** *(added 5/11/09) (updated 5/31/10)*
- **Inflammation (swelling and redness) of the cornea (the transparent front cover of the eye)** *(added 5/11/09) (updated 5/31/10)*
- **Hole in the outer layer of the eye** *(added 5/11/09) (updated 5/31/10)*
- **Damage of or clots in small blood vessels in the kidney that can cause complications, some of which are serious including abnormal destruction of red blood cells (hemolysis) of platelets (that help to clot blood) and kidney failure** *(added 8/2/10)*
- **Collections of signs and symptoms that indicate sudden heart disease in which the heart does not get enough oxygen. Sudden symptoms such as chest pain, shortness of breath, or fainting could indicate heart disease and should be reported right away. Signs such as abnormal EKG and blood tests can confirm damage to the heart** *(added 8/2/10)*

- **Gastrointestinal perforation: A tear or hole in the stomach or gut that can lead to serious complications and may require surgery to repair** *(added 8/2/10)*
- **Sore (ulcer) somewhere in the digestive tract** *(added 8/2/10)*
- **Serious, life-threatening allergic reaction requiring immediate medical treatment by your doctor. The reaction may include extremely low blood pressure, swelling of the throat, difficulty breathing, and loss of consciousness** *(added 8/2/10)*
- **Stroke caused by decreased blood flow to the brain** *(added 8/2/10)*
- **A condition in which the kidneys leak a large amount of protein into the urine that can cause complications including swelling and kidney failure** *(added 8/2/10)*
- **Abnormal hole between the vagina and another organ or tissue** *(added 8/2/10)*
- **Abnormal hole between the lower breathing tube and the body cavity that surrounds the lungs** *(added 8/2/10)*
- **Bleeding from the lungs** *(added 8/2/10)*
- **Hole in the wall that separates the nostrils of the nose** *(added 8/2/10*
- **Blockage or narrowing of a blood vessel (artery) that can cause damage or loss of function including a heart attack or stroke** *(added 8/2/10)*
- **Sudden decrease of kidney** (moved from Less Likely 12/2/11)
- (deleted 8/2/10)
- **Abnormal hole between the breathing tube (windpipe) and the tube that goes from mouth to stomach through which food passes (esophagus). This is life-threatening and potentially fatal.** *(updated 8/2/10)*

Reproductive risks: You should not become pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. Women should not breastfeed a baby while on this study. It is important you understand that you need to use birth control while on this study. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be appropriate for use in this study.

For more information about risks and side effects, ask your study doctor.

Are there benefits to taking part in the study?

Taking part in this study may or may not make your health better. While doctors hope the combination of OSI-774 and bevacizumab will be more useful against cancer compared to the usual treatment, there is no proof of this yet. We do know that the information from this study will help doctors learn more about this combination as a treatment for cancer. This information could help future cancer patients.

What other choices do I have if I do not take part in this study?

Your other choices may include:

- **Getting treatment or care for your cancer without being in a study**
- **Taking part in another study**
- **Getting no treatment**
- **Getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly, but instead tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.**

Talk to your doctor about your choices before you decide if you will take part in this study.

Will my medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The Southwest Oncology Group
- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people
- Qualified representatives of Genentech (the manufacturer for both study drugs)

[Note to Local Investigators: The NCI has recommended that HIPAA regulations be addressed by the local institution. The regulations may or may not be included in the informed consent form depending on local institutional policy.]

What are the costs of taking part in this study?

You and/or your health plan/ insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

Administration of bevacizumab will be *(provided free of charge/charged in the usual way).* The parts of the research consisting of keeping research records will be paid by those organizing and conducting the research. The research requires that you receive certain standard medical tests and examinations. These standard tests and examinations will be *(charged in the usual way/provided at a reduced rate). (local institutions must choose the option that best fits the hospital's situation)*

Genentech will provide you with the drugs bevacizumab and OSI-774 at no cost to you while you are participating in this study. However, if you should need to take the study agent much longer than is usual, it is possible that the free supply of study agent given through the study could run out. If this happens, your study doctor will discuss with you how to obtain additional drug from the manufacturer and you may be asked to pay for it.

You will not be paid for taking part in this study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage . You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

What happens if I am injured because I took part in this study?

It is important that you tell your study doctor, _____ *[investigator's name(s)],* if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at _____ *[telephone number].*

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

What are my rights if I take part in this study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer my questions about the study?

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor _____ *[name(s)]* at _____ *[telephone number].*

For questions about your rights while taking part in this study, call the _____ *[name of center]* Institutional Review Board (a group of people who review the research to protect your rights) at _____ *(telephone number).* *[Note to Local Investigator: Contact information for patient representatives or other individuals in a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can be listed here.]*

Please note: This section of the informed consent form is about additional research studies that are being done with people who are taking part in the main study. You may take part in these additional studies if you want to. You can still be a part of the main study even if you say 'no' to taking part in any of these additional studies.

You can say "yes" or "no" to each of the following studies. Please mark your choice for each study.

1. Future Contact

   I agree to allow my study doctor, or someone approved by my study doctor, to contact me regarding future research involving my participation in this study.

   Yes **No**

2. Specimen Submission for Study-Specific Testing

If you agree, samples of your cancer tissue (which were obtained at the time of your biopsy or operation) will be obtained at registration and sent to a special laboratory for scientific testing. These studies are being done in order to better understand the mechanisms of BAC and to try to predict who will be treated most effectively with this type of treatment.

Additionally, blood specimens (approximately 6 teaspoons total) will be collected before treatment and prior to the start of Cycles 2 and 3. If you go off study or if your disease gets worse prior to Cycle 2 or 3, blood will be collected at that time (approximately 2 teaspoons).

The results of the testing will not be given to you or your doctor. Although the results will not affect your treatment, the tests may help future patients. Reports about research done with your specimens will not be put in your health records. Results from these tests may be published, but you will not be identified in the publications.

My specimens may be used for the special testing described as part of this study. *(9/17/07)*

Yes No

3. Storage and Use of Tissue and Blood for Future, Unspecified Research

You are going to have a biopsy (or surgery) to see if you have cancer. Your doctor will remove some body tissue to do some tests. The results of these tests will be given to you by your doctor and will be used to plan your care. You have also had blood specimens (approximately 2 teaspoons each) taken as part of this study before treatment and before Cycles 2 and 3 of treatment.

We would like to keep some of the tissue and blood that is left over for future research. If you agree, this tissue and blood will be kept and may be used in research to learn more about cancer and other diseases. Please read the information sheet called "How are Specimens Used for Research" to learn more about specimen research.

