TITLE: A Phase II Study of OSI-774 in Combination with Cisplatin and Docetaxel in Metastatic or Recurrent Head and Neck Squamous Cell Cancer

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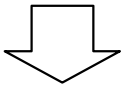
MDACC Supplied Agents:
OSI-774 (NSC #; 61,874*)* (Tarceva, erlotinib); Genentech, Inc. (San Francisco, California)
Cisplatin; commercially available
Docetaxel (Taxotere); commercially available

SCHEMA

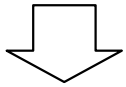
Patients with metastatic or recurrent head and neck squamous cell cancer.
No prior chemotherapy for recurrent disease.



Histologic confirmation
Baseline staging studies
Baseline serologies
Baseline biopsy for biomarker studies

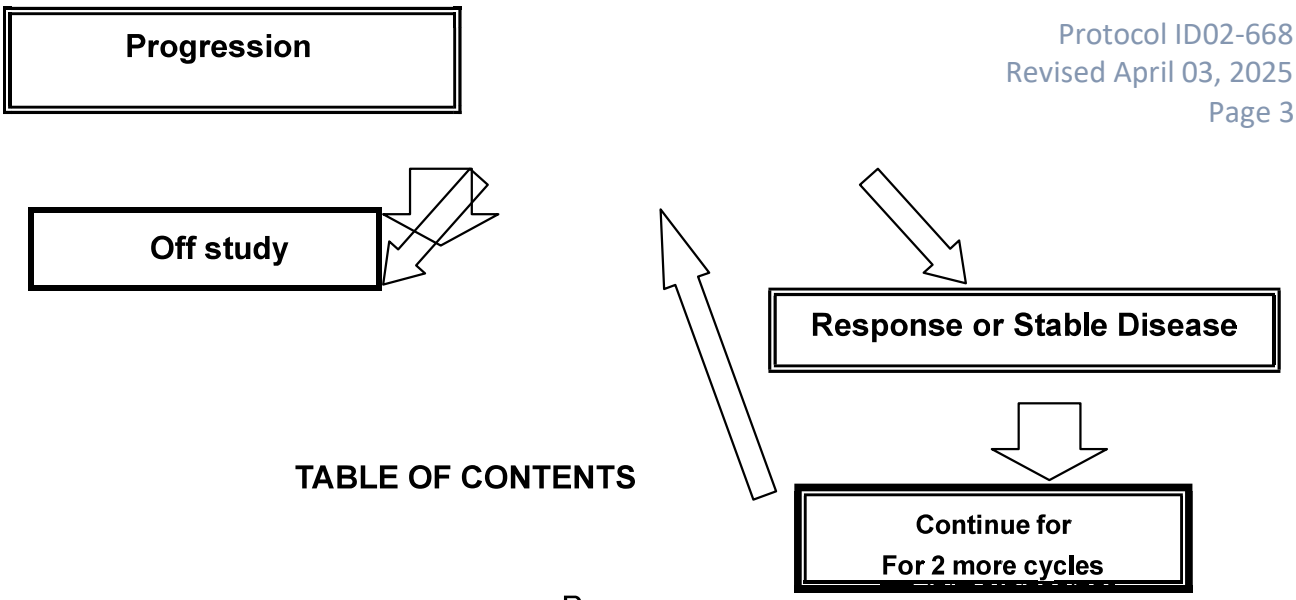
For the first 6 patients:

Cisplatin (75mg/m^2) IV q3wks
+
Docetaxel (60mg/m^2) IV q3wks
+
OSI-774 (100mg) oral daily dose



After cycle 1, if no toxicity greater than grade 2 occurs, escalate OSI-774 dose to 150 mg for cycle 2.
After 6 patients demonstrate tolerability, all patients thereafter will begin at OSI-774 150mg dose.

Restaging after 2 Cycles



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1. OBJECTIVES

1.1. The primary objective is to evaluate the response rate of the combination of cisplatin, docetaxel and OSI-774 in patients with metastatic or recurrent head and neck squamous cell cancers.

1.2. Secondary objectives are to assess the time to disease progression, overall survival as well as safety and toxicity profile.

2. BACKGROUND

2.1 *Study Disease*

Head and neck squamous cell carcinoma (HNSCC) is the 5th leading cause of cancer incidence and the 6th leading cause of cancer death. Per year in the United States, there are approximately 40,400 new cancer cases and 12,300 cancer deaths [1]. It is strongly associated with tobacco and alcohol use. In early stage disease (stage I and II) curative measures can be undertaken with surgery and radiation therapy. Unfortunately, treatment options for advanced or recurrent disease remain limited. Advanced disease (stage III and IV) has a less than 30% cure rate [2].

The traditional induction regimen consists of cisplatin and 5-fluorouracil (5-FU). Combination therapy with cisplatin and 5-FU is preferred over single agent therapy with cisplatin or 5-FU, as shown in a phase III trial (32% vs. 17% vs. 15%, p=0.035) [3]. In other randomized trials, the combination of cisplatin and 5-FU proved superior to single agent methotrexate (32% vs. 10%; p<0.001) and combination carboplatin/5-FU (response rate 21%; p=0.05) [4]. Although overall response rates to cisplatin/5-FU were higher, a median survival of only 6 months continues to be seen in recurrent or metastatic HNSCC disease regardless of regimen and/or response rate. Despite recent advances in combined cytotoxic therapy, there has been no meaningful survival advantage in patient outcomes. Current treatment options are therefore limited.

2.2 *Study Agent* : OSI-774 (Tarceva, erlotinib); Genentech, Inc. (San Franscisco, California); quinazoline (EGRF tyrosine kinase inhibitor)

The epidermal growth factor receptor (EGFR; erbB1) is a 170kD transmembrane glycosylated phosphoprotein with tyrosine kinase activity. Ligands for the receptor include EGF and transforming growth factor-[alpha] (TGF-□). EGFR is overexpressed in 80-90% of HNSCC and is a marker of decreased disease-free

and cause-specific overall survival. The level of EGFR overexpression typically corresponds with the rate of tumorigenesis. EGFR is known to participate in cell proliferation (ras/raf/MAP kinase pathway), inhibition of apoptosis (PI3 kinase/Akt pathway), tumor cell motility and metastasis.

Studies in head and neck squamous cell carcinoma cell lines and preclinical animal models have shown that inhibition of EGFR will arrest cell proliferation and tumor growth. Due to its ability to promote tumorigenesis, EGFR is a promising target for biological therapy. Several places of EGFR action are promising targets of inhibition; these include the ligand binding site, kinase activation, protein production and downstream signaling pathways. Initial clinical data on previously developed agents suggests that the addition of chemotherapy will provide more efficacy than if used as a single agent.

OSI-774 (Tarceva, erlotinib) is an active oral quinazoline that selectively inhibits EGFR tyrosine kinase, prevents autophosphorylation of EGFR, and arrests cell cycle growth in the G_0/G_1 phase [5]. It is currently under investigation in the treatment of solid tumor malignancies, specifically head and neck cancer, non-small cell lung cancer, breast cancer and other squamous cell carcinomas [6].

Studies have confirmed the selectivity of OSI-774 to the EGFR tyrosine kinase by evaluating the src homology domain that contains the adapter protein SHC. In malignant tumors, constitutive phosphorylation of SHC is often found. OSI-774 has been shown in vitro to block EGF-induced tyrosine phosphorylation of SHC. In head and neck tumor cell line (HN5), the percentage of cells arrested in G_1 phase increased from 24% to 56% with the addition of OSI-774 [7-10]. This suggests cytostasis. However, additional in vitro evidence suggests that inhibition of EGFR promotes apoptotic pathways. Animal xenograft models using HN5 carcinomas in athymic mice demonstrated significant clinical anti-tumor effect [11].

