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**TITLE: A Phase I/II Study of Bevacizumab (rhuMAb VEGF) in Combination with OSI-774 for Patients with Recurrent or Metastatic Cancer of the Head and Neck**

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## SCHEMA

Dose Level	Bevacizumab mg/kg	OSI-774 (Tarceva™) mg
Level 1	5.0	150
Level 2	10.0	150
Level 3	15.0	150
Phase II Dose Level	15.0	150

<b><u>Patient Eligibility</u></b>	<b><u>Required Laboratory Data</u></b>
<p>Histologically or cytologically documented Squamous cell ca of the head and neck  Disease stage: Metastatic and/or recurrent head and neck cancer (not eligible for curative intent surgical or radiation therapy)  Measurable disease  Performance status 0-2  Age ≥ 18 years  Non-pregnant  Prior treatment: No more than one prior regimen for recurrent disease;  Prior irradiation allowed however, must have been completed 4 weeks prior to entry onto study.  No prior EGFR-based or VEGFR-based therapy for recurrent disease;  Chemotherapy must have been completed at least 4 weeks prior to enrollment  No concomitant malignancy</p>	<p>Leukocytes ≥ 3,000/μL  Granulocytes ≥ 1,500/μl  Platelets ≥ 100,000/μl  Bilirubin ≤ WNL  AST or ALT ≥ 2.5 x ULN  Creatinine ≤ 1.5  PT/INR ≤ 1.5</p>

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## 1. OBJECTIVES

- 1.1. *Phase I:* To determine the maximum tolerated dose (MTD) and dose limiting toxicity of escalating dose of Bevacizumab (5.0, 10.0 and 15.0 mg/kg) in combination with a fixed dose of OSI-774 (150 mg) on a 21-day cycle in patients with recurrent or advanced head and neck cancer (HNC).
- 1.2. *Phase II:* To determine the objective response rate and time to disease progression.
- 1.3 Laboratory Objectives: Please see Section 7.1

## 2. BACKGROUND

### 2.1 **Bevacizumab (rhuMAb VEGF)**

#### Scientific Background:

A large body of scientific data supports the conclusion that the growth of solid tumors is dependent on angiogenesis, the formation of new blood vessels, to nourish the tumor [1, 2]. Delivery of oxygen and nutrients by the new vessels is a rate-limiting step for tumor cell proliferation and thus a target for anti-tumor therapy. Recognition that angiogenesis is crucial to tumor growth has led to the identification of angiogenic factors responsible for stimulating new blood vessel formation.

Recent work has indicated that vascular endothelial growth factor (VEGF; also known as vascular permeability factor or VPF), an endothelial cell-specific mitogen, is a major regulator of angiogenesis. VEGF is a highly conserved, homodimeric glycoprotein whose dominant isoform has a molecular mass of 45,000 Daltons. VEGF stimulates proliferation of vascular endothelial cells, with a mean effective dose of 10-50 pM. The two dominant VEGF receptors are flt-1 (also known as VEGFR-1) and flk-1 (also known as VEGFR-2 or KDR). These VEGF receptors are found predominantly on vascular endothelial cells and of the two, VEGFR-2 is thought to be more important for the proliferative response to VEGF.

VEGF gene expression is substantially increased in the majority of human tumors when compared with the surrounding tumor-free tissues. Direct evidence for a role of VEGF in tumorigenesis has been provided by studies showing that a murine anti-VEGF neutralizing antibody, alone or in combination with cytotoxic chemotherapy, is able to inhibit the *in vivo* growth of a variety of human tumor cell lines derived from breast, colon, ovary, lung, glia and head and neck. Pre-clinical data also show radiosensitization by antiangiogenic agents[3]

In-situ hybridization has demonstrated that VEGF mRNA is markedly upregulated in the majority of cancers. Specifically, VEGF expression has been shown to be upregulated in squamous cell cancer of the head and neck. [5] [4]. De Fatta et al. demonstrated elevation of eIF4E whose overexpression led to upregulation of two angiogenic factors VEGF and FGF-2 (fibroblast growth factor-2) in head and neck cancer. It is believed

that this upregulation of angiogenesis due to VEGF and other factors (e.g. FGF-2) leads to further growth and metastases of tumors. [5] The actual mechanism is poorly understood. This theoretical relationship has been demonstrated in a retrospective cohort study of 77 patients with squamous cell head and neck cancer. Those tumors that were noted to have increased VEGF expression were noted to have more likely recurred locally and distantly. Also, VEGF expression was the most significant predictor of disease free survival and overall survival. [4] This makes VEGF expression not only an important prognostic factor, but also a potential target for therapy.

Bevacizumab (rhuMab, VEGF) is a recombinant humanized anti-vascular endothelial growth factor monoclonal antibody (rhuMab VEGF) composed of human IgG, framework regions and antigen-binding complementarity-determining regions from murine monoclonal antibody (muMab VEGF) that blocks binding of human VEGF to its receptors. Approximately 93% of the amino acid sequence, including most of the antibody framework, is derived from human IgG, and 7% of the sequence is derived from the murine antibody. RhuMab VEGF has a molecular mass of 149,000 Daltons and is glycosylated. [6]

The aim of this proposal is to expand on these observations with the use of Bevacizumab in combination with epidermal growth factor receptor (EGFR) antagonist, OSI-774 (Tarceva<sup>TM</sup>), for the treatment of recurrent or metastatic head and neck cancer.

#### 2.1.1 **Pharmacokinetics in Animals:**

Bevacizumab pharmacokinetic studies were performed first in mice, rats, and monkeys. Bevacizumab was cleared slowly from the serum with a terminal half-life of 1-2 weeks in all species tested. [6] Bevacizumab also exhibited dose linearity in observed peak concentrations and total exposure (area under the curve, AUC). A tissue distribution study in male rabbits using 125I-labeled rhuMab VEGF indicated that it was distributed to various highly perfused tissues (kidney, testes, spleen, heart and lung). [6] An additional study was conducted to assess the safety and pharmacokinetics of rhuMab VEGF administered in combination with paclitaxel and carboplatin. [6] This study was performed in monkey who received Bevacizumab at a dose of 10 mg/kg twice weekly for 18 days along with paclitaxel and carboplatin. There was no difference in the pharmacokinetics between groups who received Bevacizumab alone or in combination with chemotherapy.

## 2.1.2 Pharmacokinetics in Humans:

### Phase I Studies

The pharmacokinetics in humans have been evaluated in humans in two phase I studies. Study AVF0737g evaluated rhuMAB VEGF pharmacokinetics after single and multiple-dose administration in subjects with advanced malignancies. Bevacizumab was administered as an infusion on Days 0, 28, 35 and 42 and a total of five groups were evaluated: 0.1, 0.3, 1.0, 3.0 and 10.0 mg/kg. In most subjects, rhuMAB VEGF declined more rapidly over the first 2-3 days and more slowly thereafter. In the lower dose groups, Bevacizumab was cleared more slowly, whereas clearance did not change and ranged from 2.75 to 3.27 ml/day/kg with doses of 1.0 to 10.0 mg/kg. The volume of distribution did not change and was consistent with distribution limited to the serum volume. Consistent with the more rapid clearance observed at the two lowest doses, the terminal half-life for the 0.1 and 0.3 mg/kg dose groups was shorter, 5-10 days; the terminal half-life for the 1.0-10.0 mg/kg dose groups was ~2 weeks [6]

The pharmacokinetics of rhuMAB VEGF were also assessed when it was combined with cytotoxic chemotherapy. Study AVF0761g evaluated rhuMAB VEGF disposition, when administered at a dose of mg/kg weekly for up to 8 weeks, concomitantly with the following agents: 5-fluorouracil/leucovorin (500 mg/m<sup>2</sup>/week and 20 mg/m<sup>2</sup>/week), carboplatin/paclitaxel (carboplatin dose of AUC 6 and paclitaxel dose of 175mg/m<sup>2</sup> on 28 day cycle), and doxorubicin (50 mg/m<sup>2</sup> on 28 day cycle). Estimates of systemic clearance and volume of distribution were consistent with those estimated in study AVF0737g. As with the previous study, an increase in serum VEGF concentration was observed in most subjects. Co-administration of rhuMAB VEGF with these chemotherapeutic agents did not result in an increase in systemic concentrations of the cytotoxic agents, when comparing Day 0 with Days 28 or 35. Overall, these results indicate that weekly rhuMAB VEGF administration for 5-6 weeks did not result in an increase in concentrations of 5-fluorouracil, carboplatin/paclitaxel, or doxorubicin when comparing day 0 with day 28/35[6]

### Phase II Studies:

Study AVF0780g evaluated serum rhuMAB VEGF Pharmacokinetics in subjects with colorectal cancer following multidose administration in combination with 5-fluorouracil and leucovorin. RhuMAB VEGF was administered every 2 weeks at doses of either 5 or 10 mg/kg: 5FU and leucovorin were both administered at dose of 500 mg/m<sup>2</sup> weekly for 6 weeks of each 8-week cycle. RhuMAB VEGF pharmacokinetic parameters were similar following both dosing regimens, indicating dose linearity. RhuMAB VEGF was cleared slowly with a terminal half-life of ~12 days. Following rhuMAB VEGF administration, plasma VEGF concentrations increased an average of 3.4 and 9 times over baseline concentrations for the 5 and 10 mg/kg dose groups, respectively. In subjects receiving rhuMAB VEGF and 5FU/leucovorin, there were no systemic changes in 5FU concentration-time profile at Day 0 was compared with that of Day 35 VEGF[6].

Study AVF0757g evaluated rhuMAb VEGF pharmacokinetics in subjects with non-small cell lung cancer after multidose administration in combination with carboplatin and paclitaxel. RhuMAb VEGF was administered every 3 weeks at either 7.5 or 15 mg/kg. Carboplatin was administered at a dose targeting AUC of 6 and paclitaxel was administered at 200 mg/m<sup>2</sup> once every 3 weeks. RhuMAb VEGF pharmacokinetics were similar following both dosing regimens, indicating dose linearity. RhuMAb VEGF was cleared slowly (3ml/kg/day), with a terminal elimination half-life of ~11 days and the parameters were consistent with those eliminated in AVF0780g. Following rhuMAb VEGF administration, plasma VEGF concentrations increased an average of three and seven times over baseline concentrations for the 7.5 and 15 mg/kg dose groups, respectively. Interactions between the antineoplastic agents and rhuMAb VEGF were evaluated in a subset (from 5 to 9 patients). There did not appear to be a difference in the disposition of either paclitaxel or carboplatin when each was administered either alone or in combination with rhuMAb VEGF.

In summary, at a dose of >1.0 mg/kg, rhuMAb VEGF disposition was similar in all clinical trials and was characterized by a slow clearance of ~3ml/kg/day and a terminal half-life of ~10 to 14 days allowing of drug administration every 2 to 3 weeks.

### 2.1.3 **Clinical Experience:**

The Head and Neck Oncology program at the University of Chicago has experience with Bevacizumab in an ongoing phase I/II study in patients with poor prognosis head and neck cancer who are able to receive further chemoradiotherapy (NCI Protocol #2630, University of Chicago protocol #11033b). This trial has shown thus far that this agent is safe in this patient population and is able to be effectively combined with chemotherapy and radiation. Our trial utilizes escalating doses of Bevacizumab and includes the following doses: 2.5 mg/kg, 5.0mg/kg, and 10 mg/kg. Bevacizumab is combined with two other chemotherapeutics 5-fluorouracil and hydroxyurea which act as cytotoxic agents as well as radiation sensitizers. The doses used for these agents are 5FU 600-800mg/m<sup>2</sup> continuous IV infusion for five days and HU 500-1000 mg PO BID along with once daily (single fraction) radiation given in week-on week-off schedule. The total number of cycles for this treatment ranges from 6 to 8 depending on the amount of prior radiation received.

To date this trial has accrued 6 patients with no severe toxicities observed for the 2.5 or 5.0 mg/kg dose levels of bevacizumab. Responses have been observed and are consistent with what was expected with the FHX regimen alone.

### Other Clinical Experience:

Study AVF0737g was a Phase I, dose-escalation trial of single and multiple IV administration of bevacizumab in subjects with advanced solid malignancies. Five subjects were enrolled to each of five dose groups (0.1, 0.3, 1.0, 3.0, or 10 mg/kg), for a total of 25 subjects. Bevacizumab was administered as a 90-minute IV infusion on Days 0, 28, 35, and 42. Subjects were followed through Day 72 to obtain pharmacokinetic data during the elimination phase of the drug and for safety follow-up. Bevacizumab appeared to be safe and well tolerated in this population of subjects with advanced malignancies. Dose-limiting toxicities were not observed at weekly doses of up to 10.0 mg/kg. Minimal adverse events were reported on the days of infusion. These included mild headache, fatigue, nausea, and low-grade fever. It is not known whether these events are related to bevacizumab infusion. Bleeding at the tumor site was reported as a serious adverse event in 2 subjects and as a non-serious adverse event in 1 subject. In addition, 3 subjects reported minor hemoptysis and other minor bleeding complications. Objective tumor responses were not observed [6].

A second Phase I study, AVFO761g, was conducted to evaluate multiple administration of bevacizumab in combination with chemotherapy in subjects with advanced malignancies. Carboplatin/paclitaxel, doxorubicin, or 5-FU/leucovorin were given in combination with 3 mg/kg bevacizumab. Four subjects were enrolled to each treatment group. Subjects received up to eight weekly IV doses of bevacizumab and were followed for 30 days after the last bevacizumab infusion. Bevacizumab appeared to be safe and well tolerated in this population of subjects with advanced malignancies receiving concurrent chemotherapy[6].

Three Phase II clinical trials (Studies AVF0757g, AVF0775g, and AVF0780g) have been completed. A Phase II, Genentech-sponsored study in women with metastatic breast cancer (Study AVFO776g) and an NCI-sponsored study in renal cell carcinoma are currently being conducted. In addition, an open-label extension study (Study AVF0778g) is providing continued access to bevacizumab for subjects who received bevacizumab treatment in a Genentech-sponsored bevacizumab cancer study and did not show evidence of disease progression

The efficacy and safety of bevacizumab in subjects with locally advanced non-small cell lung cancer (NSCLC) was studied in a phase II, randomized, multicenter trial. Ninety-nine subjects with advanced NSCLC were randomized to receive either carboplatin/paclitaxel alone or bevacizumab plus carboplatin/paclitaxel. All subjects were to receive up to six cycles of carboplatin/paclitaxel chemotherapy. Subjects randomized to a bevacizumab treatment arm received either 7.5 mg/kg or 15 mg/kg bevacizumab every 3 weeks in addition to carboplatin/paclitaxel. Bevacizumab treatment was to continue until disease progression. Patients who received carboplatin/paclitaxel chemotherapy alone could cross over to bevacizumab upon disease progression [6]

A number of possible safety signals were identified in this study. The most severe of these is life-threatening bleeding. Six subjects experienced a life-threatening bleed during the study; the event was fatal in four cases. Five of the 6 subjects were in the 7.5 mg/kg arm and 1 was in the 15 mg/kg arm. Four cases were clearly hemoptysis; the other two cases may have been either hemoptysis or hematemesis. All six cases may have been caused by tumor-related bleeding originating from pulmonary tumors. A comparison of the prevalence of a number of risk factors in the 6 subjects with life-threatening bleeding with matched controls and with the entire study population identified squamous cell histology and bevacizumab therapy as the most likely risk factors. There was a slight increase in the incidence of thrombotic events among subjects receiving bevacizumab. The other toxicities were thought to be either manageable: (proteinuria, hypertension, and neutropenia) or of minor clinical significance (epistaxis, fever, and rash). One subject developed clinically apparent nephrotic syndrome; this subject underwent a renal biopsy and was diagnosed with cryoglobulinemic glomerulonephritis[6]

Time to disease progression and response rate were determined. Subjects treated with 15 mg/kg bevacizumab plus carboplatin/paclitaxel had higher confirmed response rates and longer times to disease progression compared with subjects treated with carboplatin/paclitaxel alone.