The research that may be done with your specimens is not designed specifically to help you. It might help people who have cancer and other diseases in the future.

Reports about research done with your specimens will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care.

Things to Think About

The choice to let us keep the left over specimens for future research is up to you. No matter what you decide to do, it will not affect your care.

If you decide now that your specimens can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your tissue. Then any specimens that remain will no longer be used for research.

In the future, people who do research may need to know more about your health. While the Southwest Oncology Group may give them reports about your health, it will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Sometimes specimens are used for genetic research (about diseases that are passed on in families). Even if your tissue is used for this kind of research, the results will not be put in your health records.

Your specimens will be used only for research and will not be sold. The research done with your specimens may help to develop new products in the future.

Benefits

The benefits of research using specimens include learning more about what causes cancer and other diseases, how to prevent them, and how to treat them.

Risks

The greatest risk to you is the release of information from your health records. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone else is very small.

Making Your Choice

Please read each sentence below and think about your choice. After reading each sentence, circle "Yes" or "No." If you have any questions, please talk to your doctor or nurse, or call our research review board at IRB's phone number.

No matter what you decide to do, it will not affect your care.

1. My specimens may be kept for use in research to learn about, prevent, treat or cure cancer.

Yes No

2. **My specimens may be kept for use in research about other health problems (for example: diabetes, Alzheimer's disease, or heart disease).**

Yes No

3. **Someone may contact me in the future to ask me to allow other uses of my specimens.**

Yes No

If you decide to withdraw your specimens from a Southwest Oncology Group Specimen Repository in the future, a written withdrawal of consent should be submitted through your treating physician to the Southwest Oncology Group Operations Office. Please designate in the written withdrawal whether you would prefer to have the specimens destroyed or returned to the treating physician.

Where can I get more information?

You may call the National Cancer Institute's Cancer Information Service at:

1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

You may also visit the NCI Web site at http://cancer.gov/

- For NCI's clinical trials information, go to: http://cancer.gov/clinicaltrials/
- For NCI's general information about cancer, go to http://cancer.gov/cancerinfo/

You will get a copy of this form. If you want more information about this study, ask your study doctor.

Signature

I have been given a copy of all _____ *[insert total of number of pages]* pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

Participant _____

Date _____

Specimen Consent Supplemental Sheet

How are Specimens Used for Research?

Where do specimens come from?

A specimen may be from a blood sample or from bone marrow, skin, toenails or other body materials. People who are trained to handle specimens and protect donors' rights make sure that the highest standards of quality control are followed by the Southwest Oncology Group. Your doctor does not work for the Southwest Oncology Group, but has agreed to help collect specimens from many patients. Many doctors across the country are helping in the same way.

Why do people do research with specimens?

Research with specimens can help to find out more about what causes cancer, how to prevent it, how to treat it, and how to cure it. Research using specimens can also answer other health questions. Some of these include finding the causes of diabetes and heart disease, or finding genetic links to Alzheimer's.

What type of research will be done with my specimen?

Many different kinds of studies use specimens. Some researchers may develop new tests to find diseases. Others may develop new ways to treat or even cure diseases. In the future, some of the research may help to develop new products, such as tests and drugs. Some research looks at diseases that are passed on in families (called genetic research). Research done with your specimen may look for genetic causes and signs of disease.

How do researchers get the specimen?

Researchers from universities, hospitals, and other health organizations conduct research using specimens. They contact the Southwest Oncology Group and request samples for their studies. The Southwest Oncology Group reviews the way that these studies will be done, and decides if any of the samples can be used. The Southwest Oncology Group gets the specimen and information about you from your hospital, and sends the specimen samples and some information about you to the researcher. The Southwest Oncology Group will not send your name, address, phone number, social security number or any other identifying information to the researcher.

Will I find out the results of the research using my specimen?

You will not receive the results of research done with your specimen. This is because research can take a long time and must use specimen samples from many people before results are known. Results from research using your specimen may not be ready for many years and will not affect your care right now, but they may be helpful to people like you in the future.

Why do you need information from my health records?

In order to do research with your specimen, researchers may need to know some things about you. (For example: Are you male or female? What is your race or ethnic group? How old are you? Have you ever smoked?) This helps researchers answer questions about diseases. The information that will be given to the researcher may include your age, sex, race, diagnosis, treatments and family history. This information is collected by your hospital from your health record and sent to the Southwest Oncology Group. If more information is needed, the Southwest Oncology Group will send it to the researcher.

Will my name be attached to the records that are given to the researcher?

No. Your name, address, phone number and anything else that could identify you will be removed before they go the researcher. The researcher will not know who you are.

How could the records be used in ways that might be harmful to me?

Sometimes, health records have been used against patients and their families. For example, insurance companies may deny a patient insurance or employers may not hire someone with a certain illness (such as AIDS or cancer). The results of genetic research may not apply only to you, but to your family members too. For disease caused by gene changes, the information in one person's health record could be used against family members.

How am I protected?

The Southwest Oncology Group is in charge of making sure that information about you is kept private. The Southwest Oncology Group will take careful steps to prevent misuse of records. Your name, address, phone number and any other identifying information will be taken off anything associated with your specimen before it is given to the researcher. This would make it very difficult for any research results to be linked to you or your family. Also, people outside the research process will not have access to results about any one person which will help to protect your privacy.

(section deleted 11/9/11)

What if I have more questions?

If you have any questions, please talk to your doctor or nurse, or call our research review board at (Insert IRB's Phone Number).