Single agent activity of OSI-774 (150mg/day) has been studied in EGFR positive NSCLC in a phase II trial. In this study, a partial response rate of 11% and a 1 year survival of 48% was demonstrated [12]. Although promising, the data brings up the hypothesis that OSI-774 used in combination with cytotoxic agents may be more efficacious.

OSI-774 has been used in combination with chemotherapeutic agents on the HN5 model. Some of these include cisplatin (Platinol), doxorubicin HCl (Adriamycin), 5-fluorouracil (5-FU), paclitaxel (Taxol), vinorelbine tartrate (Navelbine), and gemcitabine HCl (Gemzar). There was no increase in lethality with any of the agents. In paclitaxel combination experiments, improved anti-tumor responses were seen at ½ paclitaxel MTD when compared to single agent paclitaxel or single agent OSI-774. Anti-tumor

effect was also seen at greater levels when paclitaxel and OSI-774 were given concurrently. Although no in vitro combination studies were provided for the addition of docetaxel, the paclitaxel data appears promising [6].

In humans with solid tumors, phase I single agent OSI-774 trials indicate that the MTD is 150mg daily. The most common adverse toxicities were rash and diarrhea. At higher doses, the most common side effects were diarrhea (67-86%), nausea/vomiting, headache, fatigue and rash (59%) [13]. In HNSCC, OSI-774 was tested in patients refractory to conventional treatment. Biomarker levels (EGFR, AKT and ERK) showed that EGFR activation of signal transduction pathways was inhibited by OSI-774 at 25-200mg/day [14]. A phase I trial combined OSI-774 (mg/day) with docetaxel (mg/m^2 IV Q3weeks) at various doses (100/75, 150/75, 125/75) in various solid tumors, inclusive of NSCLC, nasopharyngeal carcinoma, bladder, ovary and stomach. Dose limiting toxicity (febrile neutropenia) was reached in three of six patients. Dose reductions of docetaxel were performed and a regimen of 100/60 was reported as tolerable. Antitumor effect (stable, partial or complete response) was seen in 7 of 16 patients. Preliminary pharmacokinetic evaluation indicates that OSI-774 does not interfere with docetaxel [15].

A number of phase II trials involving OSI-774 at 150 mg/m^2 are underway involving patients with HNSCC, ovarian cancer and non-small cell lung cancer (NSCLC). The phase II HNSCC trial enrolled 114 patients with advanced/recurrent disease. Both EGFR positive and negative tumors were included. Seventy-eight patients were evaluated and 10 (13%) patients achieved PR and 23 (29%) patients had stable disease. Toxicities included acneiform rash, diarrhea, nausea, vomiting, headache and fatigue [16].

2.3 ***Other Agent(s)***

Cisplatin is an alkylating agent that crosslinks DNA. It is cytotoxic and nonspecific to cell cycle. The major side effects of cisplatin include nausea, vomiting, myelosuppression (nadir days 18-23), nephrotoxicity, and neurotoxicity. Randomized clinical trials showed that cisplatin in combination with 5-FU had a 30% response rate in advanced HNSCC. Single-agent cisplatin was shown to have a lower response rate but no difference in overall survival was seen in this patient population [17].

Docetaxel is a derivative of the diterpenoid family (taxoids) and is an extract from the Pacific yew tree (*taxus brevifolia).* Taxoids stabilize tubulin and lead to cell cycle arrest. Docetaxel specifically inhibits cells at the G_2M phase. It binds to plasma proteins, has wide bioavailability (except central nervous system), and is degraded and excreted by the liver. Phase I clinical trials established the human MTD to be 100 mg/m^2 intravenously over 1 hour every 21 days. Toxicities included fatigue, alopecia, sensory neuropathy, mucositis, fluid retention, rash, and

hypersensitivity reactions; but the usual dose-limiting toxicity was neutropenia [18, 19].

Two phase II studies in the mid-1990's showed single agent docetaxel (100 mg/m^2) had a response rate of 27% to 43% in 68 HNSCC patients [20, 21]. Docetaxel (100 mg/m^2) in combination with cisplatin (75 mg/m^2) was evaluated in a phase II multicenter trial in patients with metastatic, advanced or unresectable HNSCC disease. Four patients (22%) achieved a complete response (CR) and 9 patients (50%) a partial response (PR). In this study, there were four early deaths and three patients that withdrew due to major toxicities (neutropenia, fatigue, ototoxicity, nausea, hypotension and stomatitis) [19].

However, Glisson et al. showed that the combination of lower dose docetaxel and cisplatin was tolerable in recurrent HNSCC in a phase II trial. Docetaxel (75mg/m^2) and cisplatin (75mg/m^2) were given every 3 weeks to 36 patients with metastatic or recurrent HNSCC. The overall response rate in 32 evaluable patients **Page 8** was 40%. 6% achieved complete response. Median time to progression was 4 months and survival was 9.6 months. At 1 year, survival was 27%. Neutropenia was seen in 71% of patients but only 18% had grade 3 or higher infectious complications. Nausea and vomiting were found in only a small percentage of the patients (11% and 8%, respectively). The data from this clinical trial suggested that the combination of cisplatin and docetaxel had acceptable toxicity and a successful palliative effect on advanced or recurrent HNSCC [17].

TPF [docetaxel 80 mg/m^2 (day1), cisplatin 40 mg/m^2 (days 1-2), and 5-fluorouracil 1000 mg/m^2 (days 1-3)] has been evaluated as an induction therapy as well as TPF with leucovorin (TPFL). Of the sixteen patients evaluated in a phase II TPF study, 4 (25%) achieved CR, 8 (50%) PR and 3 (19%) had stable disease. The median time to progression was 7.5 months and median survival was 11 months. At one year, overall survival was 49% and febrile neutropenia was the most common toxicity [22]. TPFL [docetaxel 25 to 60 mg/m^2 (day 1), cisplatin 25 mg/m^2 (days 1-5), leucovorin 500 mg/m^2 (days 1-5), 5-FU 700 mg/m^2 (days 2-5)] was evaluated in a phase II trial at Dana Farber. All 23 evaluated patients responded to this regimen with 14 (61%) achieving a CR. There was some significant associated toxicity with this regimen [18]. Despite the increase in median survival time and percentage achieving CR, TPF and TPFL regimens have higher toxicity than the cisplatin and docetaxel combination.

2.4 Rationale

Combination cytotoxic chemotherapy remains the current treatment modality for HNSCC, but the overall prognosis remains poor. In theory, targeting EGFR with inhibitory agents may provide additional synergistic anti-tumor activity. There are no prior studies evaluating OSI-774 in combination with cisplatin and docetaxel in metastatic and recurrent HNSCC patients. As OSI-774 has a different toxicity profile from cisplatin and docetaxel, it is

unlikely that there will be significant overlapping adverse events. Establishment of a maximal tolerated dose with the ultimate goal of demonstrating beneficial clinical activity by response rate is essential to improve this patient population's outcomes.

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Patients must have histologically or cytologically confirmed metastatic or recurrent head and neck squamous cell carcinoma from the primary lesion and/or lymph nodes of the oral cavity, oropharynx, hypopharynx, or larynx.

3.1.2 Patients must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm with conventional techniques or as ≥10 mm with spiral CT scan. See section 9.2 for the evaluation of measurable disease.