#### *Arterial Thromboembolic Events Associated with Bevacizumab*

In the AVF2107 study, there was a 1% incidence of arterial thromboembolic events (which include myocardial infarction, transient ischemia attack, cerebrovascular accident/stroke and angina/unstable angina) in the IFL + placebo arm versus 3% in the IFL + bevacizumab arm. A pooled analysis of the rate of arterial TE events from 5 randomized studies showed that treatment with Bevacizumab increased the risk of these events two- to three- fold (up to 5%). Furthermore, certain baseline characteristics, specifically age > 65 years and prior arterial TE event, conferred additional risk.

## 2.2 **OSI-774 (Tarceva™)**

### Scientific Background:

A number of human malignancies are associated with aberrant or over expression[7] of the epidermal growth factor receptor (EGFR). Epidermal growth factor, transforming growth factor alpha, and a number of other ligands, bind to the EGFR stimulating autophosphorylation of the intracellular tyrosine kinase domain of the receptor. A variety of intracellular pathways are subsequently activated and these downstream events result in tumor cell proliferation in vitro. It has been postulated that stimulation of tumor cells via this receptor maybe important for both tumor growth and tumor survival in vivo. There is also a considerable body of indirect evidence suggesting that the EGFR and ligands that bind to it play an important role in patients with various malignancies. Detection of over-expression of EGFR in certain human tumors is considered an important prognostic indicator and based on literature, this receptor may

serve as a potential target for therapeutic intervention in several tumor types including non-small cell lung carcinoma, breast carcinoma, as well as a variety of squamous cell carcinomas including head and neck cancer [7-11]. In some instances, over expression of the tumor EGFR has been correlated with both chemoresistance and poor prognosis[12].

These results, as well as preliminary clinical data described below, suggest that the EGF receptor is a potential target for therapy in patients with a variety of human malignancies including head and neck cancer.

### 2.2.1 **OSI-774 EGFR Tyrosine Kinase Inhibitor (TKI): Pre-clinical Data [13]**

OSI-774 is an orally active, potent, selective inhibitor of the EGFR tyrosine kinase. OSI-774 inhibits the human EGFR tyrosine kinase with an  $IC_{50}$  of 2 nM (0.786 ng/mL) in an *in vitro* enzyme assay and reduces EGFR autophosphorylation in intact tumor cells with an  $IC_{50}$  of 20 nM (7.86 ng/mL). OSI-774 inhibits EGF-dependent proliferation of cells at submicromolar concentrations and blocks cell-cycle progression in the  $G_1$  phase.

OSI-774 appears to bind specifically to EGFR. In a study of OSI-774 binding specificity, affinity of OSI-774 for 67 cellular receptors was examined (15). OSI-774 was shown to bind with low affinity to peripheral benzodiazepine ( $IC_{50}$ =2.5  $\mu$ M [980 ng/ml]), adenosine  $A_1$  ( $IC_{50}$ =6.8  $\mu$ M [2700 ng/ml]), and  $\mu$ -opiate ( $IC_{50}$ =7.0  $\mu$ M [2800 ng/ml]) receptors. Binding affinities were 1250-fold higher than the  $IC_{50}$  concentration needed to inhibit purified EGFR tyrosine kinase (2 nM [0.79 ng/ml]). When tested at concentrations up to 1  $\mu$ M (390 ng/ml), no significant inhibition of ligand binding to 64 other neurotransmitter receptors, regulatory binding sites, calcium channels, opioid receptors, or neurotransmitter uptake sites were observed.

Oral administration of OSI-774 (92 mg/kg) to mice reduced the level of EGFR autophosphorylation in human tumor xenografts by >70% for over 12 hours. Daily administration of OSI-774 markedly inhibited the growth of the HN5 human head and neck carcinoma, as well as A431 squamous epidermoid carcinoma xenografts in athymic mice. Nearly complete inhibition of tumor growth during a 20-day treatment regimen was obtained at the highest doses administered.

Data on drug exposure and antitumor responses in human tumor xenograft models (HN5 and A431) were analyzed in order to estimate the plasma concentration of OSI-774 associated with antitumor activity. Based on these efficacy models, the steady-state plasma concentration targeted for clinical trials is projected to be 500 ng/mL.

#### Pharmacokinetics

The total clearance of OSI-774 correlates with hepatic blood flow in dogs and rats given intravenous (IV) doses of  $\leq 1$  mg/kg. In contrast, the total clearance decreases and the plasma drug exposure increases supra-proportionately in rats and dogs given IV doses of >1 mg/kg. *In vitro*, OSI-774 is slowly oxidized by liver microsomes. The majority of the absorbed dose is extensively metabolized in rats and dogs, and only a small amount is excreted as unchanged drug in urine, bile, and feces. The oral bioavailability of an aqueous suspension is 77% in rats and ~88% in dogs. Plasma protein binding of OSI-

774 ranges from 92% to 95% in man, monkey, rat, and mouse and is 85% in the dog. Corrected for protein binding of 95%, at the average plasma concentration responsible for 50% inhibition of tumor growth (oral dose of 10 mg/kg/day in the murine/human tumor xenograft model), the unbound concentration of drug in the plasma is estimated to be 86 nM (34 ng/mL). The estimated unbound concentration of OSI-774 in plasma is consistent (4-fold higher) with the IC<sub>50</sub> for the *in vitro* cellular phosphotyrosine reduction assay and is 43-fold higher than the IC<sub>50</sub> for the *in vitro* (isolated enzyme) tyrosine kinase assay. Finally, OSI-774 plasma protein binding depends on the levels of  $\alpha$ -1-acid glycoprotein (AGP). Thus, AGP might be a significant determinant of pharmacokinetic and possibly pharmacokinetic–pharmacodynamic relationships in patients.

### Toxicology

The major effects attributed to OSI-774 in toxicology studies involve the hepatobiliary, gastrointestinal, renal, and hematopoietic systems, as well as the cornea and skin. In a 1-month study performed in rats, treatment-related diminution in food consumption and weight gain, considered secondary to decreased gastric emptying, were observed at doses of 5 mg/kg/day. In a 6-month study in rats, this same dose resulted in elevations in serum bilirubin and hepatic transaminases, as well as renal papillary necrosis, ovarian atrophy, and hair follicle degeneration. Rats treated for 6 months with 10 mg/kg/day were noted to have increased kidney and adrenal organ weights, as well as evidence of angiectasis, hepatocyte necrosis, and cervical lymph node plasmacytosis. The no observed adverse effect level (NOAEL) in the 6-month rat study was 1 mg/kg/day.

In dogs, OSI-774 produced a low incidence of emesis. In a 1-month study, renal effects characterized by an increase in regenerating proximal tubule cells were observed. In a 12-month study in dogs, doses of 15 mg/kg/day resulted in reduced body weight gain; doses of 50 mg/kg/day were associated with marked toxicity precluding dosing beyond 14 days. At this high dose, gastrointestinal and renal toxicities were observed, as were abnormalities in hepatic function tests. Ocular findings at 50 mg/kg/day included corneal edema, ulceration, and perforation, all of which were reversible upon discontinuation of treatment. No ocular injury was observed in animals receiving the 15 mg/kg/day dose. The NOAEL in the 12-month dog study was 7.5 mg/kg/day.

In an exploratory toxicology study performed in cynomolgus monkeys, emesis and loose stools were observed in animals treated at 100 mg/kg/day for a period of 7 days. Elevations in serum bilirubin were noted in animals treated at 200 mg/kg/day for 7 days. One animal in the 200 mg/kg/day group expired. The cause of this death was not identified at necropsy. Dosing at 400 mg/kg/day was not tolerated beyond 4 days because of dermal toxicity (the appearance of cutaneous lesions) and serum bilirubin elevations.

OSI-774 does not induce microbial or mammalian cell gene mutations *in vitro* and does not produce chromosomal aberrations *in vitro* or *in vivo*. No studies to assess the effects of OSI-774 on reproductive function and teratogenicity or the potential for carcinogenicity have been performed.

OSI-774 in combination with anti-tumor agents cisplatin, doxorubicin, 5-fluorouracil, paclitaxel, vinorelbine and gemcitabine was evaluated in xenograft models. In all cases, the cytoreductive agent was used at an efficacious dose in conjunction with OSI-774 at the ED<sub>50</sub> (9.2 mg/kg/day). No increased morbidity or mortality was recorded in animals treated with the addition of OSI-774 compared to the cytotoxic agent alone, regardless of whether OSI-774 was administered before, concurrently, or after treatment with the cytostatic agent. In addition, no antagonism of therapeutic efficacy of the six conventional cytoreductive agents was detected. Drug combination studies did not identify any incompatibilities, indicating that OSI-774 can appreciably enhance the anti-tumor effects of agents such as cisplatin, doxorubicin, and gemcitabine in the HN5 head and neck carcinoma model.

### 2.2.2 **OSI-774 EGFR Tyrosine Kinase Inhibitor: Clinical Data**

Fourteen clinical trials have been initiated to study OSI-774. These include 8 phase 1 trials, of which 5 have been completed. Three of the completed phase 1 trials examined safety and pharmacokinetics among healthy volunteers. Two phase 1 trials tested escalating doses of OSI-774 in patients with advanced solid tumors. Three additional phase 1 trials are studying combination therapies of either OSI-774 plus docetaxel, paclitaxel/carboplatin, or gemcitabine/cisplatin in patients with advanced malignancies or newly diagnosed tumors. Five phase 2 studies are examining OSI-774 as a single agent in patients with advanced ovarian, squamous cell carcinoma of the head and neck, advanced non-small cell lung, and advanced breast cancers.

**Healthy Volunteer Studies.** OSI-774 was administered to healthy human volunteers before evaluations in cancer patients. Administration of a wide range of single oral doses of OSI-774 (10 to 1,000 mg) resulted in mild to moderate toxicities, including headache and a mild, diffuse, erythematous rash at the highest dose. However, all patients treated continuously with OSI-774 400 mg/d, in two divided daily doses, developed a severe papulopustular dermatitis that involved the face, scalp, chest, back, and arms. As a result, treatment was discontinued in all patients after a maximum of nine doses. The rash resolved slowly thereafter. Other, less profound effects included diarrhea, mucositis, and transient elevation of hepatic transaminases. Pharmacokinetic studies revealed drug accumulation with protracted daily treatment, which was not predicted from single-dose studies.

A single phase 3 study was recently initiated to study OSI-774 in combination with carboplatin and paclitaxel in patients with advanced non-small cell lung cancer.

**Phase I Trials in Patients with Advanced Cancer.** In this first clinical trial in patients with advanced or refractory cancer, 27 patients received weekly doses of OSI-774 ranging from 100 to 1600 mg/wk on Days 1, 8, and 15 of a 28-day cycle. This study closed for enrollment without defining the maximum tolerated dose (MTD). Preliminary data indicate that the most common adverse events attributed to OSI-774 were diarrhea and rash. All but two events were mild to moderate in severity. There was one reported case of severe diarrhea (at the 1000 mg/wk dose level) and one case of severe rash reported at the highest (1600 mg/wk) dose level. Four patients had disease stabilization for >6 months.

In the second phase 1 study, OSI-774 was administered according to three different daily dosing schedules (16). Patients with advanced solid malignancies were treated with escalating doses of OSI-774 in three study parts (A to C) to evaluate progressively longer treatment intervals. Part A patients received OSI-774 25 to 100 mg once daily, for 3 days each week, for 3 weeks every 4 weeks. Part B patients received OSI-774 doses ranging from 50 to 200 mg given once daily for 3 weeks every 4 weeks to establish the maximum tolerated dose (MTD). In part C, patients received this MTD on a continuous, uninterrupted schedule. The pharmacokinetics of OSI-774 and its O-demethylated metabolite, OSI-420, were characterized. Forty patients received a total of 123 28-day courses of OSI-774. No severe toxicities precluded dose escalation of OSI-774 from 25 to 100 mg/d in part A. In part B, the incidence of severe diarrhea and/or cutaneous toxicity was unacceptably high at OSI-774 doses exceeding 150 mg/d. Uninterrupted, daily administration of OSI-774 150 mg/d represented the MTD on a protracted daily schedule. The pharmacokinetics of OSI-774 were dose independent; repetitive daily treatment did not result in drug accumulation (at 150 mg/d [average]: minimum steady-state plasma concentration, 1.20 +/- 0.62 microg/mL; clearance rate, 6.33 +/- 6.41 L/h; elimination half-life, 24.4 +/- 14.6 hours; volume of distribution, 136.4 +/- 93.1 L; area under the plasma concentration-time curve for OSI-420 relative to OSI-774, 0.12 +/- 0.12 microg/h/mL). The recommended dose for OSI-774 administered orally on a daily, continuous schedule is 150 mg/d.

**Pharmacokinetic Data.** OSI-774 pharmacokinetics were examined in patients with advanced solid tumors who were treated daily for 21 days. Plasma samples were collected on days 1, 3, and 21 for analysis (15).

Inter-subject variability was moderate at the 150-mg/d dose level, as indicated by coefficient of variation values of 64% for day 1 AUC<sub>0-24</sub> and C<sub>max</sub>.

**Phase II Clinical Trials.** In a phase 2 study, previously treatment patients with EGFR-expressing metastatic ovarian carcinoma were initially administered a daily dose of 150-mg OSI-774 (17). Dosage was increased or decreased based on observations of toxicity. The mean daily oral dose was 158 mg and the mean duration of OSI-774 administration was 79 days. Tumor responses were documented using CT scans and bi-dimensional measurement of marker lesions beginning at 8 weeks after the start of treatment. Of the 34 patients enrolled in this study, 31 had evaluable disease. Objective partial responses were documented in three patients. One of these PRs was documented at week 8, but no follow-up images were available. Partial

responses in the other two patients were documented to last 5 and 6 months. Stable disease was documented in three patients for 5, 5, and 6 months, while an additional twelve patients had stable disease at week 8 without further imaging studies available to document the duration of response. Median time to disease progression was 62 days, and the median survival was 242 days. The most commonly reported related adverse events were rash (67.6%) and diarrhea (38.2%). Nausea and headache were reported in 35.3% and 23.5% of patients, respectively. Dry skin and dry eye were noted in 26.5% and 11.8%, respectively.

In a phase 2 study of 114 previously treated patients with squamous cell carcinoma of the head and neck, 78 patients were evaluable for objective response (18). Of these patients, 10 (13%) were observed to have partial responses, 23 (29%) had stable disease, and 45 (58%) had progressive disease. Median time to disease progression was 64 days, median survival was 174 days, and one year survival was 24%.