Southwest Oncology Group Data Operations Center
C/o Cancer Research And Biostatistics
1730 Minor Ave, Suite 1900
Seattle, WA 98101-1468
Patient Registration:
via WebReg at: http://swog.org
(24 hours a day, 7 days a week, excluding downtimes for maintenance)
or call 206-652-2267 (Mon-Fri, 6:30am-4:00pm Pacific Time, excluding holidays)

Southwest Oncology Group Operations Office
14980 Omicron Drive
San Antonio, TX 78245-3217
Phone: (210) 450-8808
Fax: (210) 677-0006

Southwest Oncology Group Registration Form

SWOG Study No.	Registration Step	Assigned Treatment Arm	Activation Date: July 15, 2007
S0635	1	1	Last Amended Date: October 1, 2007

A Phase II Trial of the Combination of OSI-774 (Erlotinib; NSC-718781) and Bevacizumab (Rhumab VEGF; NSC-704865) in Stage IIIB and IV Bronchioloalveolar Carcinoma (BAC) and Adenocarcinoma with BAC Features (AdenoBAC)

Patient's Name _____

SWOG Patient ID ☐☐☐☐☐☐

INSTRUCTIONS: All of the information on this Registration Form and the Protocol Eligibility Section must be answered appropriately for a patient to be considered eligible for registration. This Registration Form must be entirely filled out and referred to during the registration. **Do NOT submit this form as part of the patient data.**

Caller's SWOG Roster ID ☐☐☐☐☐

SWOG Investigator Number ☐☐☐☐☐

SWOG Treating Institution Number ☐☐☐☐☐

IRB Approval Date ☐☐ / ☐☐ / ☐☐☐☐

Date Informed Consent Signed ☐☐ / ☐☐ / ☐☐☐☐

Projected Start Date of Treatment ☐☐ / ☐☐ / ☐☐☐☐

Date HIPAA Authorization signed: ☐☐ / ☐☐ / ☐☐☐☐

(Not required for non-American sites)

Please indicate how the patient answered the following questions on the consent form:

1. My specimens may be kept for use in research to learn about, prevent, treat or cure cancer.	2. My specimens may be kept for use in research about other health problems (for example: diabetes, Alzheimer's disease, or heart disease).	3. Someone may contact me in the future to ask me to allow other uses of my specimens.	4. I agree to allow my study doctor, or someone approved by my study doctor, to contact me regarding future research involving my participation in this study.	5. My specimens may be used for the special testing described as part of this study.
☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No

Patient's Date of Birth: ☐☐ / ☐☐ / ☐☐☐☐

Patient Gender: ☐ Female ☐ Male **Method of Payment:** _____ **Patient's Ethnicity:** _____

Patient's Race (select all that apply):

☐ White ☐ Native Hawaiian or Other Pacific Islander ☐ American Indian or Alaska Native
☐ Black or African American ☐ Asian ☐ Unknown

If a U.S. resident:

Patient Social Security Number: ☐☐☐ – ☐☐ – ☐☐☐☐ **Patient's ZIP Code:** ☐☐☐☐☐

Country of Residence (if not USA): _____

If a resident of Canada:

Social Insurance Number: ☐☐☐ – ☐☐☐ – ☐☐☐ **Postal Code:** ☐☐☐ – ☐☐☐

Southwest Oncology Group Registration Form Code Sheet

Patient's race definitions:

White or Caucasian: a person having origins in any of the original peoples of Europe, Middle East, or North Africa.

Black or African American: a person having origins in any of the black racial groups of Africa.

Native Hawaiian or Other Pacific Islander: a person having origins in any of the original peoples of Hawaii, Guam, Samoa and other Pacific islands.

Asian: a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent. Including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand and Vietnam.

American Indian or Alaskan Native: a person having origins in any of the original peoples of North, Central or South America, and who maintains tribal affiliations or community attachment.

Patient's ethnicity (Spanish/Hispanic Origin) options:

Unknown
No (not Spanish)
Yes, Mexican
Yes, Puerto Rican
Yes, Cuban
Yes, Central American
Yes, South American
Yes, Other
Yes, NOS

Method of Payment codes:

Private
Medicare
Medicare and Private
Medicaid
Medicaid and Medicare
No insurance (self-pay)
No insurance (no means)
Other, specify at registration
Unknown
Veterans Admin
Military

Other Group codes for use in the Web Registration program:

9977 – ACOSOG
9982 – CALGB
9976 – CTSU
9995 – ECOG
9984 – GOG
9987 – MDACC
9996 – NCCTG
9981 – NCIC
9983 – NSABP
9997 – RTOG

SOUTHWEST ONCOLOGY GROUP
S0635 PRESTUDY FORM

SWOG Patient ID ☐☐☐☐☐☐ **SWOG Study No.** S 0 6 3 5 **Registration Step** 1

Patient Initials _____ (L, F M)

Institution / Affiliate _____ Physician _____

Instructions: Submit this form within 14 days of registration. All dates are **MONTH, DAY, YEAR**. Explain any blank fields or blank dates in the **Comments** section. Place an [X] in appropriate boxes. Circle **AMENDED** items in red and write **AMENDED** across top of form.

ELIGIBILITY VERIFICATION:

Each of the fields below corresponds to a criterion in Section 5 and must be completed for patient to be eligible.

PATIENT AND DISEASE DESCRIPTION

Performance status: ☐

Histology: ☐ Adenocarcinoma with BAC features ☐ Bronchioloalveolarcarcinoma

Stage: ☐ Selected IIIB ☐ IV

Type of disease: ☐ New diagnosis ☐ Recurrent

T: ☐ TX ☐ Tis ☐ T0 ☐ T1 ☐ T2 ☐ T3 ☐ T4

N: ☐ NX ☐ N0 ☐ N1 ☐ N2 ☐ N3

M: ☐ M0 ☐ M1

Smoking history:

☐ Current ☐ Former (no smoking for 1 year or more) ☐ Never (less than 100 cigarettes in lifetime)

Amount of hemoptysis: ☐.☐ teaspoons **Date hemoptysis assessed:** ☐☐ / ☐☐ / ☐☐☐☐

History of pulmonary/upper respiratory hemorrhage:

☐ Yes, Grade 2* or worse **Last date observed:** ☐☐ / ☐☐ / ☐☐☐☐

☐ Yes, Grade 1* **Last date observed:** ☐☐ / ☐☐ / ☐☐☐☐

☐ No

**** per CTCAE version 3.0***

Date of pre-treatment scan of brain: ☐☐ / ☐☐ / ☐☐☐☐

Method (select one): ☐ CT ☐ MRI

Is scan negative for brain metastases? ☐ Yes ☐ No

If No, does scan show stable or improving brain metastases following treatment for brain metastases?