3.1.3 Patients who have not received any prior systemic chemotherapy for metastatic or recurrent head and neck squamous cell carcinoma. If patients have received prior combined modality therapy, they must be off therapy for at least 6 months.

3.1.4 Age ≥18 years.
Because no dosing or adverse event data are currently available on the use OSI-774 in combination with cisplatin and docetaxel in patients <18 years of age, children are excluded from this study.

3.1.5 No acute intercurrent illness or infection.

3.1.6 ECOG performance status ≤2 (Karnofsky ≥60%; see Appendix A).

3.1.7 Patients must have normal organ and marrow function as defined below:

- leukocytes ≥3,000/□L
- absolute neutrophil count ≥1,500/□L
- platelets ≥100,000/□L

- hemoglobin □□8g/dL
- total bilirubin within normal institutional limits
- AST(SGOT)/ALT(SGPT)
- ≤2.5 X institutional upper limit of normal if alkaline phosphatase is ≤ ULN OR

Alkaline phosphatase may be up to 4 x ULN if transaminases are ≤ ULN

- creatinine ≤2.0 x ULN OR

creatinine clearance ≥60 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal.

3.1.8 The effects of OSI-774 on the developing human fetus at the recommended therapeutic dose are unknown. For this reason, as other therapeutic agents used in this trial are known to be teratogenic, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, for the duration of study participation, and for 3 months after the completion of therapy. 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 with a history of non-melanoma skin cancer, or other malignancies treated 5 years or more prior to the current tumor, from which the patient has remained continually disease-free, are eligible.

3.1.10 Ability to understand and the willingness to sign a written informed consent document.

3.2 Exclusion Criteria

3.2.1 Patients who have had chemotherapy or non-palliative radiotherapy for their recurrent or metastatic head and neck cancer.

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 History of allergic reactions attributed to compounds of similar chemical or biologic composition to OSI-774 or other agents used in the study.

3.2.5 Patient has received prior biologic therapy targeting EGFR.

3.2.6 Patient has signs or symptoms of acute infection requiring systemic therapy.

3.2.7 Patient exhibits confusion, disorientation, or has a history of major psychiatric illness that may impair patient's understanding of the informed consent.

3.2.8 Patient requires total parenteral nutrition with lipids.

3.2.9 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.10 Histology other than squamous cell carcinoma.

3.2.11 Patients refusing to sign the informed consent.

3.2.12 Patients with a history of severe hypersensitivity reaction to Taxotere®.

3.2.13 Patients with pre-existing peripheral neuropathy NCI CTC grade 2 or worse.

3.2.14 Pregnant or lactating women are excluded from this study because OSI-774 is an unknown Class agent 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 OSI-774, breastfeeding should be discontinued if the mother is treated with OSI-774. These potential risks may also apply to other agents used in this study.

3.2.15 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 OSI- 774, cisplatin, or docetaxel or other agents administered during the study. Appropriate studies will be undertaken in patients receiving combination anti-retroviral therapy when indicated.

3.2.16 **Inclusion of women and minorities.** Both men and women and members of all ethnic groups are eligible for this trial. The proposed study population will consist of patients of all ethnic backgrounds and either gender, treated at MD Anderson Cancer Center Houston, Texas.

4. TREATMENT PLAN

4.1 Agent Administration

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks for OSI-774, cisplatin and docetaxel are described in Section 6. Appropriate dose modifications for OSI-774, cisplatin, and docetaxel 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.

4.1.1 Treatment Regimen: A treatment cycle will include intravenous cisplatin (75 mg/m^2 every 3 weeks), intravenous docetaxel (60 mg/m^2 every 3 weeks), and oral OSI-774 (100 mg daily). Docetaxel at 60 mg/m^2 will be administered over a 1 hour intravenous infusion followed

by cisplatin at 75 mg/m^2 over a 2-hour infusion. Docetaxel and cisplatin treatments will be repeated every 21 days. OSI-774 will be administered orally on Day 1 at 100 mg dose. Patients will continue on daily OSI-774 until a study endpoint or removal from study is reached.

4.1.2 Intrapatient Dose Escalation: **OSI-774:** If a patient tolerates the first cycle of this treatment dosage with minimal toxicity (grade 2 or less), OSI-774 will be escalated to 150 mg daily oral dose for cycle 2. This escalated dose will begin on Day 1 of cycle 2. When 6 patients have been treated with 150 mg OSI-774 and do not report toxicity > grade 2 causing treatment delay greater than one week, further patients enrolled on study will begin treatment at 150 mg OSI-774. If significant toxicities causing treatment delays are witnessed in 3 or more patients, additional patients will be enrolled at 100 mg OSI-774 daily oral dose and continue at this dose for the duration of the protocol. Patients experiencing toxicity related treatment delays will not be dose escalated to 150 mg OSI-774 daily dose. An example of significant

toxicity would include grade 3-4 neutropenia with fever or neutropenia for more than seven days that causes treatment delay over one week.

Docetaxel: If a patient tolerates cisplatin 75 mg/m^2, docetaxel 60 mg/m^2, and OSI-774 150 mg/day with minimal toxicity (grade 2 or less), docetaxel may then be escalated to 75 mg/m^2 for remaining cycles.

4.1.3 OSI-774 Dosage, Administration and Storage: Based on dose selection, subjects will receive 100 mg or 150 mg to be taken daily, starting on Day 1 of study. Tablets should be taken preferably in the morning with up to 200 ml of water, either 1 hour before or 2 hours after meals. Subjects will be supplied with enough tablets, based on dose level, for three consecutive weeks of dosing. Patients who are unable to swallow tablets may dissolve the tablets in distilled water for administration. OSI-774 will be administered in oral 100 mg or 150mg tablets. The starting dose is 100 mg daily for 21 days (1 cycle). Patients may take tablets orally be administered via PEG or G tube. The drug is to be stored at room temperature.

4.1.4 TAXOTERE® infusion solution, if stored between 2 and 25ºC (36 and 77ºF) is stable for 4 hours. Fully prepared TAXOTERE® infusion solution (in either 0.9% Sodium Chloride solution or 5% Dextrose solution) should be used within 4 hours (including the 1 hour intravenous administration). This will be repeated every 21 days.

4.1.5 Cisplatin (Cis-Diaminedichloroplatinum) (CDDP) is administered via intravenous route over 2 hours. Mix with normal saline and give with pretreatment and posttreatment intravenous hydration and mannitol diuresis. This will be repeated every 21 days.

4.1.5.1 Stored (dry, unopened vials) at refrigeration temperature (4- to 8 degrees C). Reconstitution results in a solution that is stable for not more than 1 hour at room temperature when exposed to normal room illumination, and not more than 8 hours at room temperature when protected from light. Administration is via intravenous route and is given over 2 hours.

4.2 Supportive Care Guideline

4.2.1 It is recommended for patients to receive standard premedication with oral dexamethasone at 8mg the evening before docetaxel infusion,

8mg the morning of docetaxel infusion, and 8mg twice daily for 3 days following docetaxel infusion. Intravenous dexamethasone at 20mg and a 5-HT3 antagonist will be administered before cisplatin infusion. However, this may be modified at the discretion of the attending physician.

4.2.2 INR Monitoring for patients on concomitant anticoagulation therapy: Because of the potential for drug-drug interaction between Tarceva and warfarin, patients in this study who are receiving concomitant warfarin (including both therapeutic and prophylactic "low-dose" warfarin) or coumadin-derivative anticoagulants, should have close monitoring of the INR and prothrombin time and adjustment of the anticoagulant dose as clinically indicated.

4.2.3 Beginning in cycle 1, patients will receive treatment with: 1) Pegfilgrastim (Neulasta®) at 6mg subcutaneously every 3 weeks beginning on day 2 of cycle 1 after administration of chemotherapy. 2) Darbepoetin alfa (Aranesp®) 300mcg subcutaneously every 3 weeks starting on day 1 of cycle 1 after administration of chemotherapy if hemoglobin is < 11 g/dl. (If hemoglobin is >/= 11 g/dl and hemoglobin drops to < 11 g/dl, treatment will begin when hemoglobin drops to < 11 g/dl.)

4.3 Duration of Therapy

In the absence of treatment delays due to adverse events, chemotherapy treatment may continue for 6 cycles or more or until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse events(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.
- OSI-774 may be taken until disease progression or unacceptable toxicity or completion of study.

Patients will be evaluated (i.e. follow up visit with labs and radiologic evaluations) every 12 weeks ± 7 days while receiving continued OSI-774 and drug will be dispensed for 3 months supply. Overall survival for the patients enrolled will also be assessed. Overall survival is defined as the time from start of treatment to death from any cause. Subjects who have not died while on study or are lost to follow-up will be censored at the last date, they are known to be alive or followed up to 3 years after last treatment date. Final date of death will be verified via the Social Security Death Index Database. For subjects whose date of death cannot be verified via this mechanism, verification of patient's current status by medical chart review (i.e. ClinicStation) will be utilized. If final date of death cannot be determined by either of the mechanisms indicated, final subject status will remain unknown. Subjects who withdraw consent will be censored on the date of withdrawal.

5. DOSING DELAYS/DOSE MODIFICATIONS

5.1 Treatment of OSI-774 Toxicity and Dose Modification:

Toxicity grading is based on NCI-CTC (See Appendix) and a treatment algorithim for the most common toxicities, diarrhea and skin rash is outlined below (Dose OSI-774 at 150mg):

Toxicity NCI- CTC Grade	**Study Drug Dose Management Modification Guide**	
Diarrhea		
Grade 1	None	Consider loperamide (4mg first Onset, followed by 2mg q 2-4 Hours until free of diarrhea for 12 hours
Grade 2	None	Loperamide (4mg at first Onset, followed by 2mg q 2-4 Hours until free of diarrhea for 12 hours
Grade 3	Interrupt	Interrupt until resolution to Grade 1, and restart at 100mg

Grade 4	Interrupt	Interrupt until resolution to Grade 1, and restart at 100mg
<u>Rash</u>		
Grade 1	None	Any of the following: minocycline (200mg po bid followed by 100mg po bid for 7-10 days), topical tetracycline, topical clindamycin, topical silver sulfadiazine, diphenhydramine, oral prednisone (short course) at discretion of investigator
Grade 2	None	Managed as described above
Grade 3	Interrupt	Manage as described above;
		Dose reduction with next cycle; dose can be re-escalated when rash is Grade□□2
Grade 4	Interrupt	Manage as described above Consider removal from study

5.1.1. If grade 3 or 4 toxicity or any OSI-774 related toxicity occurs at the 150mg dose, OSI-774 will be held until the patient has □grade 1 toxicity. OSI-774 will be restarted at 100mg daily dose. Other serious adverse events of Grade 3 or 4 adverse events considered to be related to OSI-774 should be managed with dose interruption until resolution of the event (Grade □1). If unresolved for >2 weeks, the patient will be withdrawn from the study. Patients may re-start the drug at the same dose level if the following criteria are met:

- Resolution of the event to Grade 1
- ECOG performance status of less than 2

5.1.2. If, following re-initiation of study drug the adverse event recurs at Grade 2, study drug should again be held until resolution and then restarted at a lower dose. If a subject has more than two adverse events with OSI-774 related toxicity requiring reduction/discontinuation, OSI-774 will be discontinued. Patients may continue to be treated with cytotoxic chemotherapy as tolerated, if appropriate.

5.2 Dose modifications for chemotherapy:

5.2.1 Prior to receiving chemotherapy, patients must have an absolute neutrophil count $\geq$ 1,500/mm^3 and a platelet count $\geq$ 100,000/mm^3.

5.2.2 If grade 3 or 4 toxicity related to cytotoxic agents occurs while the patient is on the OSI-774 100mg dose, dose reduction for the next cycle of chemotherapy will occur. Only one of the cytotoxic agents will be dose reduced for each cycle depending on the nature of the patient's toxicity. OSI-774 will be maintained at the 100mg oral dose if cytotoxic agent dose reduction is necessary.

5.2.3 If a patient continues to experience grade 3 or 4 toxicity with the next cycle of chemotherapy, additional dose reduction of the second cytotoxic agent will occur. If persistent grade 3 or 4 toxicity remains, patient will be removed from the study.

5.2.4 Cisplatin will be dose reduced from 75mg/m^2 to 60mg/ m^2 if toxicity consistent with its side effect profile occurs. As an example, if nephrotoxicity occurs, cisplatin will be dose reduced for the next cycle.

5.2.5 Docetaxel will be reduced per the following guidelines:

Thrombocytopenia. Grade 4 thrombocytopenia requires a dose reduction. Recommended dose reduction is 25%.

Neutropenia. Patients with afebrile grade 4 neutropenia 7 days or grade 4 neutropenia associated with fever (one reading of oral temperature > 38.5° C, or three readings of oral temperature > 38.0° C in a 24-hour period) should be dose reduced.

Dose Modifications for Neutropenia

Dose Level	Taxotere® Dose (mg/m^2)	Taxotere® Dose (mg/m^2)

Dose Given That Cycle	75mg/m^2	60mg/m^2
Level –1 (for 1st dose-reduction due to neutropenia)	75mg/m^2, add growth factor support	60mg/m^2, add growth factor support
Level –2 (for 2nd dose-reduction due to neutropenia)	60mg/m^2, continue growth factor support	50mg/m^2, continue growth factor support

Hepatic Dysfunction. Liver function tests should be evaluated prior to each treatment in the q 3 wk schedule. Patients who develop abnormal liver function tests for any reason while on the study will have the following dose reductions:

Dose Modifications for Abnormal Liver Function (Taxotere®)

Bilirubin		Alkaline phosphatase		SGOT or SGPT	Action
> ULN	or	> 5 x ULN	or	> 5 x ULN	Wait ≥3 weeks. If recovered*, reduce Taxotere® dose by 25%. If not, off study.
≥ULN	and	≥5 x ULN	and	1.6 – 5 x ULN	Reduce Taxotere® dose by 25%

*Bilirubin ≥ULN *and* alkaline phosphatase ≥5 x ULN *and* SGOT or SGPT ≥5 x ULN.
Note: A maximum of two dose reductions per patient are allowed.
ULN = upper limit of normal for institution

Stomatitis. If stomatitis is present on day 1 of any cycle, treatment should be withheld until stomatitis has resolved. If Grade 3/4 stomatitis occurs, the dose of Taxotere should be reduced 25% for subsequent cycles.

Peripheral Neuropathy. The Taxotere dose should be reduced by 25% for Grade 2 neuropathies. Treatment should be discontinued for Grade 3/4 neuropathies.

Hypersensitivity Reactions. See Appendix D for guidelines for the management of hypersensitivity reactions. Treatment should be discontinued for Grade 4 hypersensitivity reactions. There are no dose reductions for hypersensitivity reactions.

Fluid Retention. See Appendix E for the treatment template for fluid retention. There are no dose reductions for fluid retention.

Other Non-Hematologic Toxicities. For Grade 3 and 4 toxicities, treatment should be withheld until the toxicity resolves to Grade 1 or less, then reinstituted (if medically appropriate) at a 25% dose reduction. If treatment is withheld for longer than three weeks due to Grade 3/4 toxicity, the patient will be withdrawn from the study.

6. AGENT FORMULATION AND PROCUREMENT

6.1 OSI-774

6.1.1 Formulation of OSI-774: In addition to the active ingredient, OSI-774, tablets contain lactose (hydrous), microcrystalline cellulose, sodium starch glycolate, sodium lauryl sulfate, and magnesium stearate. Study drug for daily oral administration will be supplied in 25, 100 and 150 mg tablets of OSI-774 in bottles.

6.1.2 Pharmacology: OSI-774 inhibits human EGFR tyrosine kinase with an IC□0 of 2nM (0.786 mg/ml) in an in vitro enzyme assay and 20nM (7.86 ng/ml) I intact tumor cells. This inhibition is selective for EGFR tyrosine kinase, results in cell cycle arrest at G1, and is reversible. Oral administration of OSI-774 in mice results in a 70% reduction in EGFR autophosphorylation in human xenografts. Marked growth inhibition of HN5 and A431 xenografts in nude mice has been demonstrated. Data on drug exposure and antitumor responses in these xenograft models were analyzed to estimate the optimal plasma concentration of OSI-774 for antitumor activity in humans. Based on these models, a target plasma concentration of □□500 ng/ml was selected.

6.1.2.1 In addition to single-agent activity in the xenograft in vivo systems, OSI-774 was evaluated in combination with a number of chemotherapy agents to determine possible interactions. There was no increase in lethality when combined with cisplatin, doxorubicin, 5-FU, paclitaxel, vinorelbine and gemcitabine. There were additive effects when OSI-774 was combined with gemcitabine, paclitaxel, doxorubicin and cisplatin.

6.1.3 Pharmacokinetics: The volume of distribution in both rats and dogs is about 3L/kg with oral bioavailability 77% and 88% respectively. OSI-774 is metabolized in dogs and rats, with only a small amount of the

compound excreted unchanged in the feces, bile and urine. In vitro studies indicate that OSI-774 and its active metabolite OSI-420 are metabolized by CYP 1A2, 3A4, 3A5 and 1A1. Potential interactions between OSI-774 and substrates and inhibitors of CYPs have not been evaluated in clinical trials. The lowest Ki for OSI-774 and OSI-420 metabolism observed in the in vitro studies was 8□M (for OSI-774 with 3A4), indicating that if OSI-774 is an inhibitor of 3A4 metabolism, it is not likely a strong inhibitor. Plasma protein binding of OSI-774 ranges from 92% to 95% in mouse, rat, monkeys and man and is 85% in dogs.
In addition, OSI-774 plasma protein binding depends on the levels of □-1-acid glycoprotein (AAG). Thus, AAG might be a significant determinant of pharmacokinetic and possibly pharmacokinetic and pharmacodynamic relationships in patients.

6.1.3.1 Review of the pharmacokinetic profiles from OSI-774 Genentech Studies 248-005 and 248-004 revealed dose-related increases in exposure to OSI-774. Exposure to the active metabolite (OSI-420) represented □□10% of the parent compound, with an inter-patient variability in exposure of □□2-fold. Repetitive daily dosing resulted in drug accumulation. The target average plasma concentration for clinical efficacy (500 ng/ml) was achieved at doses of □100 mg in both the daily (Study 248-004) and weekly (Study 248-005) dosing studies. At the recommended dose of 150mg/day, the accumulation ratio was 2.5□1.2, minimum plasma steady-state concentration averaged 1.2□0.62□g/ml, which is above the target concentration, and the mean half-life was □24 hours.

6.1.4 Toxicology: The major effects attributed to OSI-774 in toxicology studies involved the hepatobiliary, gastrointestinal, and renal systems, as well as the cornea and skin, with reversibility noted on drug discontinuation. In an exploratory toxicology study performed in cynomolgus monkeys, emesis and loose stools were observed in animals treated at 100 mg/kg/day for 7 days. Elevations in serum bilirubin were noted in animals treated at 200mg/kg/day for 7 days. One animal in the 20 mg/kg/day group expired. The cause of this death was not identified at necropsy. Dosing 400 mg/kg/day was not tolerated beyond 4 days because of serum bilirubin elevations, frequent stools, decreased activity, and dehydration in 3 of 4 animals. OSI-774 did not induce microbial or mammalian cell gene mutations in vitro and did not produce chromosomal aberrations in

vitro or in vivo. No studies to assess the effects of OSI-774 on reproductive function or the potential for teratogenicity or carcinogenicity have been performed.

6.1.4.1 Human phase I trials of OSI-774 have explored both schedule and dose to evaluate the safety, tolerability and pharmacokinetic profile of the compound. Two Phase I trials in healthy subjects and two Phase I trials inpatients with advanced malignancies have been completed. The primary toxicities consisted of diarrhea, rash, nausea, headache, emesis, and fatigue. The only dose-limiting toxicity was diarrhea. This event was dose related and was generally controlled with the addition of loperamide therapy and treatment with OSI-774 doses of <200 mg/day. The appearance of the rash seen in the clinical trials of OSI-774 conducted in healthy subjects and cancer patients has been similar. It was only loosely dose related and was seen commonly at doses of >25mg/day. The rash was variable in onset, duration and severity. The mechanistic basis of the rash demonstrated polymorphonuclear leukocyte infiltration and mild epidermal hyperproliferation. In some cases, the rash improved despite continued dosing, and in general, it gradually resolved without sequelae following discontinuation of OSI-774. The rash did not result in study discontinuation in cancer patients in either of the Phase I trials. Based on ocular changes observed in the 12-month toxicology study I dogs, screening and follow up ophthalmologic examination were instituted in the Phase I and II trials. In the weekly dosing study (Study 248-005), the only reported OSI-774-related ocular event was an episode of mild watery eyes. In the daily dosing study (Study 248-004), 1 patient experienced moderate corneal edema/keratitis attributed to wearing contact lenses, although the influence of OSI-774 was not discounted. The event resolved with temporary discontinuation of both OSI-774 dosing and contact lens use; there was no recurrence of symptoms with re-initiation of OSI-774 in the absence of continued use of contact lenses.

6.1.5 Availability: OSI-774 is an investigational agent supplied to investigators by:

Genentech, Inc. OSI-774 is provided to the MDACC under a Clinical Trials Agreement (CTA) between Genentech, Inc. and the MDACC (see Section 10.4).

6.1.6 Agent Ordering:

The Principal Investigator (or their authorized designees) of this protocol will order the drug. 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). 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.

6.1.7 Agent Accountability:

The Principle 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 MD Anderson Drug Accountability Form.

6.2 Cisplatin (Cis-Diaminedichloroplatinum) (CDDP)

6.2.2 Formulation: Each vial contains 10 mg of CDDP, 19 mg of sodium chloride, 100 mg of mannitol, and hydrochloric acid for pH adjustment. One vial is reconstituted with 10 ml of sterile water. The pH range will be 3.5 to 4.5.

6.2.3 Storage: The dry, unopened vials should be stored at refrigeration temperature (4- to 8 degrees C). Reconstitution results in a solution which is stable for not more than 1 hour at room temperature when exposed to normal room illumination, and not more than 8 hours at room temperature when protected from light.

6.2.4 Administration: Intravenous.

6.2.5 Mechanism of Action: The mechanism of action of CDDP has not been clearly elucidated. However, preliminary studies have indicated that the most likely mechanism of anti-tumor action of this drug resides in its ability to inhibit DNA synthesis and to a lesser degree, RNA and protein synthesis. It has also been shown that CDDP binds to DNA and produces interstrand cross-links. Also CDDP is not phase-sensitive, its cytotoxic activity is similar in all phases of the cell cycle.

6.2.6 Human Toxicology: The major effects in man have been the following:

Renal toxicity manifested by BUN and serum creatinine elevation, tinnitus and audiologic impairment in the high frequency range (4000 to 8000 Hz), nausea and vomiting,

hyperuricemia, mild to moderate anemia, and irreversible peripheral neuropathy.

6.3 **Docetaxel (TAXOTERE®)**

6.3.1 PREPARATION AND ADMINISTRATION PRECAUTIONS

TAXOTERE is a cytotoxic anticancer drug and, as with other potentially toxic compounds, caution should be exercised when handling and preparing TAXOTERE solutions. The use of gloves is recommended. Please refer to Handling and Disposal section.

If TAXOTERE concentrate, initial diluted solution, or final dilution for infusion should come into contact with the skin, immediately and thoroughly wash with soap and water. If TAXOTERE concentrate, initial diluted solution, or final dilution for infusion should come into contact with mucosa, immediately and thoroughly wash with water.

TAXOTERE for Injection Concentrate requires two dilutions prior to administration. Please follow the preparation instructions provided below. Note: Both the TAXOTERE for Injection Concentrate and the diluent vials contain an overfill.

A. Preparation of the Initial Diluted Solution

1. Gather the appropriate number of vials of TAXOTERE for Injection Concentrate and diluent (13% Ethanol in Water for Injection). If the vials were refrigerated, allow them to stand at room temperature for approximately 5 minutes.
2. Aseptically withdraw the contents of the appropriate diluent vial into a syringe and transfer it to the appropriate vial of TAXOTERE for Injection Concentrate. If the procedure is followed as described, an initial diluted solution of 10mg docetaxel/mL will result.
3. Mix the initial diluted solution by repeated inversions for at least 45 seconds to assure full mixture of the concentrate and diluent. Do not shake.
4. The initial diluted TAXOTERE solution (10 mg docetaxel/mL) should be clear; however, there may be some foam on top of the solution due to the polysorbate 80. Allow the solution to stand for a few minutes to allow any foam to dissipate. It is not required that all foam dissipate prior to continuing the preparation process.

   The initial diluted solution may be used immediately or stored either in the refrigerator or at room temperature for a maximum of 8 hours.

B. Preparation of the Final Dilution for Infusion

1. Aseptically withdraw the required amount of initial diluted TAXOTERE solution (10mg docetaxel/mL) with a calibrated syringe and inject into a 250mL infusion bag or bottle of either 0.9% Sodium Chloride solution or

5% Dextrose solution to produce a final concentration of 0.3 to 0.74mg/mL.

If a dose greater than 200mg of Taxotere is required, use a larger volume of the infusion vehicle so that a concentration of 0.74mg/mL TAXOTERE is not exceeded.

2. Thoroughly mix the infusion by manual rotation.
3. As with all parenteral products, TAXOTERE should be inspected visually for particulate matter or discoloration prior to administration whenever the solution and container permit. If the TAXOTERE for Injection initial diluted solution or final dilution for infusion is not clear or appears to have precipitation, these should be discarded.

The final TAXOTERE dilution for infusion should be administered intravenously as per protocol under ambient room temperature and lighting conditions. Contact of the TAXOTERE concentrate with plasticized PVC equipment or devices used to prepare solutions for infusion is not recommended. In order to minimize patient exposure to the plasticizer DEHP (di-2-ethylhexyl phthalate), which may be leached from PVC infusion bags or sets, the final TAXOTERE dilution for infusion should be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets.

6.3.2 STABILITY

TAXOTERE infusion solution, if stored between 2 and 25ºC (36 and 77ºF) is stable for 4 hours. Fully prepared TAXOTERE infusion solution (in either 0.9% Sodium Chloride solution or 5% Dextrose solution) should be used within 4 hours (including the administration time).

6.3.3 HOW SUPPLIED

TAXOTERE for Injection Concentrate is supplied in a single-dose vial as a sterile, pyrogen-free, non-aqueous, viscous solution with an accompanying sterile, non- pyrogenic, diluent (13% ethanol in Water for Injection) vial. The following strengths are available:

TAXOTERE 80 MG (NDC 0075-8001-80)

TAXOTERE (docetaxel) 80 mg Concentrate for Infusion: 80 mg docetaxel in 2 mL polysorbate 80 and diluent for TAXOTERE 80 mg. 13% (w/w) ethanol in Water for Injection. Both items are in a blister pack in one carton.

TAXOTERE 20 MG (NDC 0075-8001-20)

TAXOTERE (docetaxel) 20 mg Concentrate for Infusion: 20 mg docetaxel in 0.5 mL polysorbate 80 and diluent for TAXOTERE 20 mg. 13% (w/w) ethanol in Water for Injection. Both items are in a blister pack in one carton.

6.3.4 Storage: Store between 2 and 25°C (36 and 77ºF). Retain in the original package to protect from bright light. Freezing does not adversely affect the product.

6.3.5 Handling and Disposal: Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have **Page 24** been published. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

6.3.6 Side Effects: Hematologic (severe leukopenia and neutropenia that could lead to infection, anemia, and thrombocytopenia; isolated infections and septic deaths have been observed), alopecia, gastrointestinal toxicity (anorexia, nausea, vomiting, diarrhea, constipation, and mucosal ulcerations), asthenia, acute hypersensitivity reactions within a few minutes of infusion (chills, rigors, back pain, drug fever, dyspnea, bronchospasm, chest pain or heaviness, hypotension, hypertension, bradycardia, facial edema, epigastric discomfort, cough, malaise, confusion, and decrease of consciousness), skin toxicity (localized pruriginous maculo-papular or bullous eruption (skin rash), localized erythema with edema followed by desquamation and nail disorders), reversible peripheral neurotoxicity (paresthesias or dysesthesias, decreases in deep tendon reflexes, hypesthesia, and peripheral motor neuropathy), peripheral edema and weight gain sometimes associated with pleural effusion, pericardial effusion, ascites, or isolated pleural effusion, local toxicity including reversible vein inflammation and injection site reaction, arthralgias and myalgias. Other side effects (less than 5% incidence) include alterations in taste, lethargy, somnolence, confusion, and other neurocortical abnormalities, vertigo, syncope, postural hypotension, headache, conjunctivitis, dyspnea with restrictive pulmonary or pulmonary interstitial infiltrates, pneumothorax, hearing abnormalities, neuro-mood, heart failure, paroxysmal atrial tachycardia, atrial flutter, dysrhythmia, arrhythmia, bradycardia, tachycardia, hypertension, hypotension, thrombophlebitis, pulmonary embolism, intestinal obstruction (paralytic ileus), renal insufficiency, hepatic insufficiency, gastrointestinal bleeding.

7. CORRELATIVE/SPECIAL STUDIES

7.1 Optional biomarkers and mitotic index studies will be assessed pre-enrollment (archival tissue specimen acceptable if available) and after the second and fourth

cycles of chemotherapy. This would involve repeated optional biopsies of the patient's tumor to assess response to treatment.

7.1.1 Biomarker studies (optional) would include immunohistochemical staining of the tissue samples for EGFR/erbB1, EGFR/erbB3, TGF-□, p53, phosphorylated AKT, phosphorylated ErbB1, phosphorylated ErbB3.

7.1.1.1 Antibodies will be obtained to the above target sites from commercial indu24stry.

7.1.1.2 Tissue obtained from patients will be flash frozen, then embedded in paraffin blocks before prepared for slides.

7.1.1.3 Immunohistochemical staining will be conducted by standard practice. 7.1.1.4 Patient staining results will be compared over the course of their treatment and assessed for response.

7.1.2 Mitotic index will be an additional marker of tumor activity. This optional evaluation would be conducted by the MD Anderson Pathology Department via light microscopy analysis.

7.1.3 All patient information will be confidential and the results of these correlative studies will not be used to affect or alter clinical decisions.

8. STUDY CALENDAR

Baseline evaluations are to be conducted within a week prior to start of protocol therapy. Baseline scans and x-rays must be done 4 weeks prior to the start of therapy. All study evaluations, radiologic assessments, and/or clinic visits may be conducted within ± 7 days of the date specified in the protocol. 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	MAINTEN-ANCE	OFF STUDY[E]
OSI-774[F]		A	A	A	A	A	A	A	A	A	A	A	A	A	
CISPLATIN/DOCETAXEL[G]		B			B			B			B				
INFORMED CONSENT	X														
DEMOGRAPHICS	X														
MEDICAL HISTORY	X														
CONCURRENT MEDS	X	X----------											X	X[H]	
PHYSICAL EXAM	X	X			X			X			X			X[H]	X
VITAL SIGNS	X	X			X			X			X			X[H]	X
HEIGHT	X														
WEIGHT X	X			X		X			X			X[H]		X PERFORMANCE	
STATUS X	X		X		X			X			X[H]		X	CBC W/DIFF, PLTS	
X X X X	X X	X	X	X	X	X	X	X	X	X[H]	X	X			
C	X	X	X	X	X	X	X	X	X	X	X	X	X	H X	X
SERUM CHEMISTRY															
EKG (AS INDICATED)	X														
ADVERSEEVENT		X----------											X	X[H]	
EVALUATION															
TUMOR MEASUREMENTS	X	TUMOR MEASUREMENTS ARE REPEATED EVERY 6-8 WEEKS. DOCUMENTATION (RADIOLOGIC) MUST BE PROVIDED FOR PATIENTS REMOVED FROM STUDY FOR PROGRESSIVE DISEASE.												X[H]	E
RADIOLOGIC EVALUATION	X	RADIOLOGIC MEASUREMENTS SHOULD BE PERFORMED EVERY 6-8 WEEKS.												X[H]	X[E]
B-HCG	X[D]														
A: OSI-774: MG/DAY CONTINUOUSLY		100 OR 150	100 OR 150	100 OR 150	150	150	150	150	150	150	150	150	150	150	
DOSE AS ASSIGNED; ADMINISTRATION SCHEDULE															
B. CISPLATIN/DOCETAXEL (MG/M^2) DOSE AS ASSIGNED; ADMINISTRATION SCHEDULE		75/60			75/60 OR 75			75/60 OR 75			75/60 OR 75				

C: ALBUMIN, ALKALINE PHOSPHATASE, TOTAL BILIRUBIN, BICARBONATE, BUN, CALCIUM, CHLORIDE, CREATININE, GLUCOSE, LDH, PHOSPHORUS, POTASSIUM, TOTAL PROTEIN, SGOT [AST], SGPT [ALT], SODIUM.

D: SERUM PREGNANCY TEST (WOMEN OF CHILDBEARING POTENTIAL).

E: 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.**

F: PATIENTS WILL CONTINUE UNTIL DISEASE PROGRESSION OR UNACCEPTABLE TOXICITY. G: PATIENTS MAY TAKE UP TO 6 CYCLES OF THERAPY.

H: EVERY 3 MONTHS

9. MEASUREMENT OF EFFECT

For the purposes of this study, patients should be reevaluated for response every 6 weeks. In addition to a baseline scan, confirmatory scans should also be obtained every 6 to 9 weeks following initial documentation of objective response.

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 ≥20 mm with conventional techniques (CT, MRI, x-ray) or as ≥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.

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) and/or 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 (see section 9.3.1) and confirmation criteria (see section 9.4.1).

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

Note:

- 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.

- 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 6 weeks (+/- 14 days), no less than 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 9 weeks (+/- 14 days), not less than 6-8 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**

Duration of 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**

Time to progression or progression-free survival (PFS) will be used. PFS is defined as the duration of time from start of treatment to time of progression. This information will be documented on an on-going basis during the trial.

9.6 **Response Review**

All responses documented in this trial will be reviewed by an independent expert(s), not involved in the clinical trial, at the trial's completion. Simultaneous review of the patients' files and radiological images will be performed. The radiological images will be free of marks that might obscure the lesions or bias the evaluation of the reviewer(s).

10. Adverse Drug Events

In the event of an adverse event the first concern will be for the safety of the subject.

Definitions

A **serious adverse event** (experience) or reaction is any untoward medical occurrence that at any dose: results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability / incapacity, or is a congenital anomaly / birth defect.

The definition of serious adverse event (experience) also includes *important medical event*. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

The definition of "related" being that there is a reasonable possibility that the drug caused the adverse experience.

10.1 Adverse Event Reporting

10.1.1 Serious and/or unexpected adverse events are submitted in writing to the M.D. Anderson Cancer Center Institutional Office of Protocol Research (OPR) within 5 calendar days of the adverse experience. Unexpected fatal or life-threatening experiences are reported to the Office of Protocol Research within 24 hours. A follow up written report is submitted to OPR within 5 calendar days. All serious, related, unlabeled, (unexpected) adverse events will be reported to the FDA as required by 21 CFR 312.32. (See Appendix H)

10.1.2 Aventis: Aventis Pharmaceuticals Global Pharmacovigilance and Epidemiology Department. will be provided with a copy of all Taxotere® serious, related adverse event reports. These reports may be filed utilizing the Form FDA 3500A (MedWatch Form). This includes serious, related, labeled (expected) and serious, related, unlabeled (unexpected) adverse experiences.

These reports may be sent by **FAX** or **E-MAIL to:**

Reports by **FAX** should be sent to Aventis Pharmaceuticals Global Pharmacovigilance and Epidemiology Department (908-231-4827), within 24 hours of receipt by investigator / sponsor. **FAX transmission**

should include the following on the provided GIA SAE REPORT, fax cover form (Appendix F):

Grant-In-Aid Study #15044
Title: A Phase II Study of OSI-774 in Combination with Cisplatin and Docetaxel in Metastatic or Recurrent Head andNeck Squamous Cell Cancer
Principal Investigator: Neal Ahkave, MD

Reports by **E-MAIL** should be sent to: GPEmailbox@aventis.com ,Page within 36 24 hours of receipt by investigator / sponsor. **E-Mail transmission should include the following:**

Grant-In-Aid Study #15044
Title: A Phase II Study of OSI-774 in Combination with Cisplatin and Docetaxel in Metastatic or Recurrent Head and
Neck Squamous Cell Cancer
Principal Investigator: Neal Ahkave, MD

10.1.3 Genentech: Investigators are required to report to Genentech Drug Safety ANY serious treatment emergent adverse event (STEAE) as soon as possible.

A STEAE is any sign, symptom or medical condition that emerges during Tarceva treatment or during a post-treatment follow-up period that (1) was not present at the start of Tarceva treatment and it is not a chronic condition that is part of the patient's medical history, **OR** (2) was present at the start of Tarceva treatment or as part of the patient's medical history but worsened in severity and/or frequency during therapy, **AND** that meets any of the following regulatory serious criteria:

- Results in death
- Is life-threatening
- Requires or prolongs inpatient hospitalization
- Is disabling
- Is a congenital anomaly/birth defect
- Is medically significant or requires medical or surgical intervention to prevent one of the outcomes listed above.

All STEAEs should be recorded on a MedWatch 3500 Form and faxed to (650) 225-4682 or (650) 225-4683. (Please use the safety reporting fax cover sheet attached to this document [Appendix G] for your fax transmission)

For questions related to safety reporting, contact Genentech Drug Safety as follows:

Katherine Bass, Drug Safety Scientist

Tel: (650) 225-4203
-OR-
Rich Brotherton, Clinical Safety Associate
Tel: (650) 225-4562

MedWatch 3500 Reporting Guidelines:

In addition to completing appropriate patient demographic and suspect medication information, the report should include the following information within the Event Description (section 5) of the MedWatch 3500 form:

- Treatment regimen (dosing frequency, combination therapy)
- Protocol description (and number, if assigned)
- Description of event, severity, treatment, and outcome, if known
- Supportive laboratory results and diagnostics
- Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication

Follow-up information: Additional information may be added to a previously submitted report by any of the following methods:

- Adding to the original MedWatch 3500 report and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500 form
- Summarizing new information and faxing it with a cover letter including subject identifiers (i.e. D.O.B. initial, subject number), protocol description and number, if assigned, suspect drug, brief adverse event description, and notation that additional or follow-up information is being submitted (The subject identifiers are important so that the new information is added to the correct initial report)

Occasionally Genentech may contact the reporter for additional information, clarification, or current status of the subject for whom and adverse event was reported. For questions regarding STEAE reporting, you may contact the Genentech Drug Safety representative noted above.

Assessing Causality:

Investigators are required to assess whether there is a reasonable 38 possibility that Tarceva caused or contributed to an adverse event. The following general guidance may be used.

Yes: if the temporal relationship of the clinical event to Tarceva administration makes a causal relationship possible, and other drugs, therapeutic interventions or underlying conditions do not provide a sufficient explanation for the observed event.

No: if the temporal relationship of the clinical event to Tarceva administration makes a causal relationship unlikely, or other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the observed event.

10.1.4 For Comparator Drugs / Secondary Suspects (Concomitant Medications), all serious adverse experiences will be forwarded to the product manufacturer.

11. STATISTICAL CONSIDERATIONS

11.1 Study Design/Endpoints

11.1.1 The primary endpoint is the determination of the response rate and efficacy of the combination therapy (OSI-774, cisplatin, and docetaxel). The response rate is defined as the percentage of number of complete response or partial response in total number of patients treated.

11.1.2 A Bayesian design based on predictive probability [23] will be implemented. This design allows for "early stopping" if the evidence shows that the treatment is *ineffective*.

11.1.2.1 The treatment outcomes will be monitored for patients in cumulative cohort sizes of 15, 30, and 50. The stopping boundary is chosen by computing the predictive probability based on the observed data. Specifically, we will stop the trial if the current data indicates with

reasonable confidence that the response rate to combination therapy will not be higher than 0.30 by the end of the clinical trial.

11.1.2.2 The maximum number of patients is n=50. If X responses have been observed in the first n patients and Y represents possible number of responses in the next (N-n) patients, the predictive probability (PP) of concluding a positive trial by the end of the trial is defined as

PP = $\sum_{i}$ ^{N} ^{n} {Prob(Y=i) [Prob(response rate > 0.30 | X, Y=i, N) >0.90 | X, n]}

11.1.2.3 Therefore, the trial will be stopped if PP < 0.05, i.e., given current data, it is very unlikely that we will conclude that the treatment combination of OSI-774, cisplatin and docetaxel is efficacious by the end of the study.

11.1.2.3.1 We assume that the number of patients that respond to the treatment follows a binomial distribution with a probability of p. We also assume that p has a prior distribution of beta (0.3, 0.7). The following table lists the cumulative number of patients (n) and the rejection region in the number of response in n patients. The trial will be stopped and the treatment will be considered ineffective when the number of response first falls into the rejection region.

N	Rejection Region in Number of Response
15	3
30	4 – 9
50	10 – 19

11.1.3 The operating characteristics of the trial are as follows.

11.1.3.1 If the true response rate is 0.30 (i.e., the trial is ineffective), the probability of accepting the treatment is 0.08 (corresponding to the type I error rate). On the other hand, if the true response rate is 0.50 (i.e., the treatment is effective), the probability of accepting the treatment is 0.92 (corresponding to the power of the study). When the true response rate is 0.30 the probabilities of stopping the trial early are 0.30 and 0.32 at the end of treating the first and second cohort,

respectively. On the other hand, if the true response rate is 0.50, the corresponding probabilities of terminating the trial early are 0.02 and 0.02.

11.1.3.2 Therefore, the probability of early stopping are 0.62 and 0.04 for p=0.30 and 0.50, respectively. The expected sample sizes are 33.2 and 49.1 when the true response rates are 0.30 and 0.50, respectively.

11.1.4 The Bayesian design based on the predictive probability has similar type I and type II error rates as the Simon's optimal two-stage design but allows the trial to be stopped early when the data is suggestive that the treatment is unlikely to be effective. It also provides more flexibility in monitoring the trial. Unlike the frequentists' design, the Bayesian design allows more frequent monitoring of trial outcome (in addition to two interim analysis specified above) with similar operating characteristics. In the case of early stopping, a review of the accrued clinical data will determine if early stopping is appropriate.

11.1.5 To address the potential variability in treatment doses for this trial, an [40] additional subset analysis will be performed at the conclusion of the trial. Patients who initially started at the 100mg dose of OSI-774 and are later dose escalated will be analyzed as a separate cohort to determine if this regimen was less efficacious than the 150mg dose. Response rate, time to progression and toxicity profile will be the factors reviewed.

11.2 Sample Size/Accrual Rate

Estimated date of first patient enrolled: April 2003.
Estimated date of last patient enrolled: February 2004.

Sample size will be determined by monitoring treatment outcomes in patients in cumulative cohort size of 15, 30, 50.

11.3 Stratification Factors

Patients with metastatic or recurrent head and neck squamous cell cancer with only one prior relapse.

11.4 Analysis of Secondary Endpoints

11.4.1 Secondary endpoints include safety, toxicity profile and evaluation of time to progression. Safety and toxicity profiles will be evaluated by standard measures (see Appendix C) and evaluation of time to progression in enrolled patients will occur at the 6 and 12 month time points or whenever there is clinical indication (s) of progression.

11.4.2 Descriptive statistics will be applied to summarize the results. The confidence interval estimation will be provided whenever appropriate and

Kaplan-Meier estimates will be calculated for the time-to-progression endpoints.

11.5 Reporting and Exclusions

11.5.1 **Evaluation of toxicity.** All patients will be evaluable for toxicity from the time of their first treatment with OSI-774, cisplatin, docetaxel.

Evaluation of response. All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). [Note: By arbitrary convention, category 9 usually designates the "unknown" status of any type of data in a clinical database.]

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All of the patients who met the eligibility criteria (with the possible exception of those who received no study medication) should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered as failing to respond to treatment (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific.

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