An additional phase 2 study examined 56 patients with EGFR-positive non-small cell lung cancer, who were previously treated with platinum-based chemotherapy (19). Seven patients achieved a partial response at 8 weeks, six confirmed at 12 weeks (11%), 19 patients (34%) had stable disease, and 31 patients had tumor progression. All six responders developed cutaneous rash versus 15 of 19 with stable disease, and 23 of 31 with disease progression. Across the clinical trials the most common toxicities were rash/dermatologic changes, diarrhea, nausea/vomiting, headache, and fatigue. Based on the ocular changes observed in the 12-month toxicology study in dogs, screening and follow-up ophthalmologic examinations were instituted in the Phase 1 and 2 trials in cancer patients. The only reported OSI-774-related ocular events were an episode of mild watery eyes in a patient treated on the weekly study and an episode of moderate corneal edema/keratitis attributed to wearing contact lenses in a second patient. The event resolved with temporary discontinuation of both OSI-774 dosing and contact lens use; there was no recurrence of symptoms with OSI-774 rechallenge in the absence of continued use of contact lenses. There was no demonstrable correlation between responses and level of EGFR expression .

### 2.3 **Head and Neck Cancer**

Head and neck cancer comprises a heterogenous group of diseases that may extend from the oropharynx to the cervical esophagus. These patients usually have a history of chronic alcohol and tobacco use resulting in multiple carcinogen exposures to the entire aerodigestive tract. Therefore, despite treatment with curative intent, the annual risk of developing a second primary malignancy remains 3-7%. Distant metastases are also a site of failure in 20-30% of patients presenting initially with stage III/IV disease.

In the year 2001 alone, over 40,000 people will be diagnosed with head and neck in the United States resulting in approximately 11,800 deaths [14]. Squamous cell carcinoma represents > 90% of all head and neck carcinomas. Approximately 60% of patients will represent with locally advanced disease (AJCC stage III/IV), classified as large tumors extending into surrounding structures, with regional lymph node involvement, and/or distant metastases (the latter being rare at diagnosis).[15]

Previously, the standard of care has been surgery, if resectable, and/or radiotherapy. Despite aggressive local therapy the 5-year survival is < 30%. Hence investigative studies have attempted to improve both locoregional control and distant disease progression. Chemotherapy has since been incorporated as a radiation sensitizer and continues to be investigated in the induction (neoadjuvant) and adjuvant setting. A large meta-analysis, Meta-Analysis of Chemotherapy in Head and Neck Cancer (MACH-NC), evaluated 63 trials involving over 10,000 patients and determined an absolute benefit of 7% and 8% for concomitant chemoradiotherapy at 2 and 5 years ( $p=0.16$ ), and an overall benefit of 4%. Consequently, it is generally accepted that the management of locally advanced SCCHN (ie, stage III and nonmetastatic stage IV disease) should involve a combined modality approach in patients with a good performance status. [16] [15]

#### Recurrent Head and Neck Cancer: Standard of Care

Chemotherapy was initially institutionalized in the treatment of head and neck cancer in the palliative care setting of recurrent or metastatic disease. If untreated, the survival rate is dismal with a median survival of only 4 months [17]. Classic chemotherapy agents in recurrent and metastatic head and neck cancer have included 5-Fluorouracil, methotrexate, ifosfamide, and the platinum and taxane analogs with single-agent response rates of 20-40%. Overall, combination chemotherapy regimens have provided superior response rates in comparison to single agents. The standard combination has been cisplatin/5-FU (PF). [15, 18, 19]

A large phase III randomized trial of the combination regimen of cisplatin/5-FU vs. each respective agent was initiated by Jacobs and colleagues and determined an improved overall response rate for this doublet regimen of 32% ( $p=0.035$ ) vs. cisplatin (17%) vs. 5-FU (13%) in advanced head and neck cancer. [18]The median time to progression (TTP) is approximately 2 months for the combination ( $p=0.023$ ) and remains less than satisfactory. The median survival in all three arms was approximately 5.7 months ( $p=0.489$ ). Although the combination of cisplatin/5-FU was deemed to be superior in response, it was at the expense of increased grade 3/4 vomiting (35%) in comparison to the single agent arm of cisplatin (18%,  $p=0.02$ ).

A large, randomized phase III trial conducted by the Southwest Oncology Group (SWOG) ascertained that the response rate of cisplatin/5-FU (32%) remained superior to that of carboplatin/5-FU (21%) and exceeded single-agent methotrexate (10%).[18]The median duration of response and survival were similar in all treatment arms.

Thus, platinum-based combination regimens have evident superior activity in combination, but are often at the expense of increased toxicity in patients who often have underlying chronic treatment-related sequelae and other coexisting morbidities[20]

The failure of these phase III studies was an inability to establish any benefit of survival in a group of poor-prognosis patients in which response was the primary endpoint rather than overall survival. Chemotherapy has classically been the only option for patients with unresectable recurrent and/or metastatic head and neck cancer. However, the lack

of improved survival justifies the continued investigative pursuit of novel mechanisms for improved cytotoxic activity.

## 2.4 **Rationale**

Patients with unresectable recurrent or metastatic disease have few alternatives other than palliative chemotherapy. Response rates are <30% with a median survival of 6-8 months. Hence, cytotoxic therapies have limited activity in these heavily pretreated, poor-prognosis patients. Novel molecular targets involved in signal transduction include the epidermal growth factor receptor (EGFR) and the vascular endothelial growth factor (VEGF) receptor, which have a role in DNA synthesis and angiogenesis.

Bevacizumab is a monoclonal antibody against VEGF. *In vivo* studies have demonstrated a statistically significant correlation with the presence of metastatic disease and risk of recurrence with degree of VEGF expression. VEGF has a primary role in angiogenesis, microvessel density, and vascular permeability.

Epidermal growth factor is overexpressed in >80% of squamous cell carcinomas [11]. Overexpression of transforming growth factor alpha (TGF- $\alpha$ ) and its specific receptor, epidermal growth factor, is associated with poor prognosis and aggressive disease. OSI-774 is an oral quinazoline epidermal growth factor receptor tyrosine kinase inhibitor with promising anti-tumor activity in phase I/II clinical trials in previously treated head and neck cancer patients [21, 22]. OSI-774 has an IC<sub>50</sub> of 2nM and selectively decreases autophosphorylation in tumor cells. We have conducted a phase II investigation of a similar compound (NCI #1721: ZD-1839) with evidence of modest single-agent activity.

Eventual resistance to EGFR inhibitors has been well established but largely due to an unknown mechanism. Previous *in vitro* studies have demonstrated upregulation of VEGF expression by activation of EGFR. A correlation with resistance to anti-EGFR inhibitors and increased levels (two-fold) of VEGF mRNA in epidermoid cell line strains has been established in *in vivo*. Although VEGF levels were eventually down-regulated *in vitro* by as much as 50% following administration of an EGFR inhibitor, resistant epidermoid cell lines continued to demonstrate 2 and 4-fold increased VEGF levels in comparison to the parent cell line. Hence, combined inhibition of both EGF and VEGF receptors should result theoretically in increased apoptosis, decreased cell proliferation and vascular permeability, and improved cytostatic activity in comparison to its respective activity as a single agent. As cytostatic agents, the intent is to prevent further tumor growth with a goal of disease stabilization. However, with a decrease in cell proliferation and increased apoptosis, a reduction in tumor mass may develop. No study to date has evaluated this combination in the setting of head and neck cancer. Ideally, if dual inhibition of EGF and VEGF demonstrates promising activity in these poor prognosis patients, combined activity with a cytotoxic agent may be a future consideration.

## 3. PATIENT SELECTION

### 3.1 **Eligibility Criteria**

- 3.1.1 Patients must have histologically or cytologically confirmed Squamous Cell Cancer of the Head and Neck either (a) metastatic or (b) recurrent, judged incurable by surgery or radiation.
- 3.1.2 Therapeutic history in conformance with the following:  
No more than one prior regimen for recurrent disease;  
Prior irradiation allowed however, must have been completed 4 weeks prior to entry onto study.  
No prior EGFR-based or VEGFR-based therapy for recurrent disease;  
Chemotherapy must have been completed at least 4 weeks prior to enrollment.
- 3.1.3 Because no dosing or adverse event data are currently available on the use of Bevacizumab in combination with OSI-774 (Tarceva™) in patients <18 years of age, children are excluded from this study, but will be eligible for future pediatric phase 1 combination trials.
- 3.1.4 ECOG performance status  $\leq 2$  (Karnofsky  $\geq 60\%$ , see Appendix B).
- 3.1.5 Life expectancy of greater than 12 weeks
- 3.1.6 Patients must have normal organ and marrow function as defined below:
- |                             |  |
|-----------------------------|--|
| - INR                       | <1.5   |
| - leukocytes                | $\geq 3,000/\mu\text{l}$                         |
| - absolute neutrophil count | $\geq 1,500/\mu\text{l}$                         |
| - platelets                 | $\geq 100,000/\mu\text{l}$                       |
| - total bilirubin           | within normal institutional limits               |
| - AST(SGOT)/ALT(SGPT)       | $\geq 2.5$ X institutional upper limit of normal |
| - creatinine                | within normal institutional limits               |
- OR
- |                        |  |
|------------------------|--|
| - creatinine clearance | $\geq 60$ mL/min/1.73 m <sup>2</sup> for patients with creatinine levels above institutional normal. |
|------------------------|--|
- 3.1.7 Ability to understand and the willingness to sign a written informed consent document.
- 3.1.8 The effects of Bevacizumab and OSI-774 (Tarceva™) on the developing human fetus are unknown. For this reason women of childbearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.
- 3.1.9 Patients must have measurable disease.

## 3.2 **Exclusion Criteria**

- 3.2.1 Patients who have had chemotherapy or radiotherapy within 4 weeks (6 weeks for nitrosoureas or mitomycin C) prior to entering the study or those who have not recovered from adverse events due to agents administered more than 4 weeks earlier.
- 3.2.2 Patients may not be receiving any other investigational agents.
- 3.2.3 Patients with known brain metastases should be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events.
- 3.2.4 Patients with tumor involvement encasing a major artery or vein or deemed to have too close proximity to a major artery or vein.
- 3.2.5 History of allergic reactions attributed to compounds of similar chemical or biologic composition to rhuMAb VEGF or other agents used in the study.
- 3.2.6 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, hypertension, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.
- 3.2.7 Pregnant women are excluded from this study because Bevacizumab and OSI-774 are agents with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with Bevacizumab and OSI-774, breastfeeding should be discontinued if the mother is treated with either agent. These potential risks may also apply to other agents used in this study.

Because patients with immune deficiency are at increased risk of lethal infections when treated with marrow-suppressive therapy, HIV-positive patients receiving combination anti-retroviral therapy are excluded from the study because of possible pharmacokinetic interactions with Bevacizumab or OSI-774 or other agents administered during the study. Appropriate studies will be undertaken in patients receiving combination anti-retroviral therapy when indicated.

- 3.2.8 Significant toxicities including hemorrhage, thrombosis, hypertension, poor wound healing, and nephrotic syndrome have been noted in trials giving bevacizumab in combination with chemotherapy. Thus, patients will be excluded with any history of a bleeding diathesis, deep venous thrombosis, chronic use of aspirin or other non-steroidal anti-inflammatory agents, non-healing wounds, major surgery within 4 weeks, IV catheter placement less than

24 hours before Bevacizumab treatment, uncontrolled hypertension, or significant renal impairment (patient's with > trace proteinuria should have a 24 hour urine collection and only those with < .5 grams/24 hours can be included).

- 3.2.9 Patients with significant ophthalmologic abnormalities, including: severe dry eye syndrome, kerato conjunctivitis sicca, sjogren's syndrome, severe exposure keratopathy, disorders that might increase the risk for epithelium-related complications (e.g. bullous keratopathy, aniridia, severe chemical burns, neutrophilic keratitis)

Note: patients with mild forms of any of the above, an asymptomatic history, or a normal ophthalmologic examination may be considered for inclusion at the discretion of the investigator. An ophthalmologic exam is not needed prior to this study unless clinically indicated.

Patients with treatable conditions (e.g. infectious keratitis/conjunctivitis, allergic conjunctivitis) may be reevaluated for study eligibility after treatment or resolution of the condition.

Use of contact lenses during the course of this trial may increase the risk of corneal complications and will be strongly discouraged.

- 3.2.10 Chronic daily treatment with aspirin ( $\geq 325$  mg/d) or nonsteroidal anti-inflammatory medications.
- 3.2.11 The use of coumadin, heparin and low molecular weight heparins are contraindicated and are not allowed during therapy.
- 3.2.12 Current or recent (within 1 month) use of a thrombolytic agent or full-dose anticoagulant (except as required to maintain patency of preexisting, permanent indwelling intravenous catheters. For subjects receiving warfarin, INR should be  $\leq 1.5$ ).
- 3.2.13 Serious, non-healing wound ulcer, or bone fracture
- 3.2.14 Major surgical procedure, open biopsy or significant traumatic injury within 28 days prior to Day 1
- 3.2.15 Active infection requiring parenteral antibiotics on Day 1
- 3.2.16 History or clinical evidence of CNS disease, including primary brain tumor, seizures not controlled with standard medical therapy, any brain metastasis, or history of stroke.
- 3.2.17 Patients with know hypersensitivity of Chinese hamster ovary cell products or other recombinant human antibodies.

- 3.2.18 Patients with clinically significant cardiovascular disease (e.g. uncontrolled hypertension, myocardial infarction, unstable angina), New York Heart Association grade II or greater congestive heart failure, serious cardiac arrhythmia requiring medication, or grade II or greater peripheral vascular disease within 1 year prior to study entry.
- 3.2.19 Patients with recent (within 6 months) arterial thromboembolic events including transient ischemic attack (TIA), cerebrovascular accident (CVA), unstable angina, or myocardial infarction (MI) will be excluded. Patients with clinically significant peripheral artery disease should also be excluded.

### 3.3 Inclusion of Women and Minorities

Both men and women of all ethnic groups are eligible for this trial. The proposed study population is illustrated in the table below.

Gender	Race/Ethnicity					Total
	White, not of Hispanic Origin	Black, not of Hispanic Origin	Hispanic	Asian or Pacific Islander	Unknown	
Male	18	12	4	1	2	37
Female	5	3	1	0	0	9
Total	23	15	5	1	2	46

## 4. TREATMENT PLAN

### 4.1 Agent Administration

Treatment will be administered on an outpatient basis. Expected adverse events and appropriate dose modifications for Bevacizumab and OSI-774 (Tarceva™) are described in Section 5. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

This is a two-part trial with a phase I portion and a phase II portion. The schedule of drug administration and dose depends upon the phase of the trial. For patients who are enrolled on the phase I portion, the dose escalation will proceed as stated in the table below.

The following is a schematic representation of the above-described process:

<b>Dose-Escalation Schedule – Phase I portion</b>			
<b>Dose Level</b>	<b>Dose*</b>		
	<i>Bevacizumab mg/kg</i>	<i>OSI-774 (Tarceva™) mg</i>	
Level 1	5.0	150	
Level 2	10.0	150	
Level 3	15.0	150	
Level 4 (phase II dose)	15.0	150	

*\*Doses are stated as exact dose in units (e.g., mg/kg, and mg) rather than as a percentage.*

**One Treatment Cycle is equal to 21-days (3 weeks). There will be 3-6 patients entered onto each cohort for the phase I portion.**

#### **4.1.1 Bevacizumab-Phase 1 Portion**

Bevacizumab (rhuMAb VEGF) will be given in escalating doses (5.0 mg/kg to 15.0 mg/kg) for each level 1-3 as indicated in table above. Bevacizumab will be given on Day 1 of each 21-day cycle as an IV infusion in the outpatient setting.