☐ Yes ☐ No

Did patient have a previous fine needle aspiration or core biopsy? ☐ Yes ☐ No

If Yes, date: ☐☐ / ☐☐ / ☐☐☐☐

continued on next page

SOUTHWEST ONCOLOGY GROUP
S0635 PRESTUDY FORM

SWOG Patient ID ☐☐☐☐☐☐ **SWOG Study No.** S0635 **Registration Step** 1

Patient Initials _____ (L, F M)

LABORATORY VALUES *Document values in units listed*

Hematologic: **Collection date:**

ANC ☐,☐☐☐ / mcL ☐☐ / ☐☐ / ☐☐☐☐

Platelets ☐☐☐,☐☐☐ / mcL ☐☐ / ☐☐ / ☐☐☐☐

Hepatic: **Collection date:**

Total bilirubin ☐☐☐.☐ mg/dL **ULN** ☐☐☐.☐ mg/dL ☐☐ / ☐☐ / ☐☐☐☐

Transaminase (select one) ☐ SGOT ☐ SGPT

☐☐☐ U/L **ULN** ☐☐☐ U/L ☐☐ / ☐☐ / ☐☐☐☐

Alkaline phosphatase

☐☐☐.☐ U/L **ULN** ☐☐☐.☐ U/L ☐☐ / ☐☐ / ☐☐☐☐

Liver metastases? ☐ Yes ☐ No **Bone metastases?** ☐ Yes ☐ No

Renal: **Collection date:**

Serum creatinine ☐☐.☐☐ mg/dL **ULN** ☐☐.☐☐ mg/dL ☐☐ / ☐☐ / ☐☐☐☐

Measured creatinine clearance ☐☐☐.☐ ml/min ☐☐ / ☐☐ / ☐☐☐☐

Calculated creatinine clearance ☐☐☐.☐ ml/min ☐☐ / ☐☐ / ☐☐☐☐

Urine Protein Creatinine (UPC) ratio ☐☐.☐☐ ☐☐ / ☐☐ / ☐☐☐☐

If UPC > 0.5, please indicate 24-hour urine protein level: ☐☐☐☐☐ mg/24-hours

ADDITIONAL PRESTUDY DATA:

Albumin: ☐☐.☐☐ g/dL

LDH: ☐☐☐☐ U/L **IULN** ☐☐☐☐ U/L **Date collected:** ☐☐ / ☐☐ / ☐☐☐☐

Height: ☐☐☐ cm **Weight:** ☐☐☐.☐ kg **BSA:** ☐.☐☐ m^2

Estimated Weight Loss in Last Six Months: ☐ < 5% ☐ 5 - < 10% ☐ 10 - 20% ☐ > 20%

continued on next page

SOUTHWEST ONCOLOGY GROUP
S0635 PRESTUDY FORM

SWOG Patient ID | | | | | | | **SWOG Study No.** S 0 6 3 5 **Registration Step** 1

Patient Initials _____ (L, F M)

PRIOR TREATMENT RELATED TO THIS CANCER:

Prior systemic therapy: ☐ Yes ☐ No

If Yes, most recent date received any prior systemic therapy: | | / | | / | | | | |

Prior radiotherapy: ☐ Yes ☐ No

If Yes, date prior radiation therapy completed: | | / | | / | | | | |

Was prior radiation palliative? ☐ Yes ☐ No

Prior surgery: ☐ Yes ☐ No

If Yes, date of last prior surgery: | | / | | / | | | | |

Comments:

SOUTHWEST ONCOLOGY GROUP
BASELINE TUMOR ASSESSMENT FORM

SWOG Patient ID | | | | | | | **SWOG Study No.** S | | | | | **Registration Step** |

Patient Initials _____ (L, F M)

Institution / Affiliate _____ Physician _____

Participating Group: Group Name/Study No./Patient ID _____ / _____ / _____

Instructions: Record the requested information for all target lesions and all sites of other disease. Please refer to section 10.0 of the protocol for definitions. Choose all measurable lesions up to a maximum of 5 lesions per organ and 10 lesions in total to follow as target lesions. Record any remaining measurable lesions and all non-measurable disease as non-target disease.
All dates are **MONTH, DAY, YEAR**. Circle **AMENDED** items in red.
The same test procedures used for baseline disease assessment must be used for all required subsequent disease assessments.

TARGET LESIONS

		Longest Diameter (cm)	Assessment Type*	Assessment Date
L1	_____	.		/ /
L2	_____	.		/ /
L3	_____	.		/ /
L4	_____	.		/ /
L5	_____	.		/ /
L6	_____	.		/ /
L7	_____	.		/ /
L8	_____	.		/ /
L9	_____	.		/ /
L10	_____	.		/ /

NON-TARGET DISEASE

		Extent	Assessment Type*	Assessment Date
S1	_____	_____		/ /
S2	_____	_____		/ /
S3	_____	_____		/ /
S4	_____	_____		/ /
S5	_____	_____		/ /

List all **negative** diagnostic tests/studies used to evaluate patient for malignancy.

Tests/studies	Assessment Date	Tests/studies	Assessment Date
_____	/ /	_____	/ /
_____	/ /	_____	/ /

*** Assessment Types:**

01-Palpation
02-Visualization
03-Colposcopy
05-Endoscopy
10-Plain film/X-ray without contrast
11-Plain film/X-ray with contrast
12-CT scan
13-MRI scan
14-Radioisotope scan
15-Ultrasound
16-PET scan
17-Spiral CT scan
18-Cystoscopy
20-Histologic confirmation
21-Cytologic confirmation
99-Other (specify in Comments and indicate lesion number)

Comments:

9/1/2003

SOUTHWEST ONCOLOGY GROUP
S0635 TREATMENT FORM

SWOG Patient ID ☐☐☐☐☐☐ **SWOG Study No.** S0635 **Registration Step** 1

Patient Initials _____ (L, F M) **Current Cycle Number** ☐☐

Institution/Affiliate _____ Physician _____

Instructions: Please complete this form after each cycle (*1 cycle = 21 days*). All dates are **MONTH, DAY, YEAR**. Explain any blank dates or fields in the **Comments** section. Place an [X] in appropriate boxes. Circle **AMENDED** items in red and write **AMENDED** across top of form.

STATUS

Date of Last Contact or Death: ☐☐ / ☐☐ / ☐☐☐☐ **Vital Status:** ☐ Alive ☐ Dead *(submit Notice of Death)*

Has the patient progressed per the definition in Section 10.0 of the protocol? ☐ No ☐ Yes

(If Yes, submit Follow-Up Tumor Assessment Form, Off Treatment Notice, and Lung Carcinoma First Site(s) of Progression/Relapse)

TREATMENT FOR THIS CYCLE

Cycle start date: ☐☐ / ☐☐ / ☐☐☐☐ **Weight (first day this cycle):** ☐☐☐.☐ kg

Date of last treatment for this cycle: ☐☐ / ☐☐ / ☐☐☐☐

Were there any dose modifications or additions/omissions to protocol treatment?

- ☐ No
- ☐ Yes, planned (per protocol guidelines), specify in comments
- ☐ Yes, unplanned (not per protocol guidelines), specify in comments

Total dose OSI-774 given this cycle: ☐☐☐☐ mg

Number of days receiving OSI-774 during this cycle: ☐☐

Total dose Bevacizumab given this cycle: ☐☐☐☐☐ mg

Was G-CSF given this cycle? ☐ Yes ☐ No *(If Yes, specify dose in comments)*

Was Erythropoietin given this cycle? ☐ Yes ☐ No *(If Yes, specify dose in comments)*

Comments:

SOUTHWEST ONCOLOGY GROUP
S0635 ADVERSE EVENT FORM

SWOG Patient ID | | | | | | | **SWOG Study No.** S 0 6 3 5 **Registration Step** 1

Patient Initials _____ (L, F M) **Current Cycle Number** | | *(see instructions)*

Institution/Affiliate _____ Physician _____

Instructions: Please complete this form after each cycle *(1 cycle = 21 days)*. Report adverse events occurring up until the next cycle of treatment begins. Document the worst Grade seen during the reporting period. Do not code a condition existing prior to registration as an adverse event unless it worsens. Category lists may not include all adverse events from that category. Record any observed adverse events not listed on the blank lines at the end. All dates are MONTH, DAY, YEAR. Explain any blank dates or fields in the **Comments** section. Place an [X] in appropriate boxes. Circle **AMENDED** items in red and write **AMENDED** across top of form.

ADVERSE EVENTS

Reporting period start date: | | / | | / | | | | *(Day 1 of this Cycle)*

Reporting period end date: | | / | | / | | | | *(Day one of next cycle. If final cycle, date of first visit or contact after resolution of acute adverse events.)*

Were adverse events assessed during this time period?

☐ No ☐ Yes, but no reportable adverse events occurred

☐ Yes, and reportable adverse events occurred (report below)

	CTC Adverse Event Term	CTCAE (3.0) Grade (1 - 5)	CTC Adverse Event Attribution Code*
IM00	Allergic reaction/ hypersensitivity		
HE20	Hemoglobin		
HE00	Leukocytes (total WBC)		
HE30	Neutrophils/granulocytes (ANC/AGC)		
CA01	Cardiac-ischemia/ infarction		
CA50	Hypertension		
FL40	Fatigue (asthenia, lethargy, malaise)		
FL01	Fever ^		
FL10	Rigors/chills		
FL51	Weight loss		
SK80	Dry skin		
SK90	Hair loss/alopecia		
SK00	Injection site reaction/ extravasation changes		
SK16	Pruritus/itching		
SK11	Rash/desquamation		
SK12	Urticaria		

	CTC Adverse Event Term	CTCAE (3.0) Grade (1 - 5)	CTC Adverse Event Attribution Code*
GI01	Anorexia		
GI30	Constipation		
GI23	Dehydration		
GI20	Diarrhea		
GI66	Dysphagia		
GI61	Esophagitis		
GI51	Gastritis		
GI02	Heartburn/dyspepsia		
	Mucositis/stomatitis (functional/symptomatic)		
GIM44	Oral cavity		
GIM52	Pharynx		
GI00	Nausea		
GI43	Taste alteration		
GI10	Vomiting		
HM10	Hemorrhage, CNS		

*** Attribution codes:** 1-unrelated 2-unlikely 3-possible 4-probable 5-definite

continued on next page

^ (in the absence of neutropenia, where neutropenia is defined as ANC < 1.0 x 10^9 /L)

SOUTHWEST ONCOLOGY GROUP
S0635 ADVERSE EVENT FORM

SWOG Patient ID | | | | | | | **SWOG Study No.** S 0 6 3 5 **Registration Step** 1

Patient Initials _____ (L, F M) **Current Cycle Number** | |

ADVERSE EVENTS, *continued*

	CTC Adverse Event Term	CTCAE (3.0) Grade (1 - 5)	CTC Adverse Event Attribution Code*
	Hemorrhage, pulmonary/upper respiratory		
HML05	Lung		
HML08	Nose		
	Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils		
ICL02	Bronchus		
ICL05	Lung		
	Infection with normal ANC or Grade 1 or 2 neutrophils		
INL02	Bronchus		
INL05	Lung (pneumonia)		
	Infection with unknown ANC		
IUL02	Bronchus		
IUL05	Lung (pneumonia		
ME03	ALT, SGPT (serum glutamic pyruvic transaminase)		
ME04	AST, SGOT (serum glutamic oxaloacetic transaminase)		
ME02	Alkaline phosphatase		
ME05	Bilirubin (hyperbilirubinemia)		
ME06	Creatinine		
ME12	Proteinuria		
NR25	CNS cerebrovascular ischemia		

	CTC Adverse Event Term	CTCAE (3.0) Grade (1 - 5)	CTC Adverse Event Attribution Code*
EY10	Dry eye syndrome		
EY02	Keratitis		
EY11	Ocular surface disease		
	Pain		
PAL04	Chest/thorax NOS		
PAN37	Head/headache		
PAM11	Joint		
LU60	Cough		
LU00	Dyspnea		
LU90	Voice changes/dysarthria		
SY40	Cytokine release syndrome/ acute infusion reaction		
VA53	Thrombosis/embolism		
VA52	Thrombosis/thrombus/ embolism		

CTC Adverse Event Term, Other
(specify using CTCAE 3.0 terminology)

_____ | |
_____ | |
_____ | |
_____ | |

*** Attribution codes:** 1-unrelated 2-unlikely 3-possible 4-probable 5-definite

Comments: (Please explain any "other" adverse events reported above, e.g. Pain-other)

SOUTHWEST ONCOLOGY GROUP
FOLLOW-UP TUMOR ASSESSMENT FORM

SWOG Patient ID [ ][ ][ ][ ][ ][ ] **SWOG Study No.** S[ ][ ][ ][ ] **Registration Step** [ ]

Patient Initials _____ (L, F M) **Date form completed:** [ ][ ] / [ ][ ] / [ ][ ][ ][ ]

Institution/Affiliate _____ Physician _____

Participating Group: Group Name/Study No./Patient ID _____ / _____ / _____

Instructions: Record the requested information for all target lesions and all sites of other disease. Lesion and site numbers (L1, S1, etc.) should correspond to the same lesions and sites of disease as indicated on the baseline tumor assessment form. If a target lesion was assessed but measurements were not obtainable, complete assessment type and assessment date, and state lesion number and reason measurement was not obtained in **Comments** section on page 2. Record site of any new lesions (since baseline) in the **New Lesions** section. Place an [X] in appropriate boxes. All dates are **MONTH, DAY, YEAR**. Circle **AMENDED** items in red.