The dose of bevacizumab will be escalated as outlined in section 4.1. Dose escalation will proceed within each cohort according to the following scheme: Accrual for the next dose escalation cohort will proceed as long as no dose-limiting toxicities are encountered in the previous cohort during cycle 1 of treatment. Please see section 4.3 for definition of DLT.

#### **4.1.2 OSI-774 (Tarceva™)-Phase 1 Portion**

OSI-774 will be taken as a by mouth (PO) medication in pill form in the outpatient setting on days 1-21 of each 21-day cycle. Patients will be provided with a study calendar/diary to record their self-administration of OSI-774.

The dose of OSI-774 will be 150 mg PO QD x 21 days\*. No escalation of this dose is planned.

\*Prescribed daily doses to be taken, preferably in the morning, with up to 200 ml of water. OSI-774 should be taken at least 1 our before or 2 hours after the ingestion of any food or other medications.

#### **4.2 Agent Administration-Phase II Portion**

Patients in the phase II portion will be randomized to one of two arms (“A” and “B”) after an informed consent is signed (this randomization will be carried out in the Cancer Clinical Trials Office at the time of registration). This randomization is for the cycle 1 only. After completion of cycle 1 both groups will be treated as described below. The length of cycle 1 will be 28 days while the length of all subsequent cycles will be 21 days. Arm A of this trial will include patients who will be randomly assigned to receive OSI-774 alone days 1-28 with Bevacizumab on day 15. Arm B of this trial will include patients who will randomly be assigned to receive OSI-774 starting from day 1-28 with Bevacizumab on Day 1.

**4.2.1 Bevacizumab-Phase II Portion**

Bevacizumab (rhuMAb VEGF) will be given at the phase II determined dose of 15.0 mg/kg (see section 11.0 for rules regarding). As in the phase I portion bevacizumab will be given as an IV infusion in the outpatient setting. Bevacizumab will be given on Day 1 of each 21-day cycle except for those patients randomized to Arm A of the first cycle. As described above, Arm A patients will receive bevacizumab on Day 15. Again, after the first cycle all patients will receive bevacizumab on Day 1.

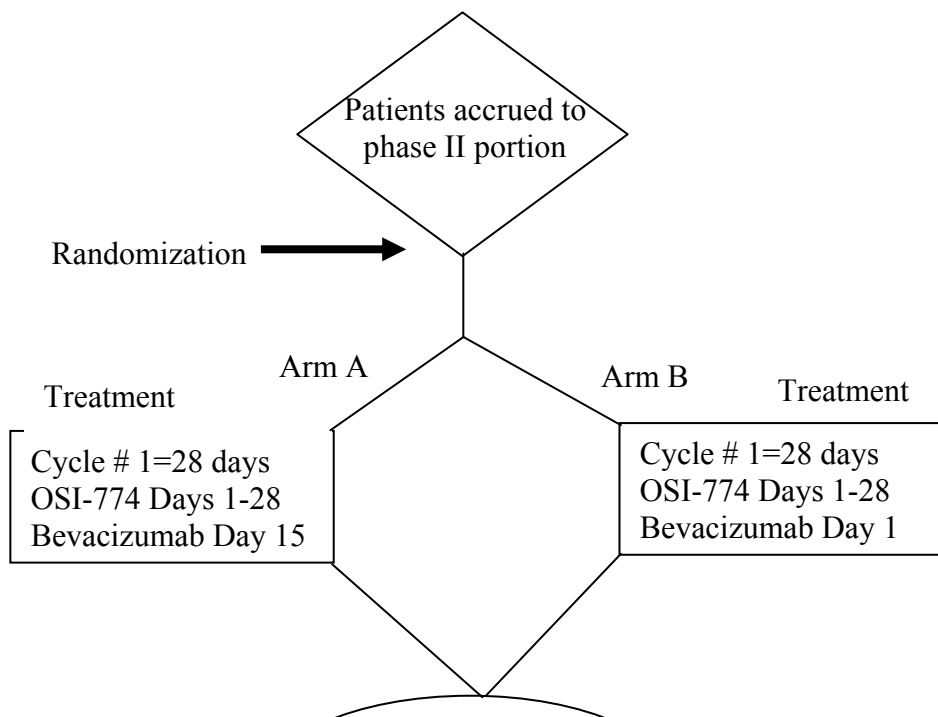
**4.2.2 OSI-774 (Tarceva™)-Phase II Portion**

OSI-774 will be taken as a by mouth (PO) medication in pill form in the outpatient setting on days 1-21 of each 21-day cycle. This applies to patients randomized to Arm A or B for the first cycle.

The dose of OSI-774 will be 150 mg PO QD x 21 days\*. No escalation of this dose is planned.

\*Prescribed daily doses to be taken, preferably in the morning, with up to 200 ml of water. OSI-774 should be taken at least 1 our before or 2 hours after the ingestion of any food or other medications.

**4.2.2 Flow Chart for Phase II Portion:**





#### 4.3 **Definition of Dose-Limiting Toxicity**

Patients will be evaluated throughout the course of the trial for evidence of acute as well as delayed toxicities. The following toxicities, if attributed to OSI-774 or Bevacizumab, will be considered dose-limiting.

- Grade 3 or grade 4 neutropenia
- Thrombocytopenia, with a platelet count of  $< 50,000/\text{mm}^3$
- Grade 3 or 4 nausea, vomiting, and diarrhea not controlled by optimal anti-emetic or anti-diarrheal
- Grade 3 or greater non-hematologic toxicities, with the exception of:
  - Alopecia
  - Fatigue
  - Hypertension that is medically controlled
- Inability, due to any toxicity, to complete a total of one (1) dosing schedule.
- Delay of the start of the next therapy cycle for greater than 7 days due to toxicity or adverse event. Treatment delays, with OSI-774, greater than 7 days.
- Development of nephrotic syndrome or severe hemorrhage

Management and dose modifications associated with the above adverse events are outlined in Section 5.2.

Dose escalation will proceed within each cohort according to the following scheme. Accrual for the next dose escalation cohort will proceed as long as no dose-limiting toxicities are encountered in the previous cohort during cycle 1 of treatment. DLT is defined above. If DLT does occur please see the table below.

Number of Patients with DLT at a Given Dose Level	Escalation Decision Rule
0 out of 3	Enter 3 patients at the next dose level.
$\geq 2$	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
1 out of 3	Enter at least 3 more patients at this dose level. <ul style="list-style-type: none"> <li>• If 0 of these 3 patients experience DLT, proceed to the next dose level.</li> <li>• If 1 or more of this group suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.</li> </ul>
$\leq 1$ out of 6 at highest dose level below the maximally administered dose	This is generally the recommended phase 2 dose. At least 6 patients must be entered at the recommended phase 2 dose.

#### 4.4 Supportive Care Guidelines

Central Access Device- is not required, but if already present or desired per patient wishes, one may be placed and utilized for intravenous infusions of drug or other supportive measures (e.g. blood transfusions).

Antiemetic Medication- may be used per investigator discretion.

Growth Factors- the effects of these medications are not known to lower white blood cell counts, thus the routine use of growth factors is not recommended. In the case of a patient with febrile neutropenia, CSF's may be utilized per investigator discretion. The use of hematopoietic growth factors (e.g. erythropoietin) may be utilized per investigator discretion.

Corticosteroids-the use of corticosteroids as premedication for bevacizumab administration has not been needed in past studies. In the event of an infusional related event, the infusion should be stopped and restarted at a slower rate. At the discretion of the treating MD corticosteroids may be employed if it is felt that they are needed. This should be given as 100 mg IVP methylprednisolone or its equivalent.

Pain Medications- The use of NSAIDS are prohibited given the potential interaction with bevacizumab.

### Management of potential infusional and allergic reactions to Bevacizumab-

Allergic reactions may occur during or following administration of Bevacizumab. Vital signs will be checked and recorded prior to the administration of bevacizumab, midway through the infusion, and 30 minutes following the end of the infusion.

The initial bevacizumab dose should be administered over a minimum of 90 minutes. If no adverse reactions occur, the second dose should be administered over a minimum of 60 minutes. Again, if no adverse reactions occur, the third and subsequent doses should be administered over a minimum of 30 minutes. If infusion-related adverse reactions occur, subsequent infusions should be administered over the shortest period that is well-tolerated. Patients may receive premedication with Benadryl 25 to 50 mg IV 30 minutes prior to bevacizumab if the patient has experienced infusional reactions.

Allergic reactions may occur during or following bevacizumab administration. As a routine precaution, patients in this study will be observed closely for any potential adverse events by the medical staff from the start of the bevacizumab infusion until at least one hour following the end of the infusion in an area with resuscitation equipment and other agents (prednisone, epinephrine, etc) available. Should an allergic or infusion reaction occur, the patient must be treated according to the best available medical practices. Patients must be instructed to report any delayed reactions to their doctor immediately.

### Anti-Diarrheal-

All patients should be instructed to begin taking loperamide at the earliest signs of diarrhea. Patients will be instructed to begin taking loperamide at the earliest signs of (1) a poorly formed or loose stool, (2) the occurrence of 1 to 2 more bowel movements than usual in one day, or (3) unusually high volume of stool. Loperamide should be taken in the following manner: 4 mg at the first onset of diarrhea, then 2 mg every two hours around the clock until diarrhea-free for at least 12 hours. Patients should not exceed 8 tablets in a 24-hour period. Patients may take 4 mg of loperamide every four hours during the night. Additional antidiarrheal measures may be used at the discretion of the treating physician.

Treatment of OSI-774 Related Skin Rash -In some patients, this rash appeared to be treatable with standard acne therapies, including topical and oral antibiotics used to treat acne. Anecdotal reports of improvement have occurred with any of the following: minocycline, topical tetracycline, topical clindamycin, topical silver sulfadiazine, diphenhydramine, oral prednisone (short course). Alternatively, minocycline 200 mg PO (loading dose) followed by 100 mg PO BID x 7-10 days may be used.

#### 4.5 **Duration of Therapy**

In the absence of treatment delays due to adverse events, treatment may continue for an unlimited number of cycles or until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

### **5. EXPECTED ADVERSE EVENTS/DOSE MODIFICATIONS**

#### 5.1 **Expected Adverse Events**

##### 5.1.1 **Bevacizumab**

Please see section 6.1.7

##### 5.1.2 **OSI-774**

Based on clinical results, nausea, headache, emesis, fatigue, diarrhea, and papula-pustular dermatosis may occur following exposure to OSI-774. The severity of the dermatosis has been variable. Adverse event data reveal that rash or dermatosis (CTC grade 1-3) has been observed during the first several days of treatment in many subjects (~50 %) and has been observed to diminish in severity after 4 weeks on treatment. The use of topical agents, diphenhydramine, corticosteroids and oral antibiotics (tetracycline) has been instituted in some patients with variable results. In a few subjects with severe rash, treatment was discontinued or the study drug dose reduced. The etiologic basis for the rash is still unknown but has been postulated to be related to the underlying mechanism of action of OSI-774.

Diarrhea and nausea have been commonly observed (~50% of subjects). Both adverse events have been transient in nature and generally have not been a cause for dose reduction. In most subjects diarrhea involved increased number of bowel movements (grade 1 to 2 diarrhea). This side effect is well controlled in most patients by either the use of loperamide or dose reduction. All ongoing clinical studies recommend the institution of therapy with loperamide. As of June 2001, no significant drug interactions have been noted with OSI-774 and loperamide.

Other common toxicities, which were study drug-related included headache, nausea, vomiting, dry skin, pruritis, fatigue, dry mouth and dry eyes.

Based on results of Phase I studies in normal volunteers and the toxicologic results in dogs dosed at 50 mg/kg/day, frequent ophthalmologic examinations were included in some subsequent Phase I and II studies. Based on the clinical experience to date, and the lack of significant ophthalmological findings, these examinations are being reduced in recently initiated protocols, except where patients report ocular symptoms.

Fertility and teratology studies with OSI-774 have not been conducted, and safety for women of child-bearing capacity cannot be implied from the existing data. OSI-774 has not been tested for carcinogenic activity in a lifetime rodent bioassay.

OSI-774 can also cause pulmonary events, specifically interstitial pneumonia and pneumonitis. Patients with new onset or worsening dyspnea, cough and/or fever should be promptly evaluated, closely monitored, and supported as clinically dictated. OSI-774 should be temporarily discontinued pending diagnosis and permanently discontinued if diagnosis is confirmed and considered to be related to the agent.

## 5.2 Dosing Delays/Dose Modifications

Both agents will be held in the event of Grade 3 or 4 toxicity and patients will be evaluated weekly until resolution to  $\leq$  grade 1. **Those patients who experience grade 3 toxicity that is either self-limiting, medically controllable or includes alopecia or fatigue will not be considered in the above statement and may continue taking medication.** If a period of greater than 3 weeks occurs before resolution to  $\leq$  grade 1, then the patient will be taken off study. At that time dosing may re-start at either a reduced dose or the same dose as the following text describes. The following sections (5.2.1 and 5.2.2) deal with the known toxicities that may occur for each agent and are listed as specific entities to help the investigator.

### 5.2.1 **Bevacizumab (rhuMAb VEGF)**

There will be no dose modification of bevacizumab in this study, however the dose will be held for the following reasons as these are the known toxicities of this agent:

- **Proteinuria:** Any subject who develops new proteinuria (greater than 1 plus on a urinalysis) will undergo additional testing, consisting of a 24-hour urine collection for total protein and creatinine clearance, urine protein electrophoresis, and urine protein/creatinine ratio. Subjects who develop > 2 g proteinuria/24 hr during the study will not receive additional doses of Bevacizumab unless the proteinuria improves to <2 g/24 hr.
- **Bleeding:**  
Minor bleeding: treatment may continue  
Moderate or major bleeding requiring transfusion or hospitalization or medical intervention should result in discontinuation of therapy
- **Thrombosis:** Any thrombotic events requiring systemic anticoagulation should lead to discontinuation of therapy
- **Allergy:** Grade 3/4 allergic reactions should lead to removal of the patient from bevacizumab therapy. Patients with grade 2 allergic reactions should be carefully assessed for potential risk of serious or life-threatening reactions to re-exposure to the antibody.
- It should be noted that interruption of bevacizumab for these reasons will not preclude the patient from continuing to receive OSI-774.
- PT/INR > 1.5 or PTT > 1.5 X the ULN for the institution.
- **Elevated Liver Function Tests:** Liver function tests (LFT) should be monitored prior to each bevacizumab administration. Bevacizumab should be withheld in the event of  $\geq$  Grade 3 bilirubin, SGOT and/or SGPT elevations and should not resume until the abnormalities have recovered to  $\leq$  Grade 1. If LFT elevations recur with retreatment, bevacizumab should be permanently discontinued.
- **Reversible Posterior Leukencephalopathy Syndrome (RPLS) related:**  
Bevacizumab should be held in patients with symptoms/signs suggestive of RPLS, pending work-up and management including control of blood pressure. Bevacizumab should be discontinued upon diagnosis of RPLS.
- Arterial thromboembolic events (including cerebrovascular ischemia,

cardiac ischemia/infarction, peripheral or visceral arterial ischemia.):

- $\geq$  Grade 3: discontinue bevacizumab
- Grade 2, if new or worsened since bevacizumab therapy: discontinue bevacizumab

### 5.2.2 **OSI-774 (Tarceva™)**

An attempt will be made to manage all non-dose-limiting toxicities with a dose-reduction as described below in the table. Interruption of dosing with OSI-774, will occur only after dose reductions and appropriate medical care of adverse events have been shown to be unsuccessful, and following discussion with the principal investigator. Therapy with Bevacizumab may continue during these periods.