The same test procedures used for baseline disease assessment must be used for all required subsequent disease assessments.

TARGET LESIONS

		Longest Diameter (cm)	Assessment Type*	Assessment Date
L1	_____	[ ][ ].[ ]	[ ][ ]	[ ][ ] / [ ][ ] / [ ][ ][ ][ ]
L2	_____	[ ][ ].[ ]	[ ][ ]	[ ][ ] / [ ][ ] / [ ][ ][ ][ ]
L3	_____	[ ][ ].[ ]	[ ][ ]	[ ][ ] / [ ][ ] / [ ][ ][ ][ ]
L4	_____	[ ][ ].[ ]	[ ][ ]	[ ][ ] / [ ][ ] / [ ][ ][ ][ ]
L5	_____	[ ][ ].[ ]	[ ][ ]	[ ][ ] / [ ][ ] / [ ][ ][ ][ ]
L6	_____	[ ][ ].[ ]	[ ][ ]	[ ][ ] / [ ][ ] / [ ][ ][ ][ ]
L7	_____	[ ][ ].[ ]	[ ][ ]	[ ][ ] / [ ][ ] / [ ][ ][ ][ ]
L8	_____	[ ][ ].[ ]	[ ][ ]	[ ][ ] / [ ][ ] / [ ][ ][ ][ ]
L9	_____	[ ][ ].[ ]	[ ][ ]	[ ][ ] / [ ][ ] / [ ][ ][ ][ ]
L10	_____	[ ][ ].[ ]	[ ][ ]	[ ][ ] / [ ][ ] / [ ][ ][ ][ ]

NON-TARGET DISEASE

		Extent	Assessment Type*	Assessment Date
S1	_____	☐ Complete disappearance ☐ Present ☐ Clear increase (describe in Comments on page 2) ☐ Not assessed	[ ][ ]	[ ][ ] / [ ][ ] / [ ][ ][ ][ ]
S2	_____	☐ Complete disappearance ☐ Present ☐ Clear increase (describe in Comments on page 2) ☐ Not assessed	[ ][ ]	[ ][ ] / [ ][ ] / [ ][ ][ ][ ]

*** Assessment Types:**

01-Palpation	12-CT scan	18-Cystoscopy
02-Visualization	13-MRI scan	20-Histologic confirmation
03-Colposcopy	14-Radioisotope scan	21-Cytologic confirmation
05-Endoscopy	15-Ultrasound	
10-Plain film/X-ray without contrast	16-PET scan	99-Other (specify in Comments on page 2 and indicate lesion number)
11-Plain film/X-ray with contrast	17-Spiral CT scan	

SOUTHWEST ONCOLOGY GROUP
FOLLOW-UP TUMOR ASSESSMENT FORM

SWOG Patient ID ☐☐☐☐☐☐ **SWOG Study No.** S☐☐☐☐ **Registration Step** ☐

Patient Initials _____ (L, F M) **Date form completed:** ☐☐ / ☐☐ / ☐☐☐☐

NON-TARGET DISEASE, continued

	Extent	Assessment Type*	Assessment Date
S3 _____	☐ Complete disappearance ☐ Present ☐ Clear increase (describe in Comments) ☐ Not assessed	☐☐	☐☐ / ☐☐ / ☐☐☐☐
S4 _____	☐ Complete disappearance ☐ Present ☐ Clear increase (describe in Comments) ☐ Not assessed	☐☐	☐☐ / ☐☐ / ☐☐☐☐
S5 _____	☐ Complete disappearance ☐ Present ☐ Clear increase (describe in Comments) ☐ Not assessed	☐☐	☐☐ / ☐☐ / ☐☐☐☐

NEW LESIONS (Specify Site)

	Assessment Type*	Assessment Date
S1 _____	☐☐	☐☐ / ☐☐ / ☐☐☐☐
S2 _____	☐☐	☐☐ / ☐☐ / ☐☐☐☐

Symptomatic deterioration: ☐ No ☐ Yes, describe in Comments **Assessment Date** ☐☐ / ☐☐ / ☐☐☐☐

*** Assessment Types:**

01-Palpation	12-CT scan	18-Cystoscopy
02-Visualization	13-MRI scan	20-Histologic confirmation
03-Colposcopy	14-Radioisotope scan	21-Cytologic confirmation
05-Endoscopy	15-Ultrasound	
10-Plain film/X-ray without contrast	16-PET scan	99-Other (specify in Comments
11-Plain film/X-ray with contrast	17-Spiral CT scan	and indicate lesion number)

Comments:

SOUTHWEST ONCOLOGY GROUP
OFF TREATMENT NOTICE

SWOG Patient ID ☐☐☐☐☐☐ **SWOG Study No.** S☐☐☐☐ **Registration Step** ☐

Patient Initials _____ (L, F M)

Institution / Affiliate _____ Physician _____

Participating Group: Group Name/Study No./Patient ID _____ / _____ / _____

Instructions: For each registration step, submit this form within 2 weeks after completion (or discontinuation) of treatment. List protocol-directed treatments that the patient received.

Systemic Therapy: List regimens, start and end dates. For multidrug regimens, do not list individual drugs separately; end date would be the date all drugs in the regimen were discontinued.

Surgery: List type of surgery, and in the "end date" column, the date of surgery.

Radiation: List sites, start and end dates (inclusive of boosts and implants).

All dates are **MONTH, DAY, YEAR**. Explain any blank fields or blank dates in the **Comments** section.

Place an ☒ in appropriate boxes. Circle **AMENDED** items in red and write **AMENDED** at the top of the form.

Treatment Start Date	Treatment End Date	Regimen or Procedure or Site(s)
☐☐ / ☐☐ / ☐☐☐☐	☐☐ / ☐☐ / ☐☐☐☐	
☐☐ / ☐☐ / ☐☐☐☐	☐☐ / ☐☐ / ☐☐☐☐	
☐☐ / ☐☐ / ☐☐☐☐	☐☐ / ☐☐ / ☐☐☐☐	
☐☐ / ☐☐ / ☐☐☐☐	☐☐ / ☐☐ / ☐☐☐☐	
☐☐ / ☐☐ / ☐☐☐☐	☐☐ / ☐☐ / ☐☐☐☐	

(If more room is needed, please continue on a separate page)

Off Treatment Reason *(select one):*

- ☐ Treatment completed per protocol criteria
- ☐ Adverse event/side effects/complications, specify: _____
- ☐ Patient withdrawal/refusal after beginning protocol therapy, specify: _____
- ☐ Patient withdrawal/refusal prior to beginning protocol therapy, specify: _____
- ☐ Disease progression, relapse during active treatment; Sites: _____
- ☐ Death on study (submit Notice of Death form)
- ☐ Other, specify: _____

For any adverse event, was treatment termination medically required?

☐ No ☐ Yes, specify: _____

For any patient refusal, was reason due to adverse event/side effects/complications?

☐ Yes, specify: _____

☐ No, specify other reason for refusal: _____

Off Treatment Date

Date of completion, progression, death or decision to discontinue therapy: ☐☐ / ☐☐ / ☐☐☐☐

Will patient receive further treatment?

☐ No ☐ Yes, specify: _____ ☐ Unknown

Date of Last Contact or Death: ☐☐ / ☐☐ / ☐☐☐☐

Vital Status: ☐ Alive ☐ Dead (submit Notice of Death form)

Comments: ***6/15/2006***

28829

SOUTHWEST ONCOLOGY GROUP
CAIA RADIOLOGY SUBMISSION FORM

SWOG Patient ID ☐☐☐☐☐☐ **SWOG Study No.** S☐☐☐☐ **Registration Step** ☐

Patient Initials _____ (L, F M)

Institution / Affiliate _____ Physician _____

Participating Group: Group Name/Study No./Patient ID _____ / _____ / _____

Instructions: Explain any blank fields or blank dates in the **Comments** section of the form. Place an ☒ in appropriate boxes. Circle **AMENDED** items in red and write **AMENDED** across the top of the form.

Submit a copy of this form to the SWOG Data Operations Center. Mail required materials and this form to the following oncologist:

Derick H.M. Lau, M.D. Ph.D.
Div. of Hematology/Oncology
Dept. of Internal Medicine
U.C. Davis Cancer Center
4501 X Street, Room 3019
Sacramento, CA 95817-2229

Assessment time (select all that apply): ☐ Prestudy ☐ 7 weeks ☐ 13 weeks ☐ End of treatment

No. of images: ☐☐

Required materials:
(if not enclosed, explain below in Comments) **Enclosed**

Original chest CT scan	☐ Yes	☐ No
Radiology report	☐ Yes	☐ No

Comments:

SOUTHWEST ONCOLOGY GROUP LUNG CARCINOMA
FIRST SITE(S) OF PROGRESSION OR RELAPSE FORM

SWOG Patient ID ☐☐☐☐☐☐ **SWOG Study No.** S☐☐☐☐ **Registration Step** 1

Patient Initials _____ (L, F M)

Institution / Affiliate _____ Physician _____

Groups Other than SWOG: Group Name/Study No./Pt. ID _____ / _____ / _____

Instructions: All dates are **MONTH, DAY, YEAR**. Place an **X** in appropriate boxes. Circle **AMENDED** items in red.

Date of last contact or death: ☐☐ / ☐☐ / ☐☐☐☐ **Status** ☐ Alive ☐ Dead

Date of progression or relapse: ☐☐ / ☐☐ / ☐☐☐☐

Site(s) of Progression or Relapse at the time progression/relapse was detected (select all that apply)**:**

A. Local (Primary Tumor)

- ☐ Lung parenchyma adjacent to primary tumor
- ☐ Bronchial stump

B. Regional/Nodal

- ☐ Ipsilateral hilar mediastinum (nodal)
- ☐ Contralateral hilar mediastinum (nodal)
- ☐ Ipsilateral pleural effusion
- ☐ Contralateral pleural effusion
- ☐ Ipsilateral supraclavicular lymph nodes
- ☐ Contralateral supraclavicular lymph nodes

C. Distant

- ☐ Separate lobe of the ipsilateral lung
- ☐ Opposite lung
- ☐ Pericardial effusion
- ☐ Brain
- ☐ Leptomeninges
- ☐ Liver
- ☐ Bone
- ☐ Adrenal glands
- ☐ Kidney
- ☐ Skin or subcutaneous
- ☐ Other site, specify: _____

For Local Progression or Relapse:
Progression/Relapse site within previous RT field? (select one):
☐ Yes ☐ No ☐ Not Applicable (No previous RT)

For Regional Progression or Relapse:
Progression/Relapse site within previous RT field? (select one):
☐ Yes ☐ No ☐ Not Applicable (No previous RT)

Notes:

SOUTHWEST ONCOLOGY GROUP
LUNG CARCINOMA FOLLOW UP FORM

SWOG Patient ID ☐☐☐☐☐☐ **SWOG Study No.** S☐☐☐ **Registration Step** ☐

(L, F M)
Patient Initials _____ Institution/Affiliate _____ Physician _____

Groups other than SWOG: Group Name/Study No./Pt. ID _____ / _____ / _____

Instructions: Please submit at each follow up after completion of treatment until recurrence, at time of recurrence, and at protocol specified intervals after recurrence. All dates are **MONTH, DAY, YEAR**. Answer all questions and explain any blank fields or blank dates in the **Comments** section. Place an [X] in appropriate boxes. Circle **AMENDED** items in red.

VITAL STATUS

Vital Status: ☐ Alive ☐ Dead Date of last contact or death: ☐☐ / ☐☐ / ☐☐☐☐

(If vital status is Dead, complete and submit Notice of Death form.)

DISEASE FOLLOW UP STATUS

Has the patient had a documented clinical assessment for this cancer since submission of the previous follow-up form?

☐ No ☐ Yes Date of Last Clinical Assessment: ☐☐ / ☐☐ / ☐☐☐☐

NOTICE OF FIRST RELAPSE OR PROGRESSION

Has the patient developed a first progression (or relapse) that has not been previously reported?

☐ No ☐ Yes Date of Relapse or Progression: ☐☐ / ☐☐ / ☐☐☐☐

(If Yes, please submit the Lung Carcinoma First Site(s) of Progression or Relapse Form.)

NOTICE OF NEW PRIMARY

Has a new primary cancer or myelodysplastic syndrome (MDS) been diagnosed that has not been previously reported?

☐ No ☐ Yes If Yes, Date of Diagnosis: ☐☐ / ☐☐ / ☐☐☐☐

New Primary Site: _____

FURTHER TREATMENT

Has the patient received further (non-protocol) treatment for this cancer?