For toxicity that is thought to be related to OSI-774, the daily dose of OSI-774 will be decreased according to the schedule displayed in the Table 1. The actual dose reduction is listed in table 2. If there is reason to believe that a patient may benefit from a further dose reduction the PI will contact the CTEP monitor to discuss and a joint decision will be made.

a) Grade 2 diarrhea and skin rash do not require temporary discontinuation of treatment as these toxicities may improve despite continued treatment. For Grade 2 skin rashes and diarrhea that are unacceptable to the patient for symptomatic reasons, OSI-774 should be temporarily held until resolution  $\leq$  grade 1 and subsequently re-started at the same dose. If symptomatic grade 2 diarrhea and skin rash recur after re-instituting treatment at the 150 mg daily dose and require temporary discontinuation, treatment should be held until resolution to  $\leq$  grade 1 and re-instituted at a reduced dose (see Table 1). For grade 2 non-hematological toxicity that is medically concerning (e.g. prolonged cardiac, pulmonary, or neurotoxicity), treatment should be held until resolution  $\leq$  grade 1 and re-instituted at a reduced dose.

b) For Grade 3 and 4 toxicity, discontinue treatment and re-evaluate at least weekly until resolution to  $\leq$  grade 1 and then re-institute at a reduced dose.

c) Patients with unresolved toxicity after 2 weeks should be taken off study. However, if it is the treating physician opinion that the patient may benefit from continued treatment the patient may continue on study. If this occurs the PI or designee will contact CTEP and the decision to proceed with treatment should be made in consultation with the CTEP drug monitor.

Patients with new onset or worsening dyspnea, cough and/or fever should be promptly evaluated, closely monitored, and supported as clinically dictated. OSI-774 should be temporarily discontinued pending diagnosis and permanently

discontinued if a diagnosis of pneumonitis or pulmonary infiltrate is confirmed and considered to be related to the agent.

**Table 1**

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

Toxicity, NCI-CTC Grade	OSI-774 Dosage Modification	Guideline for Management
<b>Keratitis</b>		
Grade 1	None	Preservative-free artificial tears, ointments, and/or other therapies as clinically indicated, with a follow-up examination within 2 weeks <sup>a</sup>
Grade 2	Dose interruption in cases of persistent Grade 2 keratitis (>2 weeks) while on therapy <sup>b</sup>	Managed as described above <sup>c</sup>
Grade 3	Dose interruption <sup>b</sup>	Managed as described above <sup>c</sup>
<b>Diarrhea</b>		
Grade ≥3 (or intolerable Grade 2)	Dose reduction in cases of diarrhea despite optimal use of loperamide	Loperamide (4 mg at first onset, followed by 2 mg q 2–4 hr until diarrhea free for 12 hr)
<b>Rash</b>		
Grade 1	None	No intervention
Grade 2	None	Any of the following: minocycline <sup>d</sup> , topical tetracycline, topical clindamycin, topical silver sulfadiazine, diphenhydramine, oral prednisone (short course)
Grade ≥3	Dose reduction	Managed as described above

- Any symptoms of keratitis (corneal inflammation/corneal ulceration) should prompt a follow-up ophthalmologic evaluation as soon as possible.
- Patients may be retreated at the discretion of the investigator, at a reduced dose, after resolution or amelioration of findings to Grade less than or equal to 1 severity.
- Patients with persistent Grade greater than or equal to 2 keratitis after 14 days of interrupted dosing will be discontinued from further participation in the trial, with scheduled follow-up ophthalmologic assessments at a frequency deemed medically appropriate by the ophthalmologist.
- Recommended dose: 200mg p.o. as a loading dose, followed by 100 mg p.o. bid x 7-10 days.

**Table 2:** Dose Reduction for OSI-774

Starting Dose (mg/day)	Reduction (mg/day)
150	100

## 6. AGENT FORMULATION AND PROCUREMENT

### 6.1 Bevacizumab NSC#704865, IND# 7921

**Note:** An extensive description of the expected adverse events associated with bevacizumab is provided in Section 6.1.7.

Bevacizumab will be provided to study participants free-of charge by Genentech and distributed by the Pharmaceutical Management Branch (PMB), Cancer Therapy Evaluation Program (CTEP), Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI).

Bevacizumab (NSC 704865) will be supplied in either 4ml glass vials each containing 100mg Bevacizumab or 40ml glass vials each containing 1000mg Bevacizumab.

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.

Classification: recombinant humanized monoclonal antibody

6.1.2 Mode of action: Inhibition of vascular endothelial growth factor (VEGF) resulting in inhibition of angiogenesis.

6.1.3 How Supplied: Bevacizumab is supplied as a clear to slightly opalescent, sterile liquid ready for parenteral administration in vials of two sizes:

- Each 100 mg (25 mg/mL – 4 mL fill) glass vial contains bevacizumab with phosphate, trehalose, polysorbate 20, and Sterile Water for Injection, USP.
- Each 1000mg (25mg/mL - 40 mL fill) glass vial contains bevacizumab with phosphate, trehalose, polysorbate 20, and Sterile Water for Injection, USP.

6.1.4 Storage: Bevacizumab is shipped on blue ice by overnight delivery. On receipt, bevacizumab should be stored in the refrigerator (2° to 8° C) and should remain refrigerated until just prior to use. Do not freeze. Do not shake.

Stability: 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. Opened vials must be used within 8 hours. Vials contain no preservative and are intended for single use only.

6.1.5 Dose Specifics: refer to treatment plan section.

Preparation: Opened vials must be used within 8 hours. Vials contain no preservative and are intended for single use only. **The calculated dose should be placed in a sterile, empty IV bag and diluted with a sufficient amount of 0.9% sodium chloride injection to obtain a final volume of 100 ml.**

Once the bevacizumab has been added to the bag with 0.9% sodium chloride injection, the solution must be administered with 8 hours. When the bevacizumab IV bag is empty, an additional 50 ml of 0.9 % sodium chloride 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 and infuse a volume equal to that of the tubing to insure complete delivery of bevacizumab. Note that this flush is not included in the infusion times below.

6.1.6 Route of Administration: Intravenous. The initial dose should be administered over a minimum of 90 minutes. If no adverse reactions occur, the second dose should be administered over a minimum of 60 minutes. Again, if no adverse reactions occur, the third and subsequent doses should be administered over a minimum of 30 minutes. If infusion-related adverse reactions occur, subsequent infusions should be administered over the shortest period that is well-tolerated.

**6.1.7 Reported Adverse Events and Potential Risks:**

*See Appendix A-1 for a list of Comprehensive Adverse Events and Potential Risks List (CAEPR) for Bevacizumab (NSC 704865).*

Reversible and marked elevations of liver function tests (total bilirubin and/or transaminase and AP) have been rarely reported when bevacizumab is used in combination with chemotherapy or concurrently with other drugs that are potentially hepatotoxic. The mechanism of such hepatic toxicities is unclear. It is possible that in rare occasions, bevacizumab may potentiate the liver side effect of a concurrent medication, although it is unclear at this time whether bevacizumab alone can cause LFT derangement.

Bowel perforation and bowel anastomotic dehiscence have been reported in clinical trials using bevacizumab alone or in combination with chemotherapy. Although these events were likely related to co-existing factors such as tumor involvement, chemotherapy, recent invasive procedures or bowel inflammation, contribution of bevacizumab to these events cannot be excluded at this time. Partial delay in wound healing has been demonstrated in animal models treated with anti-VEGF antibodies

and it is possible that bevacizumab may delay or compromise wound healing in patients.

**Reverse Posterior Leukoencephalopathy Syndrome (RPLS) or similar leukoencephalopathy syndrome:** RPLS of 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 hypointensity 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 should be in the differential diagnosis in patients presenting with unexplained mental status change, visual disturbance, seizure, or other CNS findings. RPLS is potentially 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.

Note that additional toxicities may be associated with combination chemotherapy.

#### 6.1.8 Availability

Bevacizumab and OSI-774 are provided to the NCI under a Cooperative Research and Development Agreement (CRADA) and Clinical Trials Agreement (CTA) between Genentech and OSI Pharmaceuticals, respectively, and the DCTD, NCI (see Section 10.4).

Drug orders, transfers, return, and accountability

Questions about drug orders, transfers, returns, or accountability should be addressed to the PMB by calling 301-496-5725 Monday through Friday between 8:30am and 4:30pm Eastern Time.

#### 6.1.9 Agent Ordering

NCI-supplied agents may be requested by the Principal Investigator (or their authorized designees) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that the agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained). The CTEP assigned protocol number must be used for ordering all CTEP supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through and annual submission of FDA form 1572 (Statement of Investigator), Curriculum

Vitae, Supplemental Investigator Data Form (IDF), and Financial Disclosure form (FDF). If there are several participating investigators at one institution, CTEP supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution. Completed Clinical Drug Requests (NIH-986) should be submitted to the PMB by fax (301) 480-4612 or mailed to the Pharmaceutical Management Branch, CTEP, DCTD, NCI, 9000 Rockville Pike, EPN Rm. 7149, Bethesda, MD 20892.

#### 6.1.10 Agent Accountability

The Investigator, or a responsible party designated by the Investigator, must maintain a careful record of the inventory and disposition of all agents received from DCTD using the NCI Drug Accountability Record Form.

6.1.11 *Drug Returns:* All unused drug supplies should be returned to the PMB. When it is necessary to return study drug (e.g., sealed vials remaining when a patient permanently discontinues protocol treatment, expired vials recalled by the PMB), investigators should return the study drug to the PMB using the NCI Return Agent Form available on the NCI home page (<http://ctep.info.nih.gov>) or by calling the PMB at 301-496-5725.

## 6.2 **OSI-774 (Tarceva<sup>TM</sup>) (NSC# 718781)**

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

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

**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

**How Supplied:** OSI-774 is supplied by the NCI/DCTD as 25 mg, 100 mg, and 150 mg 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, unscored, and film-coated. The white 25mg tablets [1/4 inch diameter, 3mm deep (formerly non-film coated)], white 100 mg tablets (11/32 inch in diameter, 5mm deep), and white 150mg tablets (13/32 inch in diameter, 5.1mm deep) are supplied 30 tablets/bottle.

**Storage:** The intact bottles should be stored at controlled room temperature.

**Stability:** 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.

**Route of Administration:** Oral.

**Reported Adverse Events and Potential Risks:**

- From Animal Data:

On chronic administration studies the following toxicities were observed:

Rat: decreased body weight gain and food consumption, increased total bilirubin, ALT, and AST, increased WBC, eosinophilic chief cells in stomach mucosa, rough fur, (females), hematuria, hair follicular degeneration, papillary necrosis & increased ovarian

Dog: Sporadic emesis, salivation, erythema, decreased absolute RBC counts, hematocrit and hemoglobin, (males), increased regenerating renal proximal tubules, hair loss, skin reddening, buccal mucus membranes redness, rough hair, ocular changes (tapedal fundus pigmentation not considered an adverse finding), corneal ulceration, decreased body weight gain (males)

At the highest doses administered to dogs the following toxicities were observed: decreased body weight, absence of food intake, bloody stools, decreased activity, tremors, emaciation, prostration, ocular changes (palpebral and bulbar conjunctiva redness, partially-closed eyes, lacrimation, purulent discharge, protruding nictitating membranes, corneal opacities, edema, ulceration & corneal perforation), increased neutrophils & fibrinogen, changes in RBC, HCT & HBG, increased bilirubin, alkaline phosphatase, BUN, cholesterol and triglycerides, decreased Na, Cl, albumin, and Ca, increased ALT and AST (1 male) cachexia, dehydration, discoloration of anterior chamber and/or cornea, abnormal corneal surface, kidney changes (discoloration of papilla and/or corticomedullary junction), discoloration and/or abnormal surface of digestive tract, dilatation and/or abnormal contents of gall bladder, enlarged & pale cervical lymph nodes (1 female) microscopic findings: diffuse corneal atrophy, corneal ulcers and uveal inflammation, papillary necrosis of kidneys w/ congestion at corticomedullary junction or multifocal tubular dilation, inflammation &/or hemorrhage of digestive tract, 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.

From Human data:

Adverse Events thought to be related to the administration of OSI-774

- Constitutional Symptoms: fatigue (asthenia, lethargy, malaise)
- Dermatology/Skin: dry skin, pruritus/itching, rash/desquamation, rash: acne/acneiform, hair loss/alopecia (scalp or body)
- Gastrointestinal: anorexia, diarrhea, dry mouth/salivary gland (xerostomia), nausea, vomiting, heartburn/dyspepsia, mucositis/stomatitis (functional/symptomatic), taste alteration (dysgeusia)
- Ocular/Visual: dry eye syndrome
- Pain: head/headache, oral cavity
- Pulmonary: pneumonitis/ pulmonary infiltrates, dyspnea (shortness of breath), cough
- Metabolic/Laboratory: ALT, SGPT (serum glutamic pyruvic transaminase), AST, SGOT (serum glutamic oxaloacetic transaminase), bilirubin (hyperbilirubinemia)

**Also reported on OSI-774 trials but with the relationship to OSI-774 still undetermined:**

- Constitutional Symptoms: fever
- Gastrointestinal: dehydration and increased creatinine concurrent with, and likely directly related to diarrhea; pancreatitis
- Hemorrhage: GI hemorrhage; hemorrhage-nose;
- Infection: infection with neutropenia in combination with myelosuppressive therapies; secondary skin infection from rash without neutropenia
- Neurology: anxiety; confusion; CNS ischemia;
- Ocular/visual: blurred vision; ocular surface disease; keratitis; uveitis
- Pain: abdominal pain in conjunction with diarrhea
- Other: INR in patients taking Coumadin; pneumatosis; orbital cellulitis

**Notes:** 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.

**Method of Administration:**

- 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.

**Potential Drug Interactions:** In *in vitro* human liver microsomes studies OSI-774 was slowly oxidized. OSI-774 appeared to be a substrate for CYP3A4, suggesting that OSI-774 could reduce the clearance of co-administered drugs whose metabolism is dependent on these P450 cytochrome isoenzymes.

**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.

## 7. CORRELATIVE/SPECIAL STUDIES

### 7.1 Scientific Background:

Extensive preclinical and translational data suggest that the EGFR signaling pathway and angiogenesis are critical in the carcinogenesis and prognosis of a variety of epithelial malignancies including HNC. EGFR and angiogenesis have also been identified as potential therapeutic targets.

EGFR has been shown to be consistently overexpressed in HNC cell lines and established tumors [23]; [24] and to correlate with poor prognosis. Both EGFR and its more commonly expressed ligand, TGF $\alpha$ , have been extensively studied in HNC. Dysregulation of this interaction has been noted in up to 90% of HNC and has been linked with local recurrence, distant failure, and shortened survival [25]; [26]; [11]

While a majority of head and neck cancer patients overexpress EGFR in their tissues, the degrees of overexpression vary and many patients do not respond to EGFR blockade clinically. Extracellular or intracellular blockade of EGFR function or its cellular signaling pathway have been explored as therapeutic strategies with limited single agent activity [27]. OSI-774 should not affect receptor or ligand expression but should alter autophosphorylation of EGFR. This has been demonstrated employing *in vitro* cell culture and *in vivo* transgenic models. EGFR likely exerts its effects on cellular proliferation through MAP kinases including ERK1/2. ERK1/2 activation has been linked to proliferation [28]. Changes in phosphorylated ERK and phosphorylated EGFR have been observed in patients with refractory head and neck cancer treated with OSI-774 [29]; [21]

EGFR is known to lead to phosphorylation of AKT through the Ras/PI3K pathway [30-32]. Among its functions, AKT phosphorylation has been demonstrated to lead to Hif-1 $\alpha$  gene transcription [33, 34]. This appears to be mediated through FRAP (mTOR) [35] and inhibited by PTEN. Hif-1 $\alpha$  transcription results in increased expression of VEGF [36] [35] which in turn promotes angiogenesis.

Tumor vessel angiogenesis has been shown to be a necessary component of tumor growth [37]; [1]; [2]; [38]. Microvessel density (MVD) and other measurements of tumor vascularity have suggested a correlation of tumor growth with treatment outcome in several malignancies including HNC [39]; [40]; [4]. VEGF is specific for endothelial cells and has been associated

with tumor growth and proliferation [41]; [2] It binds to two distinct but related tyrosine kinase receptors found predominantly on the surface of endothelial cells, VEGFR1 (Flt-1) and VEGFR2 (Flk-1, KDR) [42] VEGFR2 appears to be the receptor responsible for proliferative activity while VEGFR1 may serve as a decoy receptor to control angiogenesis [43]; [44] Binding of VEGFR2 receptors leads to phosphorylation of the receptor and activation of intracellular signals including the Raf/Mek/ERK pathway [45]; [46]; [47]; [48]; [49]. Retrospective studies in patients with HNC have shown that these patients have higher serum concentrations versus healthy controls [40]. Others have been able to demonstrate a negative correlation of VEGF levels with survival [4]; [50]. However, serum VEGF expression has not been studied prospectively and its alteration with therapy has not been explored in HNC.

Bevacizumab is hypothesized to disrupt VEGF binding to its receptor. This interaction prevents VEGFR2 phosphorylation, downstream protein activation, and endothelial cell proliferation. Upon exposure to Bevacizumab it is expected that levels of phosphorylated VEGFR2 will decrease.

Moreover, several investigators have explored molecular mechanisms of EGFR stimulation promoting increased VEGF expression *in vitro* [30]; [31]; [32]; [33]; [34]; [36]; [35]; [51]. Studies in preclinical models have demonstrated downregulation of VEGF and decreased MVD after exposure to anti-EGFR antibodies [52]; [53]; [54]; [55] or EGFR tyrosine kinase inhibitors [56]; [53]. Furthermore, resistance to anti-EGFR antibodies may be mediated through increased VEGF expression [57]. EGFR inhibitors may, in fact, function as antiangiogenic agents [53]; [52]; [54]; [55]; [56]; [57] while disrupting VEGF signaling may increase response rates to EGFR inhibition or circumvent anti-EGFR tumor resistance.

In attempt to correlate the clinical outcomes with what is occurring at the tumor tissue level, we will be conducting serial biopsies in patients enrolled on the phase II portion of the trial. The phase II trial design is set up to explore the relationship between inhibition of both EGFR and VEGF. As per the study rationale it is believed that inhibition of both may lead to an additive or synergistic inhibition of tumor neo-vascularization with the hope of tumor cell death. The laboratory correlative studies will be performed prior to and after 2 weeks of therapy with either OSI-774 and bevacizumab or OSI-774 alone in the phase II portion of the trial (please see sections 4.2.2 and 8.0).

The tissue obtained will be sent to the lab of Dr. David McConkey for evaluation of tumor tissue endothelial cell apoptosis using scanning laser cytometry (Shaheen RM, Tseng WW, Davis DW, Liu W, Reinmuth N, Vellagas R, Wieczorek AA, Ogura Y, McConkey DJ, Drazan KE, Bucana CD, McMahon G, Ellis LM., Tyrosine kinase inhibition of multiple angiogenic growth factor receptors improves survival in mice bearing colon cancer liver metastases by inhibition of endothelial cell survival mechanisms Cancer Res 2001 Feb 15;61(4):1464-8). It is hypothesized that EGFR inhibition by OSI-774 will lead to a modest increase in endothelial cell apoptosis that will be greatly increased by the addition of bevacizumab.

### **Quantification of surrogate biomarkers**

Tumor vessels will be quantified by laser scanning 3-5 regions of the tumor biopsy and the

vessel density will be calculated based on the number of cells counted within each region scanned (3,000-5,000 total cells). Apoptosis is quantified by scanning endothelial cells and tunnel positive cells within 3-5 regions of the tumor biopsy. The percentages of apoptotic endothelial cells tumor cells are determined by the following equation: % apoptosis = [(number of apoptotic cells/total number of cells x 100)]. Other surrogate biomarkers will be quantified by scanning the total available tumor cells.

Additional tumor tissue, if available will be utilized for the following immunohistochemical stains (IHC) in order of priority. These assays will also be analyzed using the scanning laser cytometry technology:

- VEGFR-2, p-VEGFR-2
- VEGF

If there is any remaining tissue, additional measures of antiangiogenic effect may be measured upon mutual agreement of the co-investigators and CTEP.

ELISA on plasma/serum will be performed to measure levels of the following proteins:

- VEGF (pre-therapy and week 2)
- TGF- $\alpha$  (pre-therapy, week 2, and week 8)

## 7.2 **Laboratory methodology:**

*Blood Collection for Correlative Studies:* Blood samples will be collected from patients in 7cc green top (anti-coagulant, plasma) and gold top (serum) tubes. For patients in both the phase I and II portions of the trial samples will be collected prior to therapy, after 2 weeks of therapy (for patients randomized to Arm A of the phase II portion this will be obtained prior to Bevacizumab infusion), and after 8 weeks of therapy.

*Tumor Biopsy:* Only patients in the Phase II portion of the study will have tumor tissue biopsies. Patients will be randomized to separate arms (as described in section 4.2.2) however; all patients will undergo tumor tissue biopsy pre-study and on Day 15 (prior to bevacizumab administration) regardless of treatment arm. One or more 18-gauge core biopsies total length of at least 2cm should be obtained. Biopsy of the primary tumor is preferred.

The following protocol should be followed when preparing frozen tissue:

For freezing tissues, you will need O.C.T. embedding compound (Baxter), plastic tissue molds (Baxter), 2-methylbutane (Sigma), Dry Ice, a hemastat or other clamping device, and a metal or plastic 1L container.

- Label the mold with proper tissue identification and fill partly with O.C.T.
- Dab tissue on a towel to remove any fluid, and

immediately place in tissue mold with O.C.T. and continue with protocol

- Choose the best orientation for the tissue to be frozen in, and let it settle to the bottom. Note that the bottom of the mold is where cutting will begin.
- Add more O.C.T. on top of tissue to cover it completely and fill the mold.
- Fill the plastic or metal container half way with 2-methylbutane.
- Add several small pieces of Dry Ice and wait a few moments for the temperature to drop (-40C)
- Grasp the edge of the mold with the hemostat and dip into 2-methylbutane. Note that you should NOT submerge yet. Dip only the most bottom part of the plastic mold.
- The O.C.T. will begin to turn white as it freezes
- When all of the O.C.T. is frozen, drop the mold into the cold 2-methylbutane to freeze thoroughly (~5min)
- Remove the mold from the freezing liquid, wrap the mold in foil, label it, and immediately store at -80C.

*Shipping Instructions:* The shipment of all human samples (blood, tissue) must comply with appropriate regulations as specified by the carrier. At a minimum, all samples must be packaged in dry ice within two containers with absorbent material between containers to control any spill or leakage. The outer container must be puncture resistant (e.g., cardboard mail tube, corrugated cardboard box). A biohazard sticker must be affixed to both the inner and outer containers. All samples must be accompanied by the sample transmission form located in Appendix C and shipped to:

Shipping address is:

Dr. Mark Lingen  
University of Chicago  
FMI Dock/Lab Supply  
5830 S. Ellis Ave  
Room G-02  
Chicago, IL 60637

Mailing address is:

Dr. Mark Lingen  
Department of Pathology  
University of Chicago  
5841 S. Maryland Ave., MC 3083  
Chicago, IL 60637-1470

Lab contact person:

Dr. Rifat Hasina  
Lab: 773-834-9814  
Lab: 773-702-0119  
Pager: 773-753-1880-9747  
email: rhasina@bsd.uchicago.edu

These samples will then be shipped to the lab of Dr. David McConkey at the MD Anderson Cancer Center.

*Immunohistochemistry (IHC):* Tissues will be fixed in 4% paraformaldehyde and sectioned in 4-8  $\mu$ m slices. Slides will be incubated with 1% hydrogen peroxide for endogenous peroxidase blocking. Slides will be incubated with 5% normal horse serum, Avidin, then Biotin labeling solutions. The slides will be incubated with the primary antibody overnight at 4°C. All primary antibodies are commercially available for use in IHC. The slides will be incubated with species appropriate biotinylated secondary antibody in protein blocking solution for one hour at room temperature. Avidin/Biotin complex will be applied. Slides will be developed with DAB, counterstained with hematoxylin, dehydrated, and mounted. Slides will be interpreted by Dr. Wendy Recant using a four point scoring system. This protocol may be modified to improve antigen retrieval and staining.

*Enzyme Linked Immuno-Sorbent Assay (ELISA) for serum TGF $\alpha$  and plasma VEGF Determination:* Samples will be analyzed for plasma VEGF and serum TGF- $\alpha$  using commercially available ELISA kits (R&D systems).

Any questions regarding tissue sampling, handling, preparation, or handling can be directed to Dr. Ezra Cohen (773 702 4137) or Dr. Walter Stadler (above).

## 8. STUDY CALENDAR

Baseline evaluations are to be conducted within 1 week prior to start of protocol therapy. Scans and x-rays must be done  $\leq 4$  weeks prior to the start of therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

	Pre-Study	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	Off Study <sup>c</sup>
<i>OSI-774-phase I and II **</i>		A	A	A	A	A	A	A	A	A	A	A	A	
<i>Bevacizumab-phase I and II**</i>		B			B			B			B			
Informed consent	X													
Demographics	X													
Medical history	X													
Concurrent meds	X	X-----X												
Physical exam <sup>g</sup>	X	X			X			X			X			X
Vital signs <sup>g</sup>	X	X			X			X			X			X
Height	X													
Weight <sup>g</sup>	X	X			X			X			X			X
Performance status <sup>g</sup>	X	X			X			X			X			X
CBC w/diff, plts	X	X			X			X			X			X
SerumChem. <sup>a</sup> , urinalysis,PT/INR, PTT	X	X <sup>f</sup>			X <sup>f</sup>			X <sup>f</sup>			X <sup>f</sup>			X <sup>f</sup>
EKG (as indicated)	X													
Adverse event evaluation	X	X-----X												X
Tumor measurements <sup>g</sup>	X	Tumor measurements are repeated every 6 weeks or two cycles. Documentation (radiologic) must be provided for patients removed from study for progressive disease.												X <sup>c</sup>
Radiologic evaluation <sup>g</sup>	X	Radiologic measurements should be performed every 6 weeks.												X <sup>c</sup>
B-HCG	X <sup>b</sup>													
Correlative Studies: serum <sup>E</sup>	X		X						X					
Correlative Tissue Biopsy – Tumor(phase II portion only)	X		X <sup>d</sup>											

A: *OSI-774* : 150 mg PO QD for 21 days in each 21 day cycle  
 B: *Bevacizumab*: 5.0,10.0 or 15.0 mg/kg IV every 21 days.  
 a: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.  
 b: Serum pregnancy test (women of childbearing potential).  
 c: Off-study evaluation. **Two consecutive measurements taken 4 weeks apart must be used to document progressive disease if the patient is removed from study for this reason.**  
 d: All patient will have a tumor biopsy pre-study and on Day 15 ,For patients randomized to Arm B biopsy should be prior to bevacizumab infusion . Please see treatment schedule in section 4.0.  
 E: serum for correlative studies will be drawn on all patients regardless of phase of trial  
 f: Follow-up PT/PTT tests are only required when baseline test is abnormal.  
 \*\*See section 4.0 for schema of dosing OSI-774 and Bevacizumab as depends upon which arm patient is randomized (e.s.. Arm A or B)  
 g: Patients who have been on study for longer than 12 months can be reevaluated by their treating physician and by radiography every 4 cycles (12 weeks).

## 9. MEASUREMENT OF EFFECT

Although response is not the primary endpoint of this trial, patients with measurable disease will be assessed by standard criteria. For the purposes of this study, patients should be reevaluated every six (6) weeks. In addition to a baseline scan, confirmatory scans will also be obtained six (6) weeks following initial documentation of an objective response.

Patients who have been on study for longer than 12 months can be reevaluated by their treating physician and by radiography every 4 cycles (12 weeks).

### 9.1 **Definitions**

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee [*JNCI* 92(3):205-216, 2000]. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria.

Note: Lesions are either measurable or non-measurable using the criteria provided below. The term “evaluable” in reference to measurability will not be used because it does not provide additional meaning or accuracy.

#### 9.1.1 **Measurable Disease**

Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as  $\geq 20$  mm with conventional techniques (CT, MRI, x-ray) or as  $\geq 10$  mm with spiral CT scan. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

#### 9.1.2 **Non-measurable Disease**

All other lesions (or sites of disease), including small lesions (longest diameter  $< 20$  mm with conventional techniques or  $< 10$  mm using spiral CT scan), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all non-measurable.

#### 9.1.3 **Target Lesions**

All measurable lesions up to a maximum of five lesions per organ and 10 lesions in total representative of all involved organs should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).

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

#### 9.1.4 **Non-target Lesions**

All other lesions (or sites of disease) should be identified as **non-target lesions** and should also be recorded at baseline. Non-target lesions include measurable lesions that exceed the maximum numbers per organ or total of all involved organs as well as non-measurable lesions. Measurements of these lesions are not required but the presence or absence of each should be noted throughout follow-up.

#### 9.2 **Guidelines for Evaluation of Measurable Disease**

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

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. Given the nature of locoregional failure after prior irradiation characteristic of head and neck cancer these areas are considered as progression of disease and will be included. If doubt exists on appropriate scans, then a biopsy could be performed to measure disease (this will only be done at the investigator's discretion).

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

**Clinical Lesions.** Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

**Chest X-ray.** Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

**Conventional CT and MRI.** These techniques should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen, and pelvis. Head and neck tumors and those of extremities usually require specific protocols.

**Ultrasound (US).** When the primary endpoint of the study is objective response evaluation, US should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes,

subcutaneous lesions, and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

**Endoscopy, Laparoscopy.** The utilization of these techniques for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in reference centers. However, such techniques can be useful to confirm complete pathological response when biopsies are obtained.

**Tumor Markers.** Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific additional criteria for standardized usage of prostate-specific antigen (PSA) and CA-125 response in support of clinical trials are being developed.

**Cytology, Histology.** These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain).

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

## 9.3 **Response Criteria**

### 9.3.1 **Evaluation of Target Lesions**

Complete Response (CR): Disappearance of all target lesions

Partial Response (PR): At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD

Progressive Disease (PD): At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

### 9.3.2 **Evaluation of Non-target Lesions**

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level

Incomplete Response/  
Stable Disease (SD): Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions

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

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

### 9.3.3 **Evaluation of Best Overall Response**

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria (see section 9.3.1).

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD

PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

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Note:

- X Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having “symptomatic deterioration.” Every effort should be made to document the objective progression, even after discontinuation of treatment.
  
- X In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before confirming the complete response status.

#### 9.4 **Confirmatory Measurement/Duration of Response**

##### 9.4.1 **Confirmation**

To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed four (4) weeks after the criteria for response are first met. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of six (6) weeks (see section 9.3.3).

9.4.2 **Duration of Overall Response**

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

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

9.4.3 **Duration of Stable Disease**

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

9.5 **Progression-Free Survival**

The duration of progression-free survival is the time from the start of treatment until disease progression or death.

**10. REGULATORY AND REPORTING REQUIREMENTS**

Adverse events (AE) will use the descriptions and grading scales found in the revised NCI Common Toxicity Criteria (CTC). This study will utilize the CTC version 2.0 for adverse event reporting. All appropriate treatment areas will have access to a copy of the CTC version 2.0. A table showing the expected adverse events associated with Bevacizumab and OSI-774 and the related IMT terms can be found in Appendix A. A copy of the CTC version 2.0 can be downloaded from the CTEP home page (<http://ctep.info.nih.gov/CTC3/default.htm>).

10.1 **Expedited Adverse Event Reporting**

(AE; formerly known as Adverse Drug Reaction)

10.1.1 **Reporting Requirements for Adverse Events That Occur Within 30 Days<sup>1</sup> of the Last Dose of the Investigational Agent**

	Grade 1	Grade 2	Grade 2	Grade 3		Grade 3		Grades 4 & 5 <sup>2</sup>	Grades 4 & 5 <sup>2</sup>
	Unexpected and Expected	Unexpected	Expected	Unexpected		Expected		Unexpected	Expected
				with Hospitalization	without Hospitalization	with Hospitalization	without Hospitalization		
<b>Unrelated Unlikely</b>	Not Required	Not Required	Not Required	10 Calendar Days	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days
<b>Possible Probable Definite</b>	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
<sup>1</sup> <b>Adverse events with attribution of possible, probable, or definite that occur <u>greater</u> than 30 days after the last dose of treatment with an agent under a CTEP IND require reporting as follows:</b> AdEERS 24-hour notification followed by complete report within 5 calendar days for: <ul style="list-style-type: none"> <li>• Grade 4 and Grade 5 unexpected events</li> </ul> AdEERS 10 calendar day report: <ul style="list-style-type: none"> <li>• Grade 3 unexpected events with hospitalization or prolongation of hospitalization</li> <li>• Grade 5 expected events</li> </ul> <sup>2</sup> 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.								
								December 15, 2004

***Note: All deaths on study must be reported using expedited reporting regardless of causality. Attribution to treatment or other cause should be provided.***

- **Expedited AE reporting timelines defined:**
  - “24 hours; 5 calendar days” – The investigator must initially report the AE via 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.
- **Telephone/Web** reports within 24 hours to:
  - 1) The Cancer Clinical Trials Office at 773-834-0357.
  - 2) The Principal Investigator at your site.
  - 3) The IDB via AdEERS on the web at: <http://ctep.cancer.gov> . The NCI guidelines for expedited adverse event reporting are also available at this site.
- **Fax** a copy of the expedited report within 5 calendar days to: 773-702-8855
- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of designation as expected or unexpected and attribution
- 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 provided during trial registration on all reports.

**Expected Adverse Events:**

For OSI-774 the following events are considered to be expected and do not require expedited reporting unless they are unusually severe: fatigue, headache, anorexia, diarrhea, mouth dryness, nausea, vomiting, dry skin, dry eyes, pruritus, rash.

### 10.1.2 Forms

Forms for this study are listed below.

#### **Investigational Agent(s) Obtained from the NCI:**

- X DCTD Form for Reporting AEs Occurring with Investigational Agents  
This form can be downloaded from the CTEP home page  
(<http://ctep.info.nih.gov/InfoForms/default.htm>).

#### **If the patient received no NCI-provided investigational agent on the same protocol:**

- X FDA Form 3500 (MedWatch) This form can be downloaded from the  
CTEP home page (<http://ctep.info.nih.gov/InfoForms/default.htm>).

### 10.1.3 Secondary Malignancies

Investigators are required to report secondary malignancies occurring on or following treatment on NCI-sponsored protocols using the appropriate form noted above. **Exception:** Cases of secondary AML/MDS are to be reported using the NCI/CTEP Secondary AML/MDS Report Form.

## 10.2 Data Reporting

This study will be monitored by the Clinical Data Update System (CDUS) version 2.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31. *Instructions for submitting data using the CDUS can be found on the CTEP home page (<http://ctep.info.nih.gov/CtepInformatics/CDUS/Default.htm>).*

## 10.3 CTEP Multicenter Guidelines

If an institution wishes to collaborate with other participating institutions in performing a CTEP sponsored research protocol, then the following guidelines must be followed.

#### Responsibility of the Protocol Chair

- The Protocol Chair will be the single liaison with the CTEP Protocol and Information Office (PIO). The Protocol Chair is responsible for the coordination, development, submission, and approval of the protocol as well as its subsequent amendments. The protocol must not be rewritten or modified by anyone other than the Protocol Chair. There will be only one version of the protocol, and each participating institution will use that document. The Protocol Chair is responsible for assuring that all participating

- institutions are using the correct version of the protocol.
- The Protocol Chair is responsible for the overall conduct of the study at all participating institutions and for monitoring its progress. All reporting requirements to CTEP are the responsibility of the Protocol Chair.
  - The Protocol Chair is responsible for the timely review of Adverse Events (AE) to assure safety of the patients.
  - The Protocol Chair will be responsible for the review of and timely submission of data for study analysis.

#### Responsibilities of the Coordinating Center

- Each participating institution will have an appropriate assurance on file with the Office for Protection from Research Risks (OPRR), NIH. The Coordinating Center is responsible for assuring that each participating institution has an OPRR assurance and must maintain copies of IRB approvals from each participating site.
- Prior to the activation of the protocol at each participating institution, an OPRR form 310 (documentation of IRB approval) must be submitted to the CTEP PIO.
- The Coordinating Center is responsible for central patient registration. The Coordinating Center is responsible for assuring that IRB approval has been obtained at each participating site prior to the first patient registration from that site.
- The Coordinating Center is responsible for the preparation of all submitted data for review by the Protocol Chair.
- The Coordinating Center will maintain documentation of AE reports. There are two options for AE reporting: (1) participating institutions may report directly to CTEP with a copy to the Coordinating Center, or (2) participating institutions report to the Coordinating Center who in turn report to CTEP. The Coordinating Center will submit AE reports to the Protocol Chair for timely review.
- Audits may be accomplished in one of two ways: (1) source documents and research records for selected patients are brought from participating sites to the Coordinating Center for audit, or (2) selected patient records may be audited on-site at participating sites. If the NCI chooses to have an audit at the Coordinating Center, then the Coordinating Center is responsible for having all source documents, research records, all IRB approval documents, NCI Drug Accountability Record forms, patient registration lists, response assessments scans, x-rays, etc. available for the audit.

#### Inclusion of Multicenter Guidelines in the Protocol

- The protocol must include the following minimum information:
  - The title page must include the name and address of each participating institution and the name, telephone number and e-mail address of the responsible investigator at each participating institution.
  - The Coordinating Center must be designated on the title page.
  - Central registration of patients is required. The procedures for registration must be stated in the protocol.
  - Data collection forms should be of a common format. Sample forms should be submitted with the protocol. The frequency and timing of data submission forms to the Coordinating Center should be stated.

- Describe how AEs will be reported from the participating institutions, either directly to CTEP or through the Coordinating Center.

#### Drug Ordering

- Except in very unusual circumstances, each participating institution will order DCTD-supplied investigational agents directly from CTEP. Investigational agents may be ordered by a participating site only after the initial IRB approval for the site has been forwarded by the Coordinating Center to the CTEP PIO.

#### 10.4 **Cooperative Research and Development Agreement (CRADA)/Clinical Trials Agreement (CTA)**

The agents, Bevacizumab and OSI-774, used in this protocol are provided to the NCI under a Cooperative Research and Development Agreement (CRADA) and Clinical Trial Agreement (CTA) between Genentech, Inc. and OSI Pharmaceutical, respectively, and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the Intellectual Property Option to Collaborator terms of award modifications, apply to the use of Bevacizumab and OSI-774 in this study:

1. Bevacizumab and OSI-774 may not be used for any purpose outside the scope of this protocol, nor can Bevacizumab or OSI-774 be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Bevacizumab and OSI-774 are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators.
2. For a clinical protocol where there is an investigational agent used in combination with (an)other investigational agent(s), each the subject of different CTAs or CRADAs, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):
  - a. NCI must provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NIH, the design of the proposed combination protocol, and the existence of any obligations which would tend to restrict NCI's participation in the proposed combination protocol.
  - b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval, or commercialize its own investigational agent.
  - c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will

use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own investigational agent.

3. Clinical Trial Data and Results and Raw Data developed under a CTA or CRADA will be made available exclusively to Collaborator(s), the NCI, and the FDA, as appropriate.
4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.
5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.
6. Any manuscripts reporting the results of this clinical trial should be provided to CTEP for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts should be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Copies of any manuscript and/or abstract should be sent to:

Regulatory Affairs Branch, CTEP, DCTD, NCI  
Executive Plaza North, Room 7111  
Bethesda, Maryland 20892  
FAX 301-402-1584

The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/ proprietary information.

## 10.5 Patient registration and data submission

This study will be monitored by the Clinical Data Update System (CDUS) version 1.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due on January 31, April 30, July 31, and October 31. Instructions for submitting data using CDUS can also be found on the CTEP home page (<http://ctep.info.nih.gov/CtepInformatics/CDUS/Default.htm>).

### 10.5.1 Registration

All patients must be registered with the University of Chicago Registrar Office (773-834-7839) prior to the commencement of treatment. Confirm all selection criteria listed in Section 3.0, then call the Registrar Office with the following information:

Provider of information  
Study # and Institution  
Treating Physician  
Patient name and hospital ID number  
Patient's zip code of residence  
Date of signed informed consent  
Race, gender, date of birth of patient  
Diagnosis and date of initial diagnosis

The Registrar Office will issue a confirmation of registration.

#### 10.5.2 Data Submission

Registration	Submit the <i>Phase II Affiliate Cancer Protocol Patient Registration Form</i> and all source documentation for the protocol required eligibility criteria and pre-study procedures.
Weekly	Submit the <i>Phase II Patient Weekly Flow Sheet Form</i> with supporting source documentation by noon on Friday of each week, for review at the weekly Phase II Conference. All other source documentation for protocol required procedures should be submitted within a week after it is created or modified.
Evaluations	At each response evaluation as specified in the protocol, submit supporting source documentation for the response.
Off-study/Follow-up	Submit the <i>Phase II Patient Off Treatment / Follow-up / Off Study Form</i> .

**All required forms and source documentation should either be faxed to (773) 702-4899 or mailed to: Phase II Program Data Managers  
5841 S. Maryland Avenue MC 2115  
Chicago, IL 60637**

## 10.6 Data and Safety Monitoring

Data Safety and Monitoring will occur at the weekly University of Chicago Phase II Consortium meetings, which are lead by senior level medical oncologists. At each meeting, all active Phase II Consortium studies will be reviewed for safety and progress toward completion. Toxicities and adverse events will be reviewed at each meeting and a Data Safety and Monitoring form will be filled out for each protocol and signed by either the principal investigator, the Chairman of the Phase II Consortium or by his designate if the chairman is not available.

## 11. STATISTICAL CONSIDERATIONS

### 11.1 Study Design/Endpoints

The primary purpose of this Phase I/II study is to determine the maximum tolerated dose (5.0,10.0 and 15.0 mg/kg) of Bevacizumab when used in combination with OSI-774 150 mg/ day; and to obtain estimates of the frequency of complete and partial responses and of progression-free and overall survival rates. Accordingly, the primary endpoints will be toxicity for the phase I portion of the study; and response rates (CR or PR/SD), toxicity, time to progression, and overall survival for the phase II portion.

A traditional dose escalation design (labeled “Design A” by Storer)[84] will be employed starting at 5.0 mg/kg of bevacizumab. Cohorts of three patients will be enrolled at each dose level. If none of the three patients experiences a dose-limiting toxicity, as defined in section 4.3, the dose will be escalated for the next cohort. If  $\geq 2$  of three patients experience toxicity, the phase I portion of the trial will stop and the previous dose level will be the MTD. (If this occurs at 5.0 mg/kg, then lower dose levels will be considered.) If one of the three patients experiences a dose limiting toxicity, an additional three patients will be treated at the same dose level, and if no further toxicity occurs dose escalation will continue; otherwise the trial will stop and the previous dose level will be the MTD. Dose escalation will not proceed beyond 15 mg/kg of Bevacizumab. If none of the 3 patients at the highest dose develops DLT, the cohort will be expanded to six before the MTD is determined. ***The phase I portion of this study has been completed and the phase II dose level will be 15.0 mg/kg of bevacizumab.***

For the phase II portion of the trial, since the combination of OSI-774 and Bevacizumab may have cytotoxic and/or cytostatic effects, we shall consider both response rate (CR + PR, as defined in Section 9.3) and lack of early progression (i.e., within two months) as primary endpoints. Specifically, we shall test the null hypothesis that the true response rate is less than 5 percent and the true percentage of patients not progressing within two months is less than 30 percent against the alternative that either is greater. The trial will be conducted in two stages, with 22 patients being enrolled during the first stage. (We shall include the 6 patients from phase I who received the MTD.) If at the end of the first stage fewer than two

responses are observed AND more than 14 patients progress within two months, the trial will be stopped and we shall conclude that this combination does not warrant further investigation. Otherwise we shall enroll another 24 patients for a total of 46. Only if 6 or more responses are observed OR fewer than 29 patients progress within two months will we reject the null hypothesis and conclude that OSI-774 and Bevacizumab warrants further study.

The table below shows the operating characteristics for this design under several different scenarios. Under the null hypothesis described above, the probability of accepting OSI-774/Bevacizumab for further study is 0.11 (alpha), and the probability of stopping after the first stage is 0.52. If either the true response rate is 20 percent (Alternative A) or the true rate of early progression is no more than 50 percent (Alternative B), the probability of accepting OSI-774/Bevacizumab is approximately 0.90 (power). Alternative C is one in which OSI-774/Bevacizumab has both a moderate cytotoxic and moderate cytostatic effect; the power for this alternative (0.74) is less than for those above, but is still significant.

	True Percentage			Operating Characteristics	
	<u>CR + PR</u>	<u>SD (2 mos)</u>	<u>PD</u>	<u>P(stop)</u>	<u>P(accept)</u>
Null	5	25	70	0.52	0.11
Alt. A	20	10	70	0.05	0.89
Alt. B	5	45	50	0.06	0.90
Alt. C	13	27	60	0.09	0.74

### 11.2 **Sample Size/Accrual Rate**

Sample Size: 9-18 for phase I (3-6 in each cohort) plus an additional 40-43 for the phase II portion. Only 3 patients at the phase II dose were enrolled during the phase I portion because dose-limiting toxicities were not observed. Therefore, an additional 19 patients will be enrolled to the first stage of the phase II portion and an additional 24 patients will be enrolled to the second stage if adequate responses are seen.

Estimated Monthly Accrual: 2-5

### 11.3 **Stratification Factors**

N/A

#### 11.4 **Analysis of Laboratory Endpoints**

11.4.1 We will test the hypothesis that inhibition of EGFR signaling will inhibit blood vessel formation and the combination of EGFR and VEGF inhibitors will result in greater inhibition. Tumor tissue from pre-treatment and post-treatment (day 15) biopsies will be analyzed for endothelial cell apoptosis as outlined in the correlative section. Note that each of these measurements will range over either a continuous or ordinal scale; immunohistochemistry parameters (plasma measurements of VEGF and TGF- $\alpha$ ) obtained from serum and/or plasma will be scored on a four point ordinal scale (0, 1+, 2+, or 3+).

Assuming the trial proceeds through the second stage, we will have a total of 46 patients, 23 randomized to OSI-774 alone for the first 14 days and 23 randomized to OSI-774 plus Bevacizumab for the first 14 days. (Patients in the first group will receive Bevacizumab beginning on day 15.) To determine whether inhibition of EGFR signaling inhibits blood vessel formation, differences between the pre-therapy and post-therapy measurements in the OSI-774 alone group will be assessed by paired t and Wilcoxon signed rank tests for continuous and ordinal variables, respectively. To determine whether the combination of OSI-774 and Bevacizumab leads to greater inhibition, we will compare the pre-post *changes* in these measurements between the two randomized groups, using two-sample t or Wilcoxon rank-sum tests. Note that a sample-size of 23 patients per group will provide 80% power to detect a  $0.83 \sigma_d$  true difference between the groups, where  $\sigma_d$  is the standard deviation of the within-subject differences.

11.4.2 The correlation between these molecular and immunohistochemistry parameters and a) tumor response and b) lack of early progression will be evaluated using two-sample t and Wilcoxon rank-sum tests, as appropriate, comparing responders with non-responders and comparing patients with stable or better disease versus those with early disease progression, respectively. Both baseline values of these parameters, and changes from baseline to day 14, will be analyzed to determine if either the pre-treatment levels or alterations in these components due to treatment are correlated with responses. Finally, these variables will also be entered as covariates in a Cox [85] proportional hazards regression analysis of the time to disease progression and overall survival.

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## APPENDIX A-1

### 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 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.cancer.gov/reporting/adeers.html> for further clarification. The CAEPR does not provide frequency data; refer to the Investigator's Brochure for this information. Below is the CAEPR for Bevacizumab.

Version 1.1, March 28, 2006<sup>1</sup>

Category (Body System)	Adverse Events with Possible Relationship to Bevacizumab (CTCAE v3.0 Term)	'Agent Specific Adverse Event List' (ASAEL)
<b>ALLERGY/IMMUNOLOGY</b>		
	Allergic reaction/hypersensitivity (including drug fever)	<b><i>Allergic reaction/hypersensitivity (including drug fever)</i></b>
	Allergic rhinitis (including sneezing, nasal stuffiness, postnasal drip)	
<b>BLOOD/BONE MARROW</b>		
	Leukocytes (total WBC)	
	Neutrophils/granulocytes (ANC/AGC)	
<b>CARDIAC ARRHYTHMIA</b>		
	Supraventricular arrhythmia NOS	
	Ventricular fibrillation	
<b>CARDIAC GENERAL</b>		
	Cardiac ischemia/infarction	<b><i>Cardiac ischemia/infarction</i></b>
	Cardiac troponin I (cTnI)	
	Hypertension	<b><i>Hypertension</i></b>
	Hypotension	
	Left ventricular diastolic dysfunction	
	Left ventricular systolic dysfunction	
<b>CONSTITUTIONAL SYMPTOMS</b>		
	Fatigue (asthenia, lethargy, malaise)	
	Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10 <sup>9</sup> /L)	<b><i>Fever (in the absence of neutropenia, where neutropenia is defined as ANC &lt;1.0 x 10<sup>9</sup>/L)</i></b>
	Rigors/chills	<b><i>Rigors/chills</i></b>
	Weight loss	
<b>DERMATOLOGY/SKIN</b>		
	Pruritus/itching	
	Rash/desquamation	<b><i>Rash/desquamation</i></b>
	Ulceration	
	Urticaria (hives, welts, wheals)	<b><i>Urticaria (hives, welts, wheals)</i></b>
	Wound complication, non-infectious	

Category (Body System)	Adverse Events with Possible Relationship to Bevacizumab (CTCAE v3.0 Term)	'Agent Specific Adverse Event List' (ASAEL)
<b>GASTROINTESTINAL</b>		
	Anorexia	<b>Anorexia</b>
	Colitis	
	Constipation	<b>Constipation</b>
	Diarrhea	
	Fistula, GI - Select	
	Heartburn/dyspepsia	<b>Heartburn/dyspepsia</b>
	Leak (including anastomotic), GI: large bowel	
	Mucositis/stomatitis (functional/symptomatic) - Select	<b>Mucositis/stomatitis (functional/symptomatic) - Select</b>
	Nausea	<b>Nausea</b>
	Perforation, GI - Select	
	Vomiting	<b>Vomiting</b>
<b>HEMORRHAGE/BLEEDING</b>		
	Hemorrhage GI - Select	<b>Hemorrhage GI - Select</b>
	Hemorrhage, CNS	<b>Hemorrhage, CNS</b>
	Hemorrhage, GU: vagina	
	Hemorrhage, pulmonary/upper respiratory: lung	<b>Hemorrhage, pulmonary/upper respiratory: lung</b>
	Hemorrhage, pulmonary/upper respiratory: nose	<b>Hemorrhage, pulmonary/upper respiratory: nose</b>
	Hemorrhage/Bleeding - Other (varices-gastric/esophagus)	
<b>INFECTION</b>		
	Infection with normal ANC or Grade 1 or 2 neutrophils - Select	<b>Infection with normal ANC or Grade 1 or 2 neutrophils - Select</b>
<b>METABOLIC/LABORATORY</b>		
	Alkaline phosphatase	
	ALT, SGPT (serum glutamic pyruvic transaminase)	
	AST, SGOT (serum glutamic oxaloacetic transaminase)	
	Bilirubin (hyperbilirubinemia)	
	Creatinine	
	Proteinuria	<b>Proteinuria</b>
<b>NEUROLOGY</b>		
	CNS cerebrovascular ischemia	<b>CNS cerebrovascular ischemia</b>
	Dizziness	
	Neurology – Other: (Leukoencephalopathy syndrome including reversible posterior leukoencephalopathy syndrome (RPLS))	
<b>PAIN</b>		
	Pain - abdomen NOS	
	Pain - chest/thorax NOS	<b>Pain - chest/thorax NOS</b>
	Pain - head/headache	<b>Pain - head/headache</b>
	Pain - joint	<b>Pain - joint</b>
	Pain - muscle	
	Pain - NOS	

Category (Body System)	Adverse Events with Possible Relationship to Bevacizumab (CTCAE v3.0 Term)	'Agent Specific Adverse Event List' (ASAEL)
<b>PULMONARY/UPPER RESPIRATORY</b>		
	Bronchospasm, wheezing	
	Cough	<b><i>Cough</i></b>
	Dyspnea (shortness of breath)	
	Nasal cavity/paranasal sinus reactions	
	Voice changes/dysarthria (e.g., hoarseness, loss or alteration in voice, laryngitis)	<b><i>Voice changes/dysarthria (e.g., hoarseness, loss or alteration in voice, laryngitis)</i></b>
<b>RENAL/GENITOURINARY</b>		
	Renal/Genitourinary - Other (nephrotic syndrome)	
<b>SYNDROMES</b>		
	Cytokine release syndrome/acute infusion reaction	<b><i>Cytokine release syndrome/acute infusion reaction</i></b>
<b>VASCULAR</b>		
	Thrombosis/thrombus/embolism	<b><i>Thrombosis/thrombus/embolism</i></b>
	Visceral arterial ischemia (non-myocardial)	

<sup>1</sup>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 [ADEERSMD@tech-res.com](mailto:ADEERSMD@tech-res.com). Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

**Also reported on Bevacizumab trials but with the relationship to Bevacizumab still undetermined:**

**BLOOD/BONE MARROW** - Hemoglobin; idiopathic thrombocytopenia purpura; platelets

**CARDIAC GENERAL** - Cardiac arrest; pericardial effusion

**COAGULATION** - DIC

**DEATH** - Sudden death (cause unknown)

**DERMATOLOGY/SKIN** - Hypopigmentation

**GASTROINTESTINAL** - Rectal abscess/necrosis; small bowel obstruction; taste alteration

**METABOLIC/LABORATORY** - Hyperglycemia; hypoglycemia; hypomagnesemia; hyponatremia

**MUSCULOSKELETAL/SOFT TISSUE** - Aseptic necrotic bone; gait/walking; myasthenia gravis

**NEUROLOGY** - Aseptic meningitis; confusion; encephalopathy; peripheral neuropathy; seizure; syncope

**OCULAR/VISUAL** - Cataract; watery eye

**PULMONARY/UPPER RESPIRATORY** - ARDS; pneumonitis/pulmonary infiltrates; pneumothorax

**RENAL/GENITOURINARY** - Urinary frequency

**Note:** Bevacizumab 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.

## Appendix A-2

### Comprehensive Adverse Events And Potential Risks List (CAEPR) for OSI-774 (718781)

**Bold** and *italic* text identifies expected adverse events (ASAEL), which may not be needed to be reported via AdEERS.

Version 1.0, November 29, 2004 <sup>1</sup>

Category (Body System)	Reported Adverse Events (CTCAE v3.0 Term)	'Expected' Adverse Events (ASAEL - use for expedited reporting)
<b>CONSTITUTIONAL SYMPTOMS</b>		
	Fatigue (asthenia, lethargy, malaise)	<b><i>Fatigue (asthenia, lethargy, malaise)</i></b>
<b>DERMATOLOGY/SKIN</b>		
	Dry skin	<b><i>Dry skin</i></b>
	Hair loss/alopecia (scalp or body)	
	Pruritus/itching	<b><i>Pruritus/itching</i></b>
	Rash/desquamation	<b><i>Rash/desquamation</i></b>
	Rash: acne/acneiform	<b><i>Rash: acne/acneiform</i></b>
<b>GASTROINTESTINAL</b>		
	Anorexia	<b><i>Anorexia</i></b>
	Diarrhea	<b><i>Diarrhea</i></b>
	Dry mouth/salivary gland (xerostomia)	<b><i>Dry mouth/salivary gland (xerostomia)</i></b>
	Heartburn/dyspepsia	<b><i>Heartburn/dyspepsia</i></b>
	Mucositis/stomatitis (functional/symptomatic): - Select	<b><i>Mucositis/stomatitis (functional/symptomatic): - Select</i></b>
	Nausea	<b><i>Nausea</i></b>
	Taste alteration (dysgeusia)	<b><i>Taste alteration (dysgeusia)</i></b>
	Vomiting	<b><i>Vomiting</i></b>
<b>METABOLIC/LABORATORY</b>		
	ALT, SGPT (serum glutamic pyruvic transaminase)	<b><i>ALT, SGPT (serum glutamic pyruvic transaminase)</i></b>
	AST, SGOT(serum glutamic oxaloacetic transaminase)	<b><i>AST, SGOT(serum glutamic oxaloacetic transaminase)</i></b>
	Bilirubin (hyperbilirubinemia)	<b><i>Bilirubin (hyperbilirubinemia)</i></b>
<b>OCULAR/VISUAL</b>		
	Dry eye syndrome	<b><i>Dry eye syndrome</i></b>
<b>PAIN</b>		
	Pain - head/headache	<b><i>Pain - head/headache</i></b>
	Pain - oral cavity	
<b>PULMONARY/UPPER RESPIRATORY</b>		
	Cough	
	Dyspnea (shortness of breath)	
	Pneumonitis/pulmonary infiltrates	<b><i>Pneumonitis/pulmonary infiltrates</i></b>

<sup>1</sup>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 ADEERSMD@tech-res.com. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

**Also reported on OSI-774 trials but with the relationship to OSI-774 still undetermined:**

abdominal pain in conjunction with diarrhea; anxiety; blurred vision; CNS ischemia; confusion; dehydration and increased creatinine concurrent with, and likely directly related to diarrhea, anorexia, nausea and vomiting has been seen; fever; GI hemorrhage; hemorrhage-nose; infection with neutropenia in combination with myelosuppressive therapies; INR in patients taking Coumadin; keratitis; ocular surface disease; orbital cellulitis; pancreatitis; pneumatosis; secondary skin infection from rash without neutropenia; uveitis;

**Notes:** 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.

## APPENDIX B

### Performance Status Criteria

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. 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).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

## The University of Chicago

### Tissue and Blood Sample Collection Form

Clinician/Research Nurse: Please Fill Out

**Tissue Samples**

Patient Name or Initials: \_\_\_\_\_ UC MR # (if applicable): \_\_\_\_\_

Patient Protocol ID #: **11956-**\_\_\_\_\_ Date Tissue Obtained: \_\_\_\_\_

Institution: \_\_\_\_\_ Attending Physician: \_\_\_\_\_

Site of Biopsy: \_\_\_\_\_ Site of Primary Tumor: \_\_\_\_\_

**Pre/Post Therapy** (Please circle)

Did Surgical Pathology receive tissue for diagnosis? **Yes No**

Contact Person's Phone Number and email Address at Affiliate:

**Blood Samples\***

		date drawn	time	date shipped	
Pre-Therapy:	1 green top/plasma				(batched on dry ice)
	1 gold top/serum				(batched on dry ice)
Week 2:	1 gold top/serum				(batched on dry ice)
	1 green top/plasma				(batched on dry ice)
Week 8:	1 gold top/serum				(batched on dry ice)

\* Please label tubes as either plasma or serum.

Researcher: Please Fill Out

Date Samples received: \_\_\_\_\_ Data entered into Database: **Yes No**

Name of Data Manager informed: \_\_\_\_\_ Date Informed: \_\_\_\_\_

Location in -80C freezer **UC 0** -

Approximate size and number of tissue: \_\_\_\_\_

Notes:

**Questions or Problems?** Please contact:

Dr. Rifat Hasina, University of Chicago, 5841 S Maryland, MC 3083, Chicago, IL 60637

Phone 773-834-9814 or 773-702-0119, Pager 773-753-1880-9747, email:

rhasina@bsd.uchicago.edu

## **SHIPPING DIRECTIONS**

All shipments must contain a completed Sample Identification form.

Prior to shipment please email the following person the FedEx bill number:

Rifat Hasina: rhasina@bsd.uchicago.edu

**Tissue Samples** need to be shipped on **dry ice**; may be batched at institution and shipped with Plasma/Serum samples to the below address:

Dr. Rifat Hasina  
c/o Dr. Mark Lingen  
University of Chicago  
FMI Dock/Lab Supply  
5830 S. Ellis Ave  
Room G-02  
Chicago, IL 60637  
Phone: 773-834-9814

**Plasma/Serum Samples** need to be shipped on **dry ice**; may be batched at institution and shipped with Tissue Samples to:

Dr. Rifat Hasina  
c/o Dr. Mark Lingen  
University of Chicago  
FMI Dock/Lab Supply  
5830 S. Ellis Ave  
Room G-02  
Chicago, IL 60637  
Phone: 773-834-9814