☐ No ☐ Yes If Yes, Date of first non-protocol therapy: ☐☐ / ☐☐ / ☐☐☐☐

Specify Regimen: _____

(Note: If multiple regimens were received, please specify only the first regimen received after going off protocol treatment.)

Did the patient respond to this treatment? ☐ No ☐ Yes

Has the patient received prophylactic cranial irradiation (PCI)?

☐ No ☐ Yes PCI Start Date: ☐☐ / ☐☐ / ☐☐☐☐

LONG TERM TOXICITY

Has the patient experienced (prior to treatment for progression or relapse or a second primary, and prior to non-protocol treatment) any severe (grade ≥ 3) long term toxicity that has not been previously reported?

☐ No ☐ Yes Toxicities and Grades:

_____

Comments:

SOUTHWEST ONCOLOGY GROUP
NOTICE OF DEATH

SWOG Patient ID ☐☐☐☐☐☐ **Most Recent SWOG Study No.** S☐☐☐☐

Patient Initials _____ (L, F M)

Institution / Affiliate _____ Physician _____

Participating Group: Group Name/Study No./Patient ID _____ / _____ / _____

Instructions: Answer all questions and explain any blank fields or blank dates in the **Comments** section.
Place an [X] in appropriate boxes. Circle **AMENDED** items in red.

Date of Death: ☐☐ / ☐☐ / ☐☐☐☐ (month / day / year)

CAUSES OF DEATH

Any cancer (select one):

☐ No ☐ Primary Cause ☐ Contributory ☐ Possible ☐ Unknown

If cancer was the primary cause or if cancer possibly or definitely contributed to death, and the patient had had multiple tumor types, specify those which were causes of death:

☐ Cancer of most recent SWOG study, specify cancer: _____

☐ Cancer of other SWOG study, specify cancer: _____

☐ Other cancer, specify: _____

Toxicity from disease related treatment (select one):

☐ No ☐ Primary Cause ☐ Contributory ☐ Possible ☐ Unknown

If Primary Cause, Contributory or Possible, specify treatment and toxicity:

Non-cancer and non-treatment related causes (select one):

☐ No ☐ Primary Cause ☐ Contributory ☐ Possible ☐ Unknown

If Primary Cause, Contributory or Possible, specify:

Autopsy? ☐ No ☐ Yes ☐ Unknown

Source(s) of death information:

☐ Autopsy report
☐ Medical record / Death certificate
☐ Physician
☐ Relative or friend
☐ Other, specify: _____

Comments:

19.0 APPENDIX

19.1 Determination of Expedited Adverse Event Reporting Requirements

19.2 Intake Calendar

19.1 Determination of Expedited Adverse Event Reporting Requirements

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. (Directions for routine reporting are provided in Section 14.0.) Additionally, certain adverse events must be reported in an expedited manner to allow for more timely monitoring of patient safety and care. Expedited adverse event reporting principles and general guidelines follow; specific guidelines for expedited adverse event reporting on this protocol are found in Section 16.0.

Reporting requirements may include the following considerations: 1) whether the patient has received an investigational or commercial agent; 2) the characteristics of the adverse event including the *grade* (severity), the *relationship to the study therapy* (attribution), and the *prior experience* (expectedness) of the adverse event; 3) the Phase (1, 2, or 3) of the trial; and 4) whether or not hospitalization or prolongation of hospitalization was associated with the event.

An investigational agent is a protocol drug administered under an Investigational New Drug Submission (IND). In some instances, the investigational agent may be available commercially, but is actually being tested for indications not included in the approved package label.

Commercial agents are those agents not provided under an IND but obtained instead from a commercial source. The NCI, rather than a commercial distributor, may on some occasions distribute commercial agents for a trial.

When a study includes both investigational and commercial agents, the following rules apply.

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

- *Sequential administration*: When a study includes an investigational agent(s) and a commercial agent(s) on the same study arm, but the commercial agent(s) is given for a period of time prior to starting the investigational agent(s), expedited reporting of adverse events that occur prior to starting the investigational agent(s) would follow the guidelines for commercial agents. Once therapy with the investigational agent(s) is initiated, all expedited reporting of adverse events should follow the investigational guidelines.

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

Step 1: *Identify the type of event using the NCI Common Terminology Criteria for Adverse Events (CTCAE).* The CTCAE provides descriptive terminology and a grading scale for each adverse event listed. A copy of the CTCAE can be downloaded from the CTEP home page (http://ctep.cancer.gov)**.** Additionally, if assistance is needed, the NCI has an Index to the CTCAE that provides help for classifying and locating terms. All appropriate treatment locations should have access to a copy of the CTCAE.

Step 2: *Grade the event using the NCI CTCAE version specified.*

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

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

- the current NCI Agent-Specific Adverse Event List (for treatments using agents provided under an NCI-held IND);
- the drug package insert (for treatments with commercial agents only);
- Section 3.0 of this protocol.

Step 5: *Review Table 16.1 in the protocol to determine if there are any protocol-specific requirements for expedited reporting of specific adverse events that require special monitoring.*

Step 6: *Determine if the protocol treatment given prior to the adverse event included an investigational agent(s), a commercial agent(s), or a combination of investigational and commercial agents.*

NOTE: If the patient received at least one dose of investigational agent, follow the guidelines in Table 16.1.

NOTE: This includes all events that occur within 30 days of the last dose of protocol treatment. Any event that occurs more than 30 days after the last dose of treatment and is attributed possibly, probably, or definitely to the agent(s) must be reported according to the instructions in Table 16.1.

SOUTHWEST ONCOLOGY GROUP
INTAKE CALENDAR

SWOG Patient ID | | | | | | | **SWOG Study No.** S | | | | **Registration Step** |

Patient Initials (L, F, M) _____

Institution/Affiliate _____ Physician _____

Participating Group: Group Name/Study No./Patient ID _____ / _____ / _____

Instructions for the Nurse or Research Coordinator:

Give this intake calendar to the participant for her use with contact information filled in. Instruct the participant to bring her intake calendar to each visit.

This form does not need to be returned to the Data Operations Center.

If you have any questions contact: _____ Telephone: _____

Your next appointment is: _____

Instructions for the participant:

This is a monthly calendar on which you are to record the number of tablets you take each day. Be sure you have enough calendars to last until your next appointment. If you develop any side effects from the tablets, mark this on the calendar on the day you note the effect. Bring your calendars with you each time you have an appointment.

Special instructions:

Month: _____ **Year:** _____

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday