COVER PAGE FOR PROTOCOL AND STATISTICAL ANALYSIS PLAN

Official Study Title: A Phase II Study of Induction Docetaxel, Cisplatin, Cetuximab and Bevacizumab (TPE-A) Followed by Concurrent Radiation, Cisplatin, Cetuximab and Bevacizumab (XPE-A) in Patients with Locally Advanced Head and Neck Cancer (CTRC# 11-36)

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This is an investigator-initiated study. The principal investigator, **Anand Karnad.** MD, who may also sometimes be refen ed to as the sponsor-investigator, is conducting the study and acting as the sponsor.

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RESEARCH STUDY ABSTRACT

Background

Locally advanced squamous cell carcinoma of the head and neck (SCCHN) is ti-eated with vaiious combinations of radiation and chemotherapy. Docetaxel and cisplatin have been combined in Phase II trials in recunent or metastatic head and neck cancer with very encoura ging results. Induct ion therapy with docetaxel/ci splatin followed by chemoradiotherapy was investigated in a randomized Phase II study in nasophaiyngeal cancer and showed superior PFS and OS in compa1i son with chemoradiation alone. Cetuximab is a chimerized EGFR monoclonal antibody that has produced positive results in Phase III trials in combination with either radiation for locally advanced disease or chemotherapy for metastatic disease. Upregulation of vasculai·endothelial growth factor (VEGF) has been associated with cetuximab resistance. Bevacizumab, an anti-VEGF antibody is cutTently being investiga ted in SCCHN with promising results. Two trials of bevacizumab-based regimens ai·e being conducted at UPMC (UPCI 05-002 and UPCI 05-087) with ve1y promising results. We have previously shown that cisplatin, docetaxel and cetuximab (TPE) followed by radiotherapy, cisplatin and cetuximab (XPE) is feasible and highly efficacious in locally advanced SCCHN (UPCI 05-003, presented at ASCO 2008). In this Phase II study we evaluate the addition ofbevacizumab to induction therapy with TPE (TPE-A) and to subsequent XPE (XPE-A).

Specific aims

To evaluate the rate of complete responses with induction therapy (primaiy endpoint) and progression-free survival, overall survival and objective response rates. Also, we plan to investigate a panel of EGFR and angiogenesis biomarkers in pre- and post- tt·eatment tutnor biopsies. Finally, we will evaluate the associated treatment toxicities and the quality ofl ife.

Subject population

We will emoll patients with previously untreated locally advanced SCCHN (see detailed eligibility criteria).

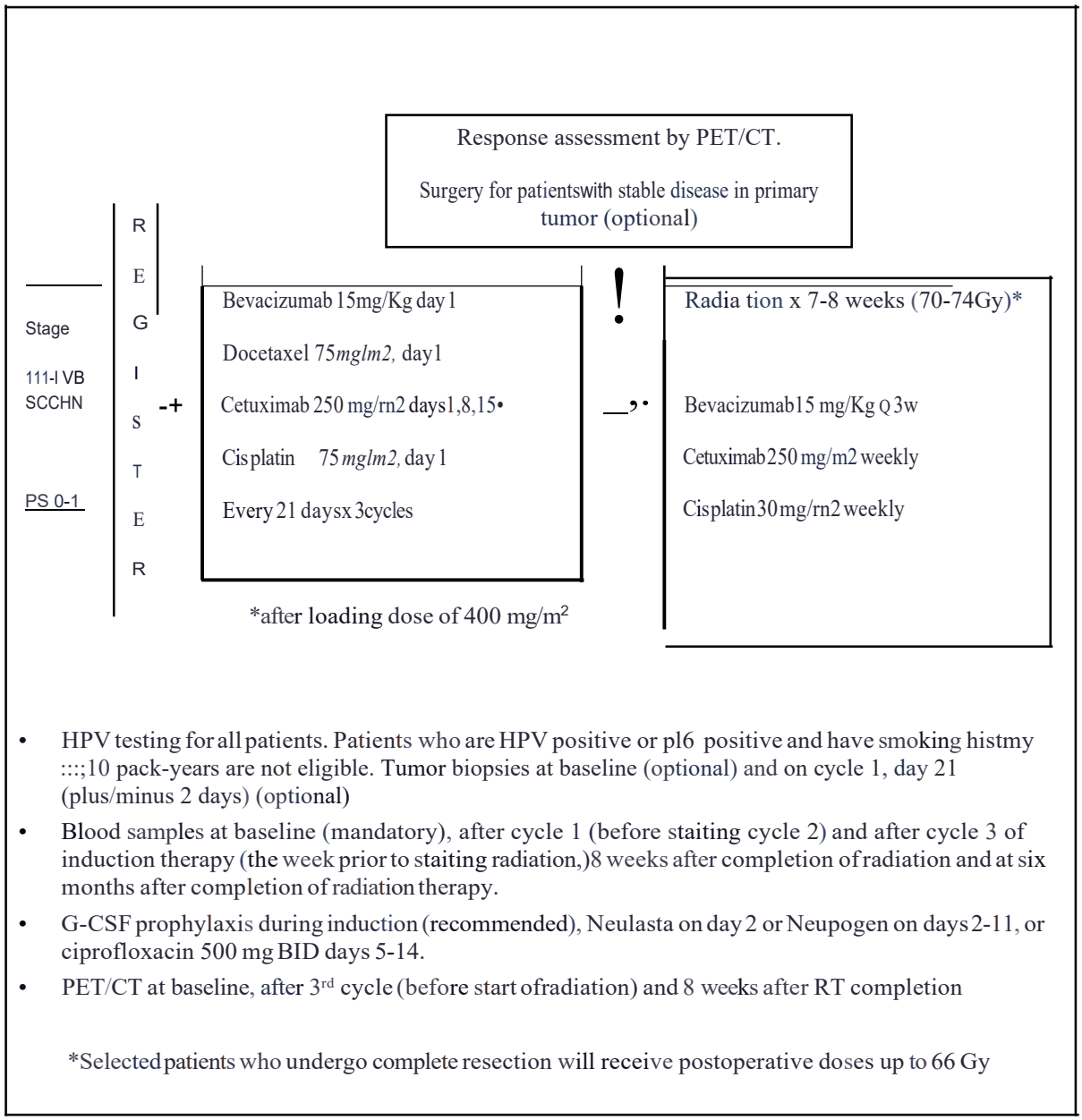
Treatment plan

Induction therapy consists of 3 cycles of bevacizumab 15mg/kgon day 1, cetuximab weekly days 1, 8, 15 (loading dose of cetuximab 400mg/m^2 on cycle 1, day 1, then 250 mg/m^2 on all subsequent administt·ation)s, cisplatin 75mg/m^2 on day 1, docetaxel 75mg/m^2 on day 1, repeated eve1y 21 days. After 3 cycles of induction therapy, patients will receive standard radiation 70-74 Gy/ 200 cGy/ daily, 5 days/ week with concmTent weekly cisplatin 30mg/m^2, cetuximab 250mg/m^2 and bevacizumab 15mg/kg eve1y 3 weeks x 3. There is optional smge1y for non-responders in the primaiy (stable disease) after TPE-A.

Statistical design and sample size

Phase II, two-stage study with complete response rate after induction therapy as the p1imaiy endpoint. The sainple size is 33 patients.

STUDY SCHEMA



- HPV testing for all patients. Patients who are HPV positive or p16 positive and have smoking history of ≤10 pack-years are not eligible. Tumor biopsies at baseline (optional) and on cycle 1, day 21 (plus/minus 2 days) (optional)
- Blood samples at baseline (mandatory), after cycle 1 (before starting cycle 2) and after cycle 3 of induction therapy (the week prior to starting radiation,) 8 weeks after completion of radiation and at six months after completion of radiation therapy.
- G-CSF prophylaxis during induction (recommended), Neulasta on day 2 or Neupogen on days 2-11, or ciprofloxacin 500 mg BID days 5-14.
- PET/CT at baseline, after 3rd cycle (before start of radiation) and 8 weeks after RT completion

*Selected patients who undergo complete resection will receive postoperative doses up to 66 Gy

1 BACKGROUNDAND RATIONALE

1.1 Head and NeckCancer

More than 45,000 new cases of head and neck cancer are diagnosed annually in the United States[1]. Of these patients, two-thirds present with locoregionally advanced disease (AJCC stage III or IV) and one-third with early stage disease (AJCC stage I or II). At presentation 10% of patients may be found to have involvementof distant organs, most commonly the lung. In addition, 20% of patients will develop clinically detected distant metastases over the course of their disease. In autopsy series up to 50% of patients with head and neck cancer are found to have metastases[2,3]. Approximately 90% of all head and neck malignancies are squamous cell carcinomas. The vast majority of head and neck malignancies can be attributed to the use of tobacco and alcohol. Human Papillomavirns has been implicated in a significant portion of oropharyngeal squamous cell carcinomas[75 77]. Due to their frequent histo1y of exposure to tobacco and alcohol patients with head and neck cancer are in high risk for other comorbidities associated with tobacco and alcohol, such as corona1y aite1y disease, chronic obstrnctive pulmona1ydisease, and liver disease[4]. In addition, they ai·e at high 1isk for the development of second primaiy tumors, synchronous or metachronous, that may involve the head and neck region as well as other organs, predominantly the lungs[5].

1.2 Chemotherapy for Locoregionally Advanced Disease

The addition of chemotherapy with RT to the overall treatment plan in patients with locoregionally advanced head and neck cancer has been studied in an effort to improve organ prese1vation, locoregional, and distant control, and srnvival rates over RT alone. Reseai·ch studies have evaluated the use of induction (neoadjuvant) or adjuvant chemotherapy, as well as conc01nitant chemotherapy and radiation. The primaiy goal of such research is to improve local control and srnvival.

1.3 Combined Modality Therapy for Organ Preservation

An imp01tant goal of adding chemotherapy to radiation therapy is to improve local control and avoid mutilating surge1y, therefore, achieve organ prese1vation in patients with resectable disease. Two-phase III randomized tiials, one by the VA La1yngeal Study Group and the other by EORTC, showed that organ prese1v ation is feasible in la1yngeal and hypophaiyngeal cancers. In both studies, induction chemotherapy with cisplatin and 5-FU followed by radiation therapy in responders allowed for organ prese1vation without a comprolnise in srnvival compai·ed to standard management with surgical resection followed by postoperative radiation[6.7]. However, one-third or more of patients required laiyngectomy for treatment failure. In the VA laiyngeal cancer study, the laiynx was prese1ved in 64% of all patients assigned to the induction chemotherapyaim, whereas in the EORTC ti"ial, in wh ic h a complete response was mandato1y to proceed with organ prese1vation, the 5-yeai·srnvival with a functioning la1ynx (censo li ng data for local failures only) was 35%, if all patients (n=l OO) who received induction chemotherapy were considered, and 58%, if only the group of 52 patients who achieved a complete response to induction chemotherapy and received radiation therapy were considered in analysis[6].

A multicenter phase III randomized study evaluated the role of concomitant chemoradiation in lruyn gea l cancer (RTOG 91-11)[8]. This three-aim study compru·ed the organ preservat ion strategy used in the VA lruyn gea l study to radiotherapy alone (without induction chemotherapy), and to concomitant chemoradiotherapy with single-agent cisplatin. Although no differences in survival were observed between aims, laiyngeal preservation was optimal in the concomitant chemoradiation treatmentaim. Therefore, concwTent chemorad iation is now considered the standru·d regimen for organ prese1vation in the management of la1yngeal cancer.

1.4 Concomitant Chemoracliotherap y

The theoretica l rat iona le and clinical experience of using concomitant chemoradiotherapy in patients with solid tumors has been reviewed[9 10]. For head and neck cancer this concept is prutic ul ar ly attract ive. It is hoped that chemotherapy will be successful at treating micrometastatic systemic disease while also enhancing the locoregionalefficacy of radiotherapy. Most of the older trials have used infusional 5-FU as the radiosensitizer based on work initially published by Byfield et al1[1]. The add ition of cisplati n[12,13], or cisplatin with 5-FU / leucovorin and hyperfractionated radiotherapy[14], or hydroxyurea[15 16] in phase I or II studies have led to velyencouraging response and smv:ival data. In a randomized study, Merlano et al1[7] demonstrated signific antly increased swvival in patients with unresectable disease treated with radiotherapy alternating with cisplatin and bolus 5-FU compared to patients treated with radiotherapy alone.

A meta-analysis that included 63 randomized studies conducted between 1965 and 1993, demonstrated an absolute swv ival benefit of 8% at 5 yeru·s with conc 01nitant chemotherapy and radiotherapy versus radiation therapy alone[18]. More recently, multiple randomized phase III trials have conclusively demonstrated that concwTent chemorad iotherapy is supe rior to radiation therapy alone in locally advanced head and neck cancer[8,19,23]. The above tiials predominantly enrolled patients with unresectable head and neck cancer, whereas three of these tii als were site-specific[8,20,22].

Three randotnized t1ials used combined chemotherapy with platinum and 5-FU along with conventional or hyperfractionated radiotherapy.[19-21] and three others used cisplatin with conventional radiation[8,22,23]. Most of these studies favored concomitant chemoradiotherapy with an approximately 20% gain in swvival at three to five years (approximately 30% versus 50%), whereas the study by Forastiere et al[24] showed that concomitant chemoradiotherapy with cisplatin in resectable la1yngeal cancer is supe1 ior in tenns of la1yngeal prese1 vation[8].

1.5 Radiation plus Cisplatin for Locally Advanced Head and Neck Cancer

A number of randomized ttials in U.S. have established conventional radiotherapy plus cisplatin 100 mg/m^2 eve1y 3 weeks as the standai·d non-surgical treatment ofl ocally advanced head and neck cancer. In unresectable disease and nasopha1yngeal cancer a smv ival advantage was demonsti·atedover radiotherapy alone[22,23], whereas in la1yngeal cancer, concmTent chemoradiotherapy with cisplatin resulted in a higher rate of organ prese1 vation[8].

For unresectable head and neck squamous cell carcinoma, concmTent chemoradiotherapy has emerged as standru·dtherapy after the results of a randomized phase III tt·ial conducted by the Southwest Oncology Group (SWOG) and Eastern Cooperative Oncology Group (ECOG)[23]. This trial enrolled 295 patients

with umesectable squamous cell head and neck cancer, before closing to slow accrual. So far, it is the only study that has allowed a comparison, even indirectly, between single and combination chemotherapy. Three treatment anns were compared: (A) conventional radiotherapyalone (70 Gy at 2 Gy per day); (B) conventional radiotherapy plus single-agent cisplatin 100 mg/m^2 eveiy 3 weeks; and (C) split course radiotherapy with concutTent cisp latin 75 mg/m^2 on day 1 and 5-FU 1000 mg/m^2/d as a continuous infusion, on days 1-4, repeated eveiy 4 weeks. Preliminaiy results showed an improvement of 3-yeai· overall survival with single-agent cisplatin compai·ed to radiotherapy alone, from 20% to 37% (p=0.016). Survival rates between the two chemotherapy arms and between CRT and radiotherapy alone were not significantly different. Split course radiotherapy has been implicated for the suboptimal perfoimance of the cisplatin and 5-FU aim in this study.

In laiyngeal cancer, RTOG 91-11 showed that the optimal laiyngeal preservation strategy is concutTent chemoradiotherapy.[8] This three-aim study, the goal of which was to deteimine whether the addition of chemotherapy to radiotherapy is necessaiy to achieve laiyngeal preservation, compared the laiyngeal preservation strategy used in the VA laiyngeal study consisting of induction chemotherapywith cycles of cisplatin and 5-FU, followed by radiotherapy for responders (aim A) to concutTent chemoradiotherapy with cisplatin 100 mg/m2 administered eveiy three weeks (aim B), and radiotherapy alone (aim C). A total of 510 patients were analyzable, and the median follow-up at the time of preliminaiy analysis was 30 months. Sixty-five percent of patien ts received all three cycles of single-agent cisplatin during concutrnnt chemoradiotherapy. Grade 3 or 4 mucositis was seen in 33% of patients in aim A, 53% in rum B, and 36% in rum C. An advantage in overall survival could not be demonstrated with the use of chemotherapy, in spite of a decrease in the rate of dist.ant metastasis; howeve r, lruyn gec tomy -free sutvival and lruyn gea l preseiv ation rates were higher in the concutTent chemora diotherapy aim. At 2 yeru·s, lruyn gectomy-free sutvival rates were 58%, 68% (p=0.07 versus A), and 53%, and la1yngeal preseivation rates 74%, 88% (p=0.0047 versus A), and 69% for aims A, B, and C, respectively.

ConcutTent chemoradiother apy with cisplatin has become standa rd therapy of locally advanced nasopha1yngeal carcinoma[25]. Updated results of the Intergroup ttial in nasophruyn gea l cru·cino ma demonstt·ated a 5-ye ar sutv ival of 67% versus 37% (p<0.001) and a 5-year PFS of 59% versus 29% (p<0.001) for patients tt·eated with chemoradiotherapy versus radiotherapy alone[26] Toxicities with concutTen t therapy were increased but tolerable. Treatment deliveiy of adjuvant chemotherapy was suboptimal; 33% of patients received no adjuvant chemotherapy. Also, only two-thirds of patientscould receive all three doses of concun ent cisplatin, a finding consistent among randomized studies with this regimen (e.g. laiyngeal R91-l l and R95-01).

While radiation plus high-dose cisplatin (i.e. 100 mg/m^2 eveiy 3 weeks x 3 during radiation) has become a st.andat·d regimen for the tteatment ofl ocally advanced SCCHN[8,24,25], this regimen results in considerable toxicities, including grade 3-4 mucositis in about 50% of patients as well as in several out-of-field toxicities, including nausea/vomiting,nephrotoxicity and others. As noted, about one-third of patients cannot receive the third cisplatin dose due to the onset of toxicities. This obseivation had led many groups to either reduce the dose of cisplatin to 75 mg/m^2 eveiy 3 weeks (for example, ongoing ECOG study E3303), or to use lower dosages on a weekly schedule of administration when cisplatin is combined with other agents and RT. In chemoradiotherapy regimens, weekly cisplatin doses of 20-40

mg/m^2 have been previously investigated and well tolerated. Low dose weekly cisplatin (20 mg/m^2) alone combined with radiation did not result in a smvival benefit in a phase III trial that compared radiation plus cisplatin with radiation alone[28]. A weekly cisplatin dose of20 mg/m^{2}used incombination with paclitaxel and RT was shown to be feasible and active in an RTOG study2[9]. Weekly cisplatin 40 mg/m^2 with RT, showed improved smvi val over radiation alone in patients with locally advanced nasopharyngeal cancer[30]. A weekly cisplatin dose of 30 mg/m^2 was employed in combination with cetuximab and RT in a recently completed phase II randomized trial by RTOG (0234)3[1].

The optimal chemotherapy regimen for incorporation into combined modality therapy has yet to be determined. It is unclear whether combination chemotherapy regimens are superior to single-agent chemotherapy in this setting.

1.6 Induction Chemotherapy

Induction chemotherapy has the goal of "downstaging" the tumor but more importantly to eradicate early micrometastatic disease and therefore improve distant-site control. The rationale for using this investigational approach has been reviewed[4,27,28]. Most regimens are used for 2 to 3 cycles, including the widely used combination of cisplatin and continuous infusion 5-FU2[9]-[34] The response rates for untreated patients with locally advanced head and neck cancer range between 60-90%, with complete response rates of 20-50%[35]. Pathologic complete responses are documented in two-thirds of patients with a clinical complete response, and this is associated with a favorable prognosis[35]. The toxicity from induction chemotherapy is considerable though and severe and, occasionally, fatal toxicity may occm with the cisplatin and 5-FU regimen, or other regimens.

In the past decade, multiple randomized studies have compared induction chemotherapy followed by definitive locoregional treatment versus immediate locoregional treatment3[5]. Onl y one study , conducted by French investigators, which included patients with oropha l yngeal cancer, demonstrated a smvival benefit with neoadjuvant chemotherapy versus locoregional therapy alone[36]. In addition, subset analysis of two other randomized studies showed a smvival advantage with induction chemotherapy[37,38] . Paccagnella et al showed an advantage in the subset of patients with unresectable disease who received radiation as their locoregional therapy[37] , whereas Richard et al, who employed intraarterial chemotherapy, found a smvival difference in the subgroupof patients with floor of mouth cancers[38]. However, several trials suggested that chemotherapy in the neoadjuvant or adjuvant setting results in a reduced incidence of distant metastases as site of first failme[6,7,37,39]-[4]_ In order to improve the efficacy of induction therapy, newer combination regimens (e.g. taxane-based) are cmTently being evaluated in this setting.

1.7 Cisplatin and Docetaxel

Cisplatin and docetaxe l have been combined in phase II ttials in recmrent or metastatic head and neck cancer. The regimen is active with response rate between 33-54%[43]-[5] This is at least comparable to the activity of cisplatin/5-FU and cisplatin/paclitaxel in the recmTent/meta static disease setting. Cisplatin and docetaxel is well tolerated even in the palliative care setting.The FDA has approved cisplatin and docetaxel for first-line therapy of metastatic NSCLC. The commonly used doses are 75 mg/m^2 for each dtug on day 1. A phase II tt·ial of cisp latin and docetaxel conducted by the EORTC rep01ted an object ive response rate of 89% in 22 previously untreated patients with locally advanced or recmTenthead and neck

cancer[44]. Another study repo1ted a response rate of 55% in patients with stage IV, locally advanced, head and neck cancer[46]. Several randomized studies have shown that triple combination with cisplatin/5-FU/docetaxel (TPF) improves overall survival (OS) and progression- free survival (PFS) in compaiison with the combination of cisplatin/5-FU (PF)[73,74].

A recently published randomized phase II study investigated the addition of induction cisplatin and docetaxel to chemoradiotherapy for locally advanced nasophatyngeal cancer. Among 65 eligible patients with advanced nasopha1yngeal cai·cinoma, 34 patients received neoadjuvant docetaxel 75 mg/m^2 and cisplatin 75 mg/m^2 eve1y 3 weeks for 2 cycles followed by cisplatin 40 mg/m^2/ weekly concmrnnt with radiation, whereas **31** patients were randomized to receive the same chemoradiotherapy without induction therapy. Patients who received induction therapy had superior PFS and OS [78].

1.8 Epidermal Growth Factor Receptor (EGFR) and Cetuximab

1.8.1 EGFR

The epidennal growth factor receptor (EGFR) is a member of the erb B receptor tyrosine kinase family that also includes erbB,-2 erbB-3, and erbB-4[28]. It consists of an extracellulai·ligand-binding domain, a transmembrane region that anchors the receptor to the plasma membrane, and a cytoplasmic region containing a tyrosine kinase domain. Among the known natural ligands of EGFR include epidennal growth factor (EGF) and transfonning growth factor a, (TGF-a) which both activate the receptor by binding to the extracellular domain and inducing the fom1ation of receptor homodimers or heterodimers, followed by internalization of the receptor/ligand complex and auto-phospho1ylation. It is now accepted that the EGFR signal transduction network plays an imp01tant role in multiple tum01igenic processes , includ ing cell cycle progression, angiogenesis, and metastasis, as well as protection from apoptosis[28,29]. In this signal network, erbB-2 is the major paitner of EGFR because activated heterodimer complexes containing erbB-2 are more stable at the cell smface than complexes containing other EGFR family members[30,31]. In addition erb B-2 can decrease the rate of ligand dissociation from the cognate receptor EGFR[32].

1.8.2 EGFR Inhibition and the Cell Cycle

The effects of EGFR blockade on cell cycle progression have been investigated in several hmnan cell types, including DiFi colon adenocarcinoma cells, non-transf01med breast epithelial MCFIOA cells, A431 squamous epithelial cai·cinoma cells, and DU145 prostatic cancer cells. These studies suggest that blocking EGFR with monoclonal antibodies such as cetuximab leads to cell cycle atTest in G**1** which is accompanied by a decrease in cyclin dependent kinase (CDK) 2 activity, and an increase in the expression of CDK inhibitor p27K1Pl[33,34]. In addition to inducing GI-phase atTes,t EGFR blockade was also shown to lead to cell death via apoptosis in DiFi colon adenocarcinoma cells[35].

1.8.3 Cet11ximab

Cehtximab binds specifically to the epide1mal growth factor receptor (EGFR, HERi, c-ErbB-1) on both nonnal and tumor cells, and competitively inhibits the binding of epide1mal growth factor (EGF) and other ligands, such as transf01ming growth factor-alpha[36]. Binding of cehlximab to the EGFR blocks phosph01ylation and activation of receptor-associated kinases, resulting in inhibition of cell growth,

induction of apoptosis, and decreased matrix metalloproteinase and vascular endothelial growth factor production. The EGFR is constitutively expressed in many n01mal epithe lial tissues , incl uding the skin and hair follicle. Overexpression of EGFR is also detected in many human cancers including those of the colon and rectum[37].

In vitro assays and in vivo animal studies have shown that cetuximab inhibits the growth and survival of tumor cells that over-express the EGFR. No anti-ttllllor effects of cettIXimab we re observed in h1llllan tumor xenografts lacking EGFR expression. The addition of cettIXimab to i1inotecan or iti notecan plus 5-fluorouracil in animal studies resulted in an increase in anti-tumor effects compared to chemotherapy alone.

1.8.4 Human Pharmacokinetics

Cetuximab administered as monotherapy or in combination with concomitant chemotherapy or radiotherapy exhibits nonlinear phaimacokinetics[36]. The ai·ea under the concentration time curve (AUC) increased in a greater than dose proportional manner as the dose increasedfrom 20 to 400 mg/m2. Cetuximab cleai·ance (Cl) decreased from 0.08 to 0.02 L/h/m^2 as the dose increased from 20 to 200 mg/m^2, and at doses >200 mg/m^2, it appeai·ed to plateau. The volume of disttibution (Vd) for cetuximab appeai·ed to be independent of dose and approximated the vascular space of 2-3 L/m^2.

Following a 2-hour infusion of 400 mg/m^2 of cetuximab, the maximum mean semm concentration (Cmax) was 184 µg/mL (range: 92-327 µg/mL) and the mean elitnination half-life was 97 hours (range 41-213 hours). A I-hour infusion of 250 mg/m^2 produced a mean Cmax of 140 µg/mL (range 120-170 µg/mL). Following the recommendeddose regimen (400 mg/m^2 initial dose/250 mg/m^2 weekly dose), cetuximab concentrations reached steady-state levels by the third weekly infusion with mean peak and trough concentt·aitons across studies ranging from 168 to 235 and 41 to 85 µg/mL, respectively. The mean half-life was 114 hours (range 75-188 hours).

Cen1ximab administe red as monotherapy or in combination with concomitant chemotherapy or radiotherapy exhibits nonlinear phaim acokinetics.The phaimacokinetics of cen1ximab were similai·in patients with squamous cell carcinoma of the head and neck (SCCHN) and those with colorectal cancer[36].

1.8.5 Randomized Clinical Trials of Cetuximab in Head and Neck Cancer

1.8.5.1 Cetuximab in Locally Advanced Squamous Cell Carcinoma of Head and Neck

The efficacy and safety of cetuximab were studied in combination with radiation therapy in a randomized, controlled ttial of 424 patients with locally or regionally advanced squamous cell cai·cinoma of the head and neck versus radiation alone[38]. In a multicenter contt·olled clinical ttial, 424 patients with stage III/IV SCC of the orophaiynx, hypopha1ynx or laiynx with no p1ior thera py were randomized 1:1 to receive cetuximab plus radiation therapy (211 patients) or radiation therapy alone (213 patients). Stratification factors were Kamofsky Performance Status (60-80 versus 90-100), nodal stage (NO vers us **N+),** tumor stage (Tl -3 versus T4 using American Joint Committee on Cancer 1998 staging clite1ia), and radiation therapy fractionation (concomitant boost versus once-daily versus twice daily). Radiation therapy was administered fonn 6-7 weeks as once daily, twice daily or concomitant boost. The planned radiation

therapy regimen was chosen by the investigator prior to enrollment. For patients with **Nl** neck disease, a post-radiation therapy next dissection was recommended. Staiting 1 week before radiation, cetuximab was administered as a 400-mg/m^2 initial dose, followed by 250 mg/m ^{2} weekly for the duration of radiation therapy (6-7 weeks). All cetuximab-treated patients received a 20-mg test dose on Day **1.** Cetuximab was administered **1** hour p1ior to radiation therapy, beginning week 2. Of the 424 randomized patients, 80% were male and 83% were Caucasian. The median age was 57 yeai·s (range 34-83). There were 258 patients enrolled in US sites (61%) and 166 patients (39%) in non-US sites. Ninety percent of patients had baseline Karnofsky Perf01mance Status 80%; 60% had orophaiyn geal, 25% laiyn geal, and 15% hypophaiyn geal p1imaiy tumors; 28% had AJCC T4 tumor stage. The patient characte1istics were similar across the sn1dy aims. Fifty-six percent of the patients received radiation therapy with concomitant boost, 26% received once-daily regimen, and 18% twice-daily regimen.

The main outcome measure oft his tiial was duration ofl ocoregional control. Overall survival was also assessed. Results are presented below:

Table 1 Clinical Efficacy in Locoregionally Advanced SCCHN

	Cetuximab + Radiation (n = 211)	Radiation Alone (n = 213)	Hazard Ratio (95% CI*)	Stratified Log-rank p-value
Locoregional control MedianDuration	24.4 mo	14.0mo	0.68 (0.52-0.89)	0.005
Overall Survival Medianduration	49.0 mo	29.3 mo	0.74 (0.57-0.97)	0.03

*Cl = confidence inteival.

1.8.5.2 Cetuximab in Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck

More recently the results of EXTREME t:ial[47] have been repo1ted. In this multicenter study 442 patients, with unti·eated recunent or metastatic squamous cell carcinoma of the head and neck, enrolled. 220 patients were randomly assigned to receive cisplatin (at a dose of 100mg/m^2, on day 1) plus 5FU (at a dose of 1000mg/m^2, for 4 days) evely three weeks for a maximum of 6 cycles and 222 patients to receive the same regimen plus cetuximab (at an initial loading dose of 400mg/m^2, then weekly doses of 250mg/m^2) for 6 cycles. Patients who didn't progress continued monotherapy of cetuximab until disease progression. The patients in each coho1twere well- balanced regarding gender, age, pe1formance status (P$) primaiy tumor site, extent of disease and histologic type. About ninety percent of the patients had PS> 80%. Results are presented below:

Table 2 Clinical Efficacy in Locoregionally Advanced SCCHN

	Cetuximab + chemo	Chemo Alone	Hazard Raffo or Odds Ratio (95% CI*)	p-value
Overall survival	10.1 mo	7.4mo	0.80 (0.64-0.99)	0.04
Progrt>ssi o n Free Survival	5.6mo	3.3 mo	0.54 (0.43-0.67)	<0.001
Time to treatment failure	4.8mo	3.0mo	0.59(0.48- 0.73)	<0.001
Disease control	81% (75-86%)	60% (53-67%)	Odds Ratio 2.88 (1.87-4.44)	<0.001

*Cl = confidence interval.

A phase ill tlial ofradiation cisplatin with or without cetuximab is ongoing in the RTOG (0522).

1.8.6 Other Cetuximab Trials in Head and Neck Cancer

Cetuximab alone was studied in a single-rum, multicenter clinical trial in 103 patients with recurrent or metastatic SCCHN with documented progression within 30 days after 2-6 cycles of a platinum-based chemotherapy[48]. Patien ts received a 20-mg test dose of cetuximab on Day 1, followed by a 400-mg/m^2 initial dose, and 250 mg/m^2 weekly until disease progression or unacceptable toxicity. Upon progression, patients were given the option ofr eceivingcetuximab plus the platinum regimen that they failed plior to emollment. Tumor response and progression were assessed by an Independent Radiographic Review Committee (IRC). The median age was 57 years (range 23-77), 82% were male, 100% Caucasian, and 62% had a Kamofsky perfmmance status of 80. The objective response rate on the monotherapy phase was 13% (95% confidence interval 7%-21%). Median duration of response was 5.8 months (range 1.2-5.8 months).

A phase II study conducted at Memorial-Sloan Kettering Cancer Center explored the combination of radiation, cisplatin, and cetuximab[49]. This study employed altered fractionation radiotherapy with accelerated boost. There were 2 deaths during treatment (one patient died of pneumonia and the other from unknown cause) in a total of 22 patients and 3 other out-of field serious adverse events (arrhythmia, myocru·dial infarction , and bacteremia). However, the progression-free survival was promising (80% at 2 yerus)[49]. It was thought that a lower dose of cisplatin than 100 mg/m^2 would be safer with this combination regimen. A phase II study with cisplatin, radiation, and cetuximab was completed in ECOG (E3303). This study employed a lower cisplatin dose of75 mg/m^{2}evely 3 weeks x 3.

Expelience with TPE followed by XPE at the University of Pittsburgh

The proposed study is building on our previous expelience at the University of Pittsburgh with induction with cisplatin, docetaxel, and cetuximab (TPE). This phase II tlial (UPCI 05-003)completedaccrnal of 39 patients in 2007. Results have been presented at ASCO 2008 (abstl·act 6002) and the manuscript was published in JCO in 2010 (Argiris et al JCO 2010). The treatlnent regimen consisted of 3 cycles of induction (TPE) therapy with docetaxel (T) 75mg/m^2 dl, cisplatin (P) 75mg/m^2 dl and cetuximab (E)

dl ,8,15 (q21d) followed by (XPE) RT (X) 70Gy, cisplatin (P) 30mg/m^2/ weekly and then cetuximab (E) maintenance for 6 months. Treatment was associated with expected and manageable toxicities.. Of 39 emolled patients, 36 had stage IV disease and 23 an oropha1yngeal p1ima1y.Acute toxicities during TPE includedneutropenic fever (10%) and dmi ng XPE, grade 3 or 4 oral mucositis (54%) and hypomagneselnia(39%). After TPE, we observed two complete responses (CRs) and 30 partial responses (PRs), overall response rate (ORR) of 86% (95% CI, 75% to 98%) in 37 evaluable patients. The complete response using PET p01tion of PET/CT was 21%. After XPE, we observed an ORR of 100% (95% CI, 91% to 100%), 24% CRs and 76% PRs, in 33 evaluable patients. In another paper by Passero et al (Annalsof Oncology 2010;21:2278-83), we demonstrated that reposnse by PET but not using RECIST 1.0 con elated with progression-free survival. With a median follow-up of 36 months, 3-year progression-free smvival and overall smvival were 70% and 74%, respectively. Eight patients progressed in locoregional sites, three in distant, and one in both. HPV positivity was not associated with treatment efficacy. No progression-free patient remained G-tube dependent. The H&N subscale QOL scores showed a significant decrement at 3 months after XPE, which normalized at I year. We concluded that this cetuximab-containing regimen resulted in excellent long-te1msmv ival and safety, and wa1rnnts fmther evaluation in both HPV-positive and -negative head and neck cancer.

Safety of Cetuximab in Clinical Ttials

1.8.6.1 Anticipated Adverse Events

Squamous Cell Cancer of the Head and Neck

Except where indicated, the data desc1ibed below reflect exposure to cehlximab in 208 patients with locally or regionally advanced HNSCC who received cetuximab in combination with radiation and as monotherapy in I 03 patients with recmrnnt or metastatic HNSCC. Of the 103 patients receiving cetuximab monotherapy, 53 continued to a second phase with the combination of ceh1ximab plus chemotherapy. Patients receivingcetuximab plus radiation therapy received a median of 8 doses (range **1-11** infusions). The population had a median age of 56; 81% were male and 84% Caucasian. Patients receiving cetuximab monotherapy received a median of 11 doses (range 1-45 infosions). The population had a median age of 57; 82% were male and 100% Caucasian.

The most **se1ious adverse reactions** associated with cetuximab in combination with radiation therapy in patients with head and neck cancer were:

- Infusion reaction(3%)
- Cardiopulmona1y atTest (2%)
- De1matologic toxic ity(2.5%)
- Mucositis (6%)
- Radiation de1matitis (3%)
- Confosion (2%)
- Dian hea (2%)
- Fomteen (7%) patients receiving cetuximab plus radiation therapy and 5 (5%) patients receiving cetuximab monotherapy, discontinued treatment primai·ily because of adverse events
- The most common adverse events seen in 208 patients receiving cetuximab in combination with radiation therapy were acnefonn rash (87%), mucositis (86%), radiation de1matitis (86%), weight

loss (84%), xerostomia (72%), dysphagia (65%), asthenia (56%), nausea (49%), constipation (35%), and vomiting (29%)

- The most common adverse events seen in 103 patients receiving cetuximab monotherapy were acnefonn rash (76%), asthenia (45%), pain (28%), fever (27%), and weight loss (27%).

The data in the table that follows are based on the experience of 208 patients with locoregionally advanced HNSCC treated with cetuximab plus radiation therapy compared to 212 patients treated with radiation therapy alone.

Table 3 Incidence of Selected Adverse Events (10%) in Patients with Locoregionally Advanced HNSCC

Body System PrefenedTenn	Cetuximab plus Radiation (n=208)		RadiationTherapyAlone (n=212)	
	Grades 1 - 4	Grades 3 and4	Grades 1 - 4	Grades 3 and4
	% of Patients			
Body as a Whole				
Asthenia/Malaise	56	4	48	5
Fever[1]	29	1	13	< 1
Headache	19	<1	8	<1
Infusion Reaction[2]	15	3	2	0
Infection	13	1	9	1
Chills[1]	16	0	5	0
Digestive				
Mucositis/Stomatitis	93	56	94	52
Xerostomia	72	5	71	3
Dysphagia	65	26	63	30
Nausea	49	2	37	2
Constipation	35	5	30	5
Vmniting	29	2	23	4
Anorexia	27	2	23	2
Diauhea	19	2	13	1
Dyspepsia	14	0	9	1
Metabolic/Nutritional				
Weight Loss	84	11	72	7
Dehydration	25	6	19	8
Respiratory				
Pharyngitis	26	3	19	4
Cough Increased	20	<1	19	0
Skin/Appendages				
Acnefonn Rash[3]	87	17	10	1
Radiation Dermatitis	86	23	90	18
Application Site Reaction	18	0	12	1
Pruritus	16	0	4	0

Table 3 Incidence of SelectedAdverse Events (10%) in Patients with Locore!rlona ll v Adva n ced HNSCC

Body System Prefened Te1m	Cetuximab plus Radiation (11=2 08)		RadiationTherapy Alone (n = 212)	
	Grades 1 - 4	Grades 3 and4	Grades 1 - 4	Grade s 3 and4
	% of Patients			

[1] Includes cases also reported as infilsion reactions.

[2] Infilsion reaction is defined as any event desc1ibed at any time dming the clinical study as "allergic reaction" or "anaphylactoidreaction" or any event on the first dayof dosing desc1ibed as "allergicreaction", "anaphylactoidreaction", "fever", "chills", "chills and fever" or "dyspnia".

[3] Acnefonn rash as defined as any event desc1ibed as "acne", "rash", "maculopapularash", "pustular rash", "d1yskin" or "exfoliative dermatitis".

The data in the table below are based on the experience of 222 patients with recmrnnt or metastatic HNSCC treated with cetuximab plus chemotherapy compared to 220 patients treated with chemotherapy alone.

Table 4 Incidence of Selected Adverse Events (5%) in Patientswith Metastaticor recurrent HNSCC

Event	Cetuximab plus chemo (n=222)		chemo Alone (n=220)	
	Grades 3 - 4	Grade 4	Grades 3 - 4	Grade4
	% of Patients			
Any event	82	**31**	76	31
Neutropenia	22	4	23	8
Anemia	13	1	19	I
Thrombocytopenia	11	0	11	I
Skin reaction*	9	2	**<1**	0
Hypokalemia	7	1	5	**<1**
Card iac events	7	5	4	3
Vomiting	5	0	3	0
Asthenia	5	< 1	6	**<1**
Anorexia	5	1	1	**<1**
Hypomagne se m ia	5	4	1	**<1**

*S kin reactions include: acne, msh, maculopapular rash, ceUulities, face edema, dry skin, erysipelas, folliculitis, nail disorder, paronychia, skin hyperpigmentation and skin necrosis.

Six patien ts (3%) developed infusion- related reaction grade 3 or 4. Grade 2 skin reaction was observed in about 35% of the patients in cetuximab group.

Late Radiation Toxicity

The overall incidence of late radiation toxicities (any grade) was higher in cetuximab in combination with radiation therapy compared with radiation therapy alone. The following sites were affected: saliva1y

glands (65% versus 56%), larynx (52% versus 36%), subcutaneous tissue (49% versus 45%), mucous membrane (48% versus 39%), esophagus (44% versus 35%), skin (42% versus 33%), brain (11% versus 9%), lung (11% versus 8%), spinal cord (4% versus 3%), and bone (4% versus 5%). The incidence of Grade 3 or 4 late radiation toxicities were generally similar between the radiation therapy alone and the cetuximab plus radiation treatment groups.

1.8.6.2 Infusion Reactions

In clinical trials, severe, potentially fatal infusion reactions were rep01ted. These event s include the rapid onset of aiiway obstruction (bronchospasm, st:ridor and hoarseness), mticaria, and/or hypotension. In studies in advanced colorectal cancer, severe infusion reactions were obse1ved in 3% of patients receiving cetuximab plus iii.notecan and 2% of patients receiving cetuxiinab monotherapy. Grade 1 and 2 infusion reactions, including chills, fever, and dyspnea usually occmTing on the first day of initial dosing, were obse1ved in 16% of patients receiving cetuxiinab plus iti.notecan and 19% of patients receiving cetuximab monotherapy.

A 20-mg test dose was administered intr·avenously over IO mi nute s p1i.or to the initial dose to all patients in earlier studies. The test dose did not reliably identify patients at risk for severe allergic reactions.

Severe infusion reactions occmTed with the administration of cetuxiinab in approximately 3% of patients, rarely with fatal outcome (<1 in 1000). Approximately 90% of severe infusion reactions were associated with the first infusion of cetuximab despite the use of prophylacticantihistamines. These reactions were characte1.zed by the rapid onset of aiiway obstrnction (bronchospasm, stridor and hoarseness), urticai.a, and/or hypotension.

1.8.6.3 Pulmonary Toxicity

Interstitial lung disease (ILD) was rep01ted in 3 of 774 (<0.5%) patients with advanced colorectal cancer receiving cetuximab. Interstitial pnemnonitis with non-cardiogenicpulmona1yedema resulting in death was rep01ted in one case. Two patient s had pre-existing fibrotic lung disease and expe1i.encedan acute exacerbation of theiI·disease while receiving cetuximab in combination with iti.notecan. In the clinical investigational prograin, an additional case of interstitial pneumonitis was rep01ted in a patient with head and neck cancer treated with cetuximab and cisplatin. The onset of symptomsoccmrnd between the fomth and eleventh doses of treatment in all reported cases.

1.8.6.4 Dermatologic Toxicity

In cynomolgus monkeys, cetuximab, when administered at doses of approximately 0.4 to 4 times the weekly human exposme (based on total body smfa ce ai·ea) resulted in dermatologic findings, including inflammation at the injection site and desquamation of the external integument[50]. At the highest dose level, the epithelial mucosa of the nasal passage, esophagus, and tongue were similai·ly affected, and degenerative changes in the renal tubulai· epithelium occmTed. Death s due to sepsis were obse1ved in 50% (5/10) of the animals at the highest dose level beginning after approxiinately 13 weeks of treatment.

In clinical studies of cetuxiinab, dennatologic toxicities, including acneform rash, skin dty ing and fissming, and inflammat01y and infectious sequelae (eg, blepharitis, cheilitis, cellulitis, cyst) were repo1ted[50]. In patients with advanced colorectal cancer, acnefo1m rash was repo1ted **in** 88% (686/774) of

all treated patients, and was severe (Grade 3 or 4) in 12% (79/633) of these patients. Subsequent to the development of severe de1matologic toxicities , complicat ions including S. *aureus* sepsis and abscesses requiiing incision and drainage were repo1ted.

Non-suppura tive acnefo1m rash described as "acne", "rash", "maculopapular rash", "pustularrash", "diy skin", or "exfoliativede1matitis" was observed in patients receiving cetuximab plus ilinotecan or cetuximab monotherapy[50]. One or more of the de1matological adverse events were repo1ted in 88% (14% Grade 3) of patients receiving cetuxilnab plus ilinotecan and in 90% (8% Grade 3) of patients receiving cetuxilnab monotherapy. Acnefmm rash most commonly occurred on the face, upper chest, and back, but could extend to the extremities and was characte1ized by multiple follicular- or pustular-appea1ing lesions. Skin diying and fissming were common in some instances, and were associated with inflammato1yand infectioussequelae (eg, blepha1itis, cellulitis, cyst). Two cases of *S. aureus* sepsis were repo1ted. The onset of acnefo1m rash was generally within the first two weeks of therapy. Although in a majmity of the patients the event resolved following cessation of treatment, in nearly half of the cases, the event continued beyond 28 days.

A related nail disorder, occm1ing in 14% of patients (0.4% Grade 3), was characte1ized as a paronychial inflammation with associated swelling of the lateral nail folds of the toes and fingers, with the great toes and thumbs as the most commonly affected digits.

1.9 Induction Chemotherapy Followed by Chemoradiotherapy

Squamous cell carcinomas of the head and neck are chemosensitive neoplasms. However, multiple randomized trials have failed to demonstrate that the addition of induction chemotherapy to surge1y and/or radiotherapy confers a survival advantage in patients with locally advanced head and neck cancer. The rationale of induction therapy was questioned and its use was thought to be expe1imental[33,51,53]. ConcmTent chemoradiotherap y was felt to be the most promising approach and was studied extensively in the 1990s. Neve1theless, a number of studies of induction chemotherapy have shown a decreased rate of distant metastasis with the use of induction chemotherapy and a few have repo1t ed encouraging survival data. A study by Pacagnella et al that compared induction chemotherapy with cisplatin/5-FU followed by surge1y and/or radiation showed a survival benefit but only in patients with unresectable tumors[37]. Domenge et al[36] repmted the only positive trial that enrolled 318 patients with locally advanced oropha1yn geal cancer. Disease-free smvival was ilnproved in the induction chemotherapy arm but the difference did not reach statistical significance (p=O.1 1); overa ll smv ival was superior in the induction chemotherapy aim ($p<0.05$). These two tlials were included in a metaanalysis by Pignonet al published in 2000[18]. In this metaanalysis, when all induction chemotherapy studies were examined together, there was no smv ival benefit with induction chemotherapy. However, when the subset of ti·ials with platinum/5-FU was examined, a statistical significant ilnprovement in smvival with the addition of induction chemotherapy was obse1ved with a hazard ratio of0.88 (95% CI 0.79-0.97). A study by Taylor et al suggested that concmTent therapy on an alternate week schedule produced better disease control and comparable smvival to induction chemotherapy[54]. However, no study has evaluated the role of the addition of induction chemotherapy when concmrnnt chemoradiotherapy is used in both aims in head and neck cancer.

Multiple chemotherapy regimens have been tested in the induction setting in head and neck cancer. The most widely used has been cisplatin and 5-FU. Carboplatin may be inferior to cisplatin as demonstrated in a randomized comparison between cisplatin/5-FU and carboplatin/5-FU in the induction setting[55] Also, the activity of carboplatin/5-FU in recun ent/metastaticdisease is inferior to that of cisplatin/5-F.U[56] The combination of platinum and the taxanes has been paiticularly active in head and neck cancer. Moreover, the incidence of stomatitis seen with this regimen is less than what is observed when 5-FU is a pait of the regimen. Cai-bop latin and pacl itaxe l have been used in many studies with objective response rates 80% or higher[57].

The combination of cisplatin and docetaxel is active in recmTent/metastatic head and neck cancer with objective response rates between 33-54%[434 5] as well as in locally advanced head and neck cancer with objective response rates between 55-89%[4446] ,which is compai·able to the activity of cisplatin/5-FU and cisplatin/paclitaxel. The feasibility of platinum-based induction chemotherapy for 2-3 cycles followed by cisplatin or paclitaxel concmTently with radiotherapy has been demonstrnted in multiple trials[57 ;59] However, no study has yet shown the feasibility of cisplatin/docetaxel followed by cisplatin concmrent with standard radiation. One of the concerns is whether cumulative toxicities from the induction regimen will compromise dose delive1ydming subsequentchemoradiotherapy. A consistent finding among sn1dies with cisplatin 100 mg/m^2 eve1y 3 weeks plus radiation has been that all three doses of "high-dose" cisplatin can only be delivered in approximately 60% of patients. In this study, we will allow the use of cai·bopatin; if out of field cisplatin-related toxicities occm.

Studies with cisplatin and 5-FU have shown that the response rate is higher with 3 versus 2 cycles[60] , whereas a plateau may be reached after 3 cycles[61]. Shin et al have observed that with additional cycles of induction chemotherapy, the rate of complete response to carboplatin/ifosfamide/paclitaxel increased from 23% after 2 cycles to 60% after 4 cycles[62]. **For this study we elected to use 3 cycles of chemotherapy that will allow adequate systemic exposure to chemotherapy.** An ongoing study in om institution is evaluating cisplatin and docetaxel followed by radiation and cisplatin 100 mg/m^2 eve1y 3 weeks x 3 in unresectable patients with head and neck cancer.

1.10 BevacizumabClinical Experience

Bevacizumab has been studied in a multitude of Phase I, II, and III clinical trials in more than 5000 patients and in multiple tumor types. In addition, data are available from 3,863 patients enrolled in two postmai·keting studies in metastatic colorectal cancer (CRC). Approximately 130,000 patients have been exposed to bevacizumab as a mai·keted product or in clinica l trials. The following discussion summarizes bevacizumab's safety profile and presents some of the efficacy results pe1tinent to this pa1ticulai·trial. Please refer to the bevacizumab Investigator Brochme for descriptions of all completed Phase I, II, and III tiials rep01ted to date.

In a large phase III study (AVF2107g)[63] in patients with metastatic colorectal cancer, the addition of bevacizumab, a monoclonal antibody directed against vascular endothelial growth factor (VEGF), to iiinotecan/5-fluoromacil/leucovorin (IFL) chemotherapy resulted in a clinically and statistically significant increase in dmation of survival, with a hazai·d ratio of death of 0.67 (median smv ival 15.6 vs. 20.3 months; $p < 0.001$). Similar increases were seen in progression-free smvival (6.2 vs. 10.6 months; $p < 0.001$), overall response rate (35% vs. 45%; $p < 0.01$) and duration of response (7.1 vs. 10.4 months;

p < 0.01) for the combination arm versus the chemotherapy only arm (bevacizumab Investigator Brochure, October 2005).

Based on the survival advantage demonstrated in Study AVF2107g, bevacizumab was designated for pri01ity review and was approved on 26 February 2004 in the United States for first-line treatment in combination with IV 5-FU- based chemotherapy for subjects with metastatic colorectal cancer.

Additional data from Phase III tlials in metastatic CRC (£3200)64, non- small cell lung cancer (NSCLC; £4599)[65], and metastatic breast cancer (£ 2100)[66] havealso demonsti·ated clinical benefit from bevacizumab when added to chemotherapy. In Study E3200, the addition of bevacizumabto FOLFOX chemotherapy resulted in improved overall survival compared with FOLFOX alone (13.0 vs. 10.8 months, respectively, HR = 0.75; p < 0.01) in a populationof previously ti·eated CRC patients .

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

Safety Profile

In the initial Phase I and II clinical tiials, four potential bevacizumab-associated safety signals were identified: hypertension, proteimnia, thromboembolic events, and hemon hage. Additional completed Phase II and Phase III studies of bevacizumab as well as spontaneous repo1t s have finther defined the safety profile of this agent. Bevacizumab-associated adverse events identified in phase III trials include congestive heait failure (CHF) p1imai·ily in metastatic breast cancer, gastrointestinal perforations, wound healing complications, and al1eli al thromboembolic events (ATE). These and other safety signals ai·e described in finther detail as follows and in the bevacizmnab Investigator Brochure.

Hypertension: An increased incidence of hype1tension has been observed in patients ti·eated with bevac izumab. Grade 4 and 5 hypertensive events ai·e rai·e. Clinica l seque lae of hype 1tens ion ai·e rare but have included hype1tensive crisis, hype1tensive encephalopathy , and reversib le posterior leukoencephalopathy syndrome (RPLS)[67,68].

There is no inf01m atio n on the effect of bevacizumab in patients with uncontrolled hype1tension at the time of initiating bevacizumab therapy. Therefore, caution should be exercised before initiating bevacizumab therapy **in** these patients. Monito1ing of blood pressure is recommended dming bevacizumab therapy. Optimal control of blood pressure according to standai·d public health guide lines is reco mmended for patients on ti·eatment with or without bevacizumab.

Temporaiy intenu ption of bevacizmnab therapy is recommended in patients with hype1tension requiring medical therapy until adequate conti·ol is achieved. If hype1tension cannot be controlled with medical

therapy, bevacizumab therapy should be permanently discontinued. Bevacizumab should be permanently discontinued in patients who develop hypeitensive crisis or hypertensive encephalopathy.

Prnteinuria : An increased incidence of proteinuria has been observed in patients treated with bevacizumab compared with control aim patients. In the bevacizumab-containing treatment aims of clinical tiials (across all indications), the incidence of proteinuria (repoited as an adverse event) was up to 38% (metastatic CRC Study AVF2192g). The severity of proteimui a has ranged from asymptomatic and ti·ansient events detected on routine dipstick urinalysis to nephrotic syndrome; the majority of proteinuria events have been grade 1. NCI-CTC Grade 3 proteinuria was repmted in up to 3% of bevacizumab-ti·eated pa tients , and Grade 4 in up to 1.4% of bevacizumab-treated patients. The proteinuria seen in bevacizumab clinical trials was not associated with renal impailment and rai·ely requil·edpennanent discontinuation of bevacizumab therapy. Bevacizumab should be discontinued in patients who develop Grade 4 proteinuria (nephrotic syndrome)

Patients with a histoiy of hypeitension may be at increased iisk for the development of proteinuria when ti·eated with bevacizumab. There is evidence from the dose-finding, Phase II tiials (AVF0780g, AVF0809s, and AVF0757g) suggesting that Grade 1 proteinuria may be related to bevacizumab dose.

Proteinmi a will be monitored by mine protein: creatinine (UPC) ratio at least eveiy 6 weeks. If the UPC ratio is not available, a dipstick mi nalysis may be used to allow ti·eatment to proceed.

Thromboembolic Events: Both venous and ait eiial thromboembolic(TE) events, ranging in seveii ty from catheter-associated phlebitis to fatal, have been repoited in patients treated with bevacizumab in the colorectal cancer tlials and, to a lesser extent, in patients ti·eated with bevacizumab in NSCLC and breast cancer tlials.

Venous Thrnmboembolism (including deep venous thrombosis, pulmonary embolism, and thrombophlebitis): In the phase III pivotal tli al in metastatic CRC, there was a slightly higher rate of venous TE events in patients ti·eated with bevacizumab plus chemotherapy compai·edwith chemotherapy alone (19% vs. 16%).

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

The incidence of NCI-CTC Grade 3 venous VTE events in one NSCLC tiial (E4599) was higher in the bevacizumab-containing aim compared to the chemotherapyconti·ol aim (5.6% vs. 3.2%). One event (0.2%) was fatal in the bevacizumab-containing aim; not fatal events were repoited in the cai·boplatin/paclitaxel aim (see Bevacizumab *Investigator* Brochure). In metastatic CRC clinical ti·ials, the incidence of VTE events was silnilai·in patients receiving chemotherapy+ bevacizumab and those receiving the control chemotherapy alone.

In clinical tlials across all indications the overall incidence of VTE events was 2.8%- 17.3% in the bevacizumab-containing aims compared with 3.2%- 15.6% in the chemotherapycontrol aims. Thuse of bevacizumab with chemotherapy does not substantially increase the iisk of VTE event compared with

chemotherapy alone. However, patients with metastatic CRC who receive bevacizumab and experienced a VTE event may be at higher risk for rec1mence of VTE event.

AI'tel'ial Thromboembotic Events: An increased incidence of ATE events was observed in patients treated with bevacizumab compared with those receiving control treatments. ATE events include cerebrovascular accidents, myocardial infarction, transient ischemic attacks (TIAs), and other ATE events. In a pooled analysis of data from five randomized Phase II and III trials (mCRC [AVF2107g, AVF2192g, AVF0780g]; locally advanced or metastatic NSCLC [AVF0757g]; metastatic breast cancer [AVF2119g]), the incidence rate of ATE events was 3.8% (37 of963) in patients who received chemotherapy+ bevacizumab compared with 1.7% (13 of782) in patients treated with chemotherapy alone. ATE events led to a fatal outcome in 0.8% (8 of963) of patients treated with chemotherapy+ bevacizumab and 0.5% (4 of782) of patients treated with chemotherapy alone. Cerebrovascular accidents (including TIAs) occurred in 2.3% of patients treated with chemotherapy+ bevacizumab and 0.5% of patients treated with chemotherapy alone. Myocardial infarction occ1med in 1.4% of patients treated with chemotherapy+ bevacizumab compared with 0.7% of patients treated with chemotherapy alone (see the Bevacizumab Investigator Brochure for additional details).

Aspirin is a standard therapy for primaiy and secondaiy prophylaxis of aite1i al thromboembolic events in patients at high risk of such events, and the use of aspitin ::: 325 mg daily was allowed in the five randomized studies discussed above. Use of aspit-in was assessed routinely as a baseline or concomitant medication in these tria,ls though safety analyses specifically regai·dingaspit-in use we re not prep lanned. Due to the relatively small numbersof aspit·in users and a1terial thromboembolic events, retrnspective analyses of the ability of aspi1in to affect the risk of such events were inconclusive. However, similarly retrospective analyses suggested that the use of up to 325 mg of aspitin daily does not increase the1isk of grade 1-2 or grade 3-4 bleeding events, and similar data with respect to metastatic colorectal cancer patients were presented at ASCO 2005 (Hambleton et al., 2005). Frnt her analyses of the effects of concomitant use of bevacizumab and aspirin in colorectal and other tumor types ai·e ongo ing.

Ga stl'ointestinal Perforation Patients with metastatic carcinoma may be at increased 1i sk for the developmentof gastrointestinalperforation and fistula when treated with bevacizumab and chemotherapy. Bevacizumab should be pe1manently discontinued in patients who develop gastrointestinal perforation. A causal association of intra-abdominalinflammat01y processes and gastrointestinal perforation to bevacizumab treatment has not been established. Neve1thele,ss caution should be exercised when treating patients with intra-abdominal inflammat01y processes with bevacizumab. Gastrointestinal pe1foration has been rep01ted in other hi als in non-colorectal cancer populations (e.g., ova1ian, renal cell, pancreas, breast, and NSCLC) and may be higher in incidence in some tumor types.

Fistula: Bevacizumab use has been associated with se1ious cases of fistulae including events resulting in death. Fistulae in the GI h·act ai·e common (1%- 10% incidence) in patients with metastatic CRC, but uncommon (0.1%- 1%) or rai·e (0.01%-0 .1%) in other indications. In addition, fistulae that involve ai·eas of the body other than the GI h·act (e.g., tracheoesophageal , bronchop leural, urogenital, biliaiy) have been repo1t ed uncommonly (0.1**%- 1%)** in patients receiving bevacizumab in clinical studies and postmai·keting

reports . Events were repo1ted at various timepoints during treatment, ranging from 1 week to 1 year following initiation of bevacizumab, with most events occrnTing within the first 6 months of therapy.

Pe1manently discontinue bevacizumab in patients with tracheoesophageal fistulae or any Grade 4 fistula. Lilnited infmmation is available on the continued use ofbevacizumab in patients with other fistulae. In cases of internal fistula not a1ising in the GI tract, discontinuationof bevacizumab should be considered.

Wound healing complications: Wound healing complications such as wound dehiscence have been repo1ted in patients receiving bevacizumab. In an analysis of pooled data from two trials in metastatic colorectal cancer, patients undergoing surge1y28-60 days before study treatment with 5-FU/LV plus bevacizumab did not appear to have an increased risk of wound healing complications compared to those treated with chemotherapy alone69. Surge1y in patien ts cun ently receiving bevacizumab is not recommended. No definitive data are available to define a safe inte1val after bevacizumab exposure with respect to wound healing risk in patients receiving elective surge1y; however, the estimated half life of bevacizumab is 21 days. Bevacizumab should be discontinued in patients with severe wound healing complications.

If patients receiving treatment with bevacizumab require elective major surge1y, it is recommended that bevacizumab be held for 4-8 weeks prior to the surgicalprocedure. Patients lmdergoing a major surgical procedure should not begin or resta1tbevacizumab until 4 weeks after that procedure (in the case of high-risk procedures such as liver resection, thoracotomy, or neurosurge1y, it is recommended that chemotherapy be restaited no eai·lier than 6 weeks and bevacizumab no eai·lier than 8 weeks after surge1y).

Hem01Thage: Overa ll, grade 3 and 4 bleeding events were obse1ved in 4.0% of 1132 patients treated with bevacizumab in a pooled database from eight phase I, II, and III clinical trials in multiple tumor types (bevacizumab Investigator Brochure, October 2005). The hemonhagic events that have been obse1ved in bevacizumab clinical studies were predominantly tumor-as sociated hemonhage (see below) and lninor mucocutaneous hemorrhage.

Tumor-Associated Hemorrhage: Major or massive pulmonaiy hemonhage or hemoptysis has been obse1ved p1imaii ly in patients with NSCLC. Life-threatening and fatal hemoptysis was identified as a bevacizumab-related adverse event in NSCLC trials. These events occrnTed suddenly and presented as major or massive hemoptysis. Among the possible 1i sk factors evaluated (including squamous cell histology, treatment with anti-rheumatic/anti-inflammato1ydrngs, treatment with anticoagulants, p1ior radiotherapy, bevacizumab therapy, previous medical histo1yof atherosclerosis, central tumor location, and cavitation of tumors drning therapy), the only variables that showed statistically significant con-elations with bleeding were bevacizumab therapy and squamous cell histology.

GI hemonhages, including rectal bleeding and melena have been rep01ted in patients with CRC, and have been assessed as tumor-associated hemon hages.

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

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

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

Reversible Posterior Leukoencephalopathy Syndrome: There have been rare repo1ts of beva.cizum ab-trea.ted patients developing signs and symptoms that are consistent with RPLS, a rare neurologic disorder that can present with the following signs and symptoms (amongothers): seizures, headache, altered mental status, visual disturbance, or co1tical blindness, with or without associated hype1tension. Bra.in imaging is manda.to1y to confnm the diagnosis ofRPLS. In patients who develop RPLS, treatment of specific symptoms, including control of hype1tension, is recommended along with discontinuation of beva.cizumab. The safety ofreinitia.ting beva.cizumab therapy in patients previously experiencing RPLS is not known[67,68].

Congestive heait failure: In clinical trials CHF was observed in all cancer indications studied to date, but predominantly in patients with metastatic breast cancer. In the Phase III clinical trial of metastatic breast cancer (AVF2119g), 7 (3%) beva.cizuma.b-treated patients expe1ienced CHF, compared with two (1%) control a.nn patients. These events varied in seve1ity from a.symptomatic declines in left ventlicular ejection fraction (LVEF) to symptomatic CHF requiiing hospitalization and treatment. All the patients treated with bevacizumab were previously ti·eated with anthracyclines (doxombicin cumulative dose of 240(360 mg/m2). Many of these patients also had p1ior radiotherapy to the left chest wall. Most of these patients showed improved symptoms and/or left venti·icula.r function following approp1ia.te medical therapy (Miller et al. 2005).

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

No inf01mation is available on patients with preexisting CHF of New York Hea1t Association (NYHA) Class II- N at the time of initiating beva.cizumab therapy , as these patients were excluded from clinical trials.

Prior anthracyclinesexposure and/or p1ior radiotherapy to the chest wall may be possible1isk factors for the development of CHF. Caution should be exercised before initiating bevacizumab therapy in patients with these risk factors.

A Phase II tiial in patients with refract01y acute myelogenous leukemia repo1ted 5 cases of cardiac dysfunction (CHF or LVEF decrease to < 40%) among 48 patients treated with sequential cyta.ra.bine , mitoxanti·one, and bevacizuma.b. All but 1 of these patients had significant prior exposure to anthracyclines as well[70].

Two additional studies investigated concmTent administi·aiton of anthracyclinesand bevacizumab. In 21 patients with inflammat01y breast cancer ti·eated with neoadjuvant docetaxel, doxombicin, and

bevacizmnab, no patients developed clinically apparent CHF; however, patients had asymptomatic decreases in LVEF to < 40%[71]. In a small Phase II study in patients with soft tissue sarcoma, 2 of the 17 patients treated with bevacizumab and high-dose doxornbicin (75 mg/m^2) developed CHF (one Grade 3 event after a cumulative doxornbicin dose of 591 mg/m^2 one Grade 4 event after a cumulative doxornbicin dose of 420 mg/m^2) ;an additional 4 patients had asymptomatic decreases in LVEF[72].

Other studies in patients with valious tumor types and either a histo1yof anthracycline exposure or concomitant use with bevacizumab are ongoing.

Patients receiving concomitant anthracyclines or with prior exposure to anthracyclines should have a baseline MUGA scans or echocardiograms (ECHOs) with a nmmal LVEF.

Neutropenia: Increased rates of severe neutropenia, feb1ile neutropenia, or infection with severe neutropenia (including some fatalities) have been observed in patients treated with some myelotoxic chemotherapy regimens plus bevacizumab in compatison to chemotherapyalone[65].

Additional Adverse Events: See the bevacizumab Inves tigator Brochure for additional details regarding the safety expeti ence with bevacizumab.

1.11 BevacizumabStudies in Head and Neck Carcinoma at the University of Pittsburgh

A phase II study investigating the combination of pemetrexed and bevacizumab in recmTent or metas tatic HNSCC is ongoing with encouraging results (UPCI 05-002). 38 patients have been enrolled. In 29 evaluable patients, 9 (31%) have had an objective response (3CR + 6PR), 16 (55%) SD, whereas 4 (19%) patients developed PD. The median TTP was 4.9 months and the median OS was approximately 12 months. We had 6/38 (16%) grade 3-5 bleeding events (2 fatal), none after modificationsin eligibility were made to exclude patients with prior histo1yof tumor-related bleeding and do not allow retreatment after a first serious tumor-related bleeding.

Another trial with cetuximab and bevacizumab (UPCI 05-087) has enrolled 32 patients. Prelimina1y results (ASCO 2009) suggest that the regimen is active and safe. Only one grade 3 bleedingin 32 patients has been observed. The objective response rate is 20%, the median PFS 2.8 months and the median OS 8.1 months.

In addition, another phase II randomized trial of radiation, cetuximab and pemetrexed with or without bevacizumab is ongoing, as well (UPCI 07-021). The regimen is feasible. No bleeding events have occutTed in 8 patients treated.

1.12 Study Rationale

Induction chemotherapy is gaining momentum in the management of locally advanced squamous cell cai·cinoma of the head and neck (SCCHN). The combination of docetaxel, cisplatin, and 5-FU (TPF) was supe1ior compared with PF in a Phase ill clinical ttials[73,1][4] We have completed a Phase II clinical trial that showed that docetaxel, cisplatin, and cetuximab (TPE) is highly active and well tolerated as induction chemotherapy in SCCHN (Argitis et al. ASCO 2008; A6002). Preliminaiy survival results are very encouraging. 39 patients were enrolled and with median follow up 26 months the 2-yeai· PFS was 70% and the 2-year OS 84%.The combination of chemotherapy plus cetuximab is afready a standat·d treatment

in rectment or metastatic SCCHN4[7]. Therefore, TPE can be used as the platfonn for the addition of novel agents.

EGFR and VEGF are among the most imp01tant and validated molecular targets in cancer therapy. The incorporation of novel targeted therapies to chemotherapy and radiotherapy is of particulru· interest in head and neck cancer, and may improve efficacy without significantly increasing toxicity. A Phase III trial of carboplatin/paclitaxel/bevacizumab with or without cetuximab in advanced NSCLC has been proposed by SWOG. Bevacizumab is CllllTently being inves tigated in SCCIIN with promising results. A Phase II study investigating the combination of pemetrexed and bevacizumab (UPCI 05-002) as well as a Phase II trial of cetuximab and bevacizumab (UPCI 05-087) in recU1Tent or metastatic SCCHN ru·e ongoing at the University of Pittsburgh with encomaging results (ASCO 2008 and ASCO 2009). In this study, 32 have been afready emolled. There was only I patient with grade 3 hemo1Thage. The objective response rate is 20%, the median PFS 2.8 months and the median OS 8.1 months.

In order to ftnther improve the efficacy of TPE and the rate of complete responses we propose to add bevacizumab to the TPE followed by XPE regimen we developed at the University of Pittsbmgh. Due to non-overlapping toxicities and based on om p1ior experience we anticipate that the regimen will be well tolerated. Moreover, we plan to obtain tumor biopsies and blood samples in the first cycle and evaluate the modulation of biomru·kers post combi nation thera py. Data from induction with TPE (presented at ASCO 2009) indicate the potential significance of cytokine levels in patient outcome. Also, we will evaluate the feasibility of subsequent concllllrnnt radiation, cisplatin, cetuximab and bevacizumab. Patients with stable disease in the prima1y could be considered candidates to smgical resection at the discretion of their physician, if the tumor is resectable.

2 OBJECTIVES

2.1 P1imar y

To eva luate the rate of complete responses with induction with cisplatin, docetaxel, cetuximab and bevacizumab (TPE-A) in patients with locally advanced head and neck cancer.

2.2 Secondary

- To evaluate selum cytokines and to co1Te l ate wit h com p lete respo n se ra te post induction therapy.
- To collect tumor tissue from pretreatment and post-treatment (optional) biopsies for biomarker studies on tumor tissue. We plan to investigate a panel of EGFR and angiogenesis biomarkers on Tissue Microrurnys (TMAs).
- To evaluate the toxicities associatedwith induction TPE-A and subsequent concU1Tent rad iation, cis platin , cetuximab and bevacizumab (XPE-A).
- To evaluate the objective response rate post XPE-A, and the progression- free survival and overall survival and quality of life.

3 STUDY DESIGN

3.1 Induction Therapy (TPE-A)

3.1.1 Treatment and Premedications

Note: If a cycle is missed or a subject's treatment and/or testing days need to be rescheduled due to the subject's inability to comply with the study calendar (i.e., hospitalizations, business and vacation travel plans, illness, transp01tation issues, holidays, family emergencies, etc.), a window of± one (1) week is available for rescheduling of treatment and procedures per the discretion of the treating physician investigator, and as discussed with the principal investigator.

Cycles will be repeated eve1y 21 days for 3 cycles

Chemotherapy will be given on day 1 of a 21-day schedule and repeated eve1y 21 days for a total of 3 cycles. The doses of docetaxel, cetuximab, and cisplatin will be calculated using the patient's actual body weight on day 1 of each cycle. Fluids given during the administration of docetaxel, bevacizumab and cetuximab is counted as pa1t of cisplatin pre-hydration.

- Bevacizumab 15mg/kg IV, day 1 of each cycle.

  The bevacizumab dose should be delivered over 30 minutes as a continuous IV infusion prior to all chemotherapy infusions. Dexamethasone pre- and post-medication for docetaxel and as an antiemetic (see below). Dexamethasone decreases incidence and seve1ity and delays the onset of late-occm1ing fluid retention and may decrease the incidence and severity of acute hypersensitivity reactions. Dexamethasone 8 mg po bid x 3 days, starting 12-24 hours before the planned docetaxel infusion has been an effective schedule.
- Docetaxel 75 mg/m^2 IV over 1 hour, day I.
- In an effo1t to prevent a hypersensitivity reaction from cetuximab, all patients should be premedicated with diphenhydraminehydrochloride (Benadlyl) 50 mg (or an equivalent antihistamine) by IV given 30 minutes prior to the first dose of cetuximab.Premedication may be adlninistered p1ior to subsequent doses, but at the Investigator's discretion, the dose of diphenhyd·la1nine(or a similar agent) may be reduced.
- Cehlximab 400 mg/m^2 IV over 1201ninutes on day 1 of cycle 1 ONLY.
- Cehlximab dose will be 250 mg/m^2 IV over 60 1ninutes weekly on ALL subsequent adlninistrations(days 8 and 15 of cycle 1 and days 1,8,15 of cycles 2 and 3).
- Cisplatin 75 mg/m^2 IV over 1-2 hours, day 1. It is strongly recommended that patients receive G-CSF sta1ting on day 2 of each TPE-A cycle. If this is not possible, patients will receive prophylactic ciprofloxacin 500 mg twice daily for 10 days, on days 5-14.
- Furosemide will be given as needed.
- Antiemetic therapy, acute and delayed, includingdexamethasone and serotonin receptor antagonists, for 4 days is recommended. Aprepitant should be used with caution due to the possibility of a d1llg-dlu g interaction with docetaxel via CYP3A4 pathway.

The following hydl·ation regimen is recommended:

- Cisplatin will require aggressive hydl·ation. Any preexisting dehydl·ation should be coITected. Pre-cisplatin hydration will consist of 1 L NS administered over 2 hours (taking into account the fluid volumes received from prior dlug administration). Mannitol 12.5 g IV bolus can be given just before or concun ently with cisplatin. Pre-cisplatin hydl·ation can occur while patient is receiving

infosions of bevacizmnab, cetuximab, docetaxel. Hydration must not occur in the same IV line as chemotherapy (i.e. use patient' s other ann).

- Cisplatin will be administered in 500 -1000 cc of IV fluids over 1-2 hours and following adequate hydration and the establishment of adequate urina1youtput.
- Post cisplatin hydration will consist of 1 L ½ NS + 30 meq KCL/L over 2 hours (mannitol 25 g IV may be added).

3.1.2 Cet11ximab Administration

In an effo1tto prevent an infosion reaction, all patients should be premedicated with diphenhydra1nine hydrochloride 50 mg (or an equivalent antihistamine) by IV given 30-60 minutes prior to the first dose of cetuximab. Premedication may be administered prior to subsequent doses, but at the Investigator's discretion, the dose of diphenhydramine (or a similar agent) may be reduced.

The initial dose of cetuximab is 400 mg/m^2 intravenously administered over 120 minutes, followed by weekly infosions at 250 mg/m^2 IV over 60 minutes. The infosion rate of cetuximab must never exceed 5 mL/min. Patients must be continuously observed dming the infosion for signs of anaphylaxis.

Patients will be closely monitored for treatment-related adverse events, especially infosion reactions (see management of cetuximab adverse events).

For the duration that patients are on study therapy, adverse event monitoring will be done continuously. Patients will be evaluated for adverse events at each visit and are to be instmcted to call their physician to repmt any clinically significant adverse events between visits.

3.1.3 Bevaciz111nab Administration

Bevacizumab will be diluted in a total volume of 100mL of 0.9% Sodimn Chloride Injection, USP. Administration will be as a continuous IV infosion. Anaphylaxis precautions should be obse1ved during study dmg administration. It is not necessaiy to con-ect dosing based on ideal weight.

Initial and all subsequent doses will be delivered over 30 minutes. If a subject expe1iences an infusion-associated adverse event, he or she may be premedicated (aceta1ninophen, diphenhydramine, steroids or other medications given for symptom control) at the investigators discretion, plior to the next sn1dy dmg infosion; however , the infosion time may not be decreasedfor the subsequent infosion. Surge1y for

3.1.4 Selected Patients after Induction Therapy and as Salvage

Patients will be evaluated after completion of induction therapy with PET/CT. Patients with SD in the primaiy could be considered candidates for surgical resection at the discretion of their treating physicians, if the tumor is resectable. Salvage surge1y should be perfonned if there is progressive disease or residual disease in the prima1y at the end of therapy . At least 4 weeks should elapse between last bevacizumab dose and any surge1y. Neck dissection should be considered, if there is high probability for residual disease in the neck after completion of chemoradiotherapy (>8 weeks later).

3.2 Concun ent Radiothe.-apy, Cisplatin , Cetu ximaband Bevacizumab (XPE-A)

Bevacizumab, 15 mg/kg IV over 30 minutes (if this infosion rate was well tolerated), eve1y 3 weeks until completion of radiation;

Followed by:

Cetuximab, 250 mg/m.^{2} IV over 60 minutes, weekly x 7-8 weeks dU1i.ng days of radiation (Benadty l premedication 30-60 minutes prior to cetuxim.ab infusion as required, see 3.1.1);

Cisplatin, 30 m.g/m.^{2} over 1 hom, weekly x 7-8 weeks dming days of radiation (the same day that cetuximab is given).

Patients who receive radiation over 8 weeks m.ay receive an 8th dose of cisplatin and cetuxim.ab.

Radiation therapy 70 Gy/200 cGy/daily, 5 days/week (see 3.3):

- One hom of observation should elapse before staiting cisplatin (dming that pe1iod of time patients will be receiving pre-cisplatin hydt·ation).
- Bevacizumab will be given first followed by cetuximab (when it should be given) and finally cisplatin on the same day (only on days that radiation is administered).
- Radiation will be administered following cisplatin adtninistration.

Radiotherapy will sta1t approximately 3-4 weeks after Cycle 3, Day 1.

Administrationof Cisplatin
Cisplatin will require aggressive hydt·ation. Any preexisting dehydt·ation should be co1Tec ted. The following hydration regimen is recommended:

- Pre-cisplatin hydration will consist of 1 L NS adtninistered over 2-3 homs (taking into account the fluid volumes received from prior dtug administration). Mannitol 12.5 g IV bolus can be given just before or concmrently with cisplatin.
- Cisplatin will be adtninistered in 500 -1000 cc of IV fluids over 1-2 homs and following adequate hydration and the establishment of adequate mina1y output.
- Post cisplatin hydt·ation will consist of 1 L ½ NS + 30 m.eq KCL/L over 2-4 hours (mannitol 25 g IV m.ay be added).

Furosemide **will** be given as needed.

Antiemetic therapy, acute and delayed, including dexam.ethasone and serotonin receptor antagonists is recoIIIIIlended .

3.3 Radiation Thernpy

3.3.1 Physical Factors

- Equipment: Lineai·acce lerator with appropriate photon and electron energies for supplemental boosting to the nodes.
- Photon energies of 1.25 to 6 MV and/or approp1iate electron energies for boosting the nodes are allowed. Photon energies > 6 MV may be utilized when appropriate to boost tai·get loca lized centra lly.
- Minim.um. treatment distance must be =::>: 80 cm SSD (or SA D for isocentiic techniques).

3.3.2 Localization Requiremenst

3.3.2.1 Simulation

Simul ation of all fields is mandato1y. Patients must be reproducibly immobilized. Radio-opaque markers should be used to delineate the extent of nodal disease and whenever possible, the prima1ytumor, if conventional treatment planning is used. The use of customized Ce1rnbend blocks is recommended to shape the field and limit dose to nonnal strnctures. Use of multileaf collimator to shape the field is suggested. For CT simulation, I. V. contrast is recommended and the data should be acquired using 3 mm slice width and spacing using the spiral mode of scanner.

3.3.2.2 Verification

Check films should be weekly. Beam po1tal films must be obtained to each field. Electron fields utilized for supplemental nodal boosting must be ve1ified by po1tal ve1i fication, simu lation, or diagram.

3.3.3 RadiationDose

Treatment to the plimruy tumor and upper neck will be given at 2 Gy/fraction once each day, five days a week. A total dose of70 Gy/35 fraction/7weeks will be delivered. Fields must be reduced to exclude the spinal cord at 36 Gy with dose calculated in the central plane. The entire neck must be inadiated to a total dose of at least 46- 50 Gy (even in NO stage) at anatomic levels of lymph nodes usually 2-4 cm beneath the skin surface. Clinically positive neck nodes should also receive a dose of 70 Gy/35 fractions given continuously for 7 weeks. An electron beam should be used to supplement the dose to the posterior cervical chain nodes after the spinal cord has been shielded. Hence, the total dose to the p1imruy tumor and clinically positive nodes will be 70 Gy/35 continuous fractions/7 weeks. The ante1ior lower neck will be trea ted at 2 Gy/fraction once a day (3 cm depth) from the ante1ior to a total dose of 46-50 Gy/25 continuous fractions (if clinically negative) in 5 weeks. The maximum dose pe1mitted to the spinal cord will not exceed 45 Gy as dete1mined by a separate off-axis point dose calculation.

Patients who undergosurge1y post TPE-A can strut XPE-A within an interval of 4-10 weeks after surge1y (6 weeks recommended). In that case the total postoperative radiation dose will be up to 66 Gy.

3.3.4 Target Volume Irradiation and Radiation Doses

A combination of lateral opposing fields is recommended for the treatment of the prima1y tumor site and upper neck. A single anterior AP field will be used to treat the lower neck below the fields of the plima1y tumor/upper neck. When there are clinically involved lymph nodes in the lower neck, an additional posterior (PA) field may be necessruy to deliver a supplemental dose to the positive nodes. All fields must be treated at each treatment session. The upper and lower fields should be matched using a "three dimensional" technique (i.e., approp1iate rotation of the treatment table and appropriate angulation of the collimator or beam split technique). However, if such a three-dimensional match is not possible, the upper neck and supraclaviculru· fields may be abutted at the skin. The latter case, a small block should be placed either in the lower lateral position in the upper neck fields, or in the midline of the ante1ior supraclav icular field (wh icheve r is approp1iate and does not block tumor) to the shield ru·eas of potent ial over lap of dive rgin g beams over the spinal cord.

3.3.5 Upper Neck Primary Volume

- The p1ima1y treatmen t fields should encompass the p1ima1y n1mor and/or suspected lymph node

disease in the upper neck using the shrinking field technique as follows:

- The initial target volume should include the primruy tumo r, pos iti ve nodes w ith an approximately 3.0 cm mru·gin and the next echelon of uninvolved lymphatic nodal drainage sites to a dose of 50 Gy. Included in the target volume is the first field reduction occmTing off the sp inal cord at 36 Gy.
- The secondfield reduction will occur at 50 Gy and continue to 60Gy with the new tat·get volume encompass ing the p1ima1y tumor and known areas of nodal disease with at approximately 2.0 cm margm.
- The third and final field reduction will occur at 60 Gy and continue to 70 Gy with the new target volume encompassing the prima1y tumor and known ru·eas of nodal disease with at approximately 1.0 cm margin.

As a general mle, both ipsilateral and contralateral posterior cervical nodal chain and the adjacent echelon of uninvolvedlymphatic nodal drainage sites will be treated to a dose of 46-50 Gy/5 weeks.

3.3.6 Lower Neck Volume

- A single lower neck field will be used to treat the lower neck and the supraclavicular fossae. When there is (are) positive node(s) in the lower neck, an additional poste1i or field may be necessa1y to deliver a supplemental dose to the positive node(s). The boost dose should not exceed 70 Gy.
- The lower border of the lower neck field will be just below the clavicular head with appropriate mru·gins when there ru·e pos iti ve nodes in the Supraclavicular fossa. The lateral borders of the lower neck field will extend to the intersection of the stemocleidomastoid muscle and the clavicle.
- For all patients with clinically positive nodes greater than 6 cm, or with clinically positive supraclaviculru· nodes , a med iast ina1 "T " field may be used. The lateral limbs of the T field will extend below the clavicular heads with mru·gin, and the central po1tion of the field extends 5 cm more inferiorly to include the upper mediastinum.

3.3.7 Boost Doses

Additional boost doses may be given through reduced field to persistent tumor and/or clinically positive nodes, or to compensate for significant intem1ptions in radiation therapy treatments (i.e., > 57 elapsed days). The additional boost dose should not exceed 4 Gy (i.e., 74 Gy maximum). The spinal cord must be excluded from any boost field.

3.3.8 Dose Calculations

Photon Beam Portal An angements

- Dose specification for two parallel-opposed coaxial equally weighted beams is to be on the central ray at mid-separation of the beams.
- Dose specification for two or more intersecting beams is at the intersection of the central ray of the beams.
- For other complex treatment rurnngemen ts, dose is specified at the center of the clinical tru·get volume.

Note: There may be several target volumes.

- For a single anterior AP lower neck field, the prescribed does will be delivered at a depth of 3.0 cm as determined by an off-axis "supraclavicular point". When AP-PA fields are used to treat the lower neck, the dose shall be prescribed at the mid-separation of the two beams along the central ray.

3.3.9 Isodose Distributions

Isodose distribution at central axis is required. All trnatment volumes and critical stmctures should be indicated. Complete isodose curves are required. Attempts should be made to keep the dose variation within the planning target volume to be within +/- 5% of the target dose.

3.3.10 Electron Beam Dose Specifications

The target dose shall be prescribed at the depth of maximum dose. The energy and field size shall be chosen so that the target volume is encompassed within 90% of the presc1ibed dose.

3.3.11 Time and Dose Modifications

- Treatment intem.1ptions are strongly discouraged. Treatment breaks must be clearly indicated in the treatment record when they occur. If the total treatment inte1ruptions exceed ten treatment days, the treatment will be considered a protocol deviation. The intenuption of radiation therapy for grade 4 mucositis/denn atitis/dysphagia is at the discretion of the treating oncologist.
- The maximum permitted spinal cord dose is 45 Gy.
- Mandibular osteoradionecrosis will rarely occur if pretreatment dental evaluation is conducted prior to radiation therapy treatment. Pretherapy extractions of badly diseased teeth should be canied out with conservation of restorable teeth when possible. If an extraction site in the mandible has to be included in the ilrndiated field, 10 to 14 days should be allowed for healing before the initiation of ilrndiation.

3.3.12 RadiotherapyGuidelines/IMRT

Intens ity Modulated Radiation (IMRT) is recommended in this study.

3.3.12.1 Proposed Radiotherapy Guidelines

- All patients will have immobilization devices with treatment planning based on Computerized Tomography (CT) information in treatment position. The CT slice thickness through target will be 3 mm.
- CT and Magnetic Resonance Imaging (MRI) data will be used to define the vaiious targets and contour normal stmctures. MRI infonnation will be used when indicated. Image fusion will be used to relate CT/MRI data when necessaiy.
- The field sizes and atTangements will be at the discretion of the attending Radiation Oncologist. ICRU 50 guidelines will be used for vaiious Tumor and Target Nomenclature:
    - The Gross Tumor Volume (GTV): All gross disease detemlined from clinical exatmnation and radiographic studies (CT/MRI).
    - The Clinical Tai·get Volume (CTV): The ai·ea that potentially contains microscopic disease. Lymph node groups at risk of microscopic disease will be outlined as pait of

corresponding CTV. The margin between each GTV and co1Tesponding CTV can vruy from 0.2 cm to 2.5 cm depending upon the proximity to the critical and uninvolved strnctures.

- The Planning Tru·get Vol ume (PTV): Provides a margin around CTV to compensate for internal motion and set up errors. Typically a 5 mm margin may be used around CTV.

3.3.12.2 Radiation Target and Dose Specifications

The following is the definition of tru·gets and their dose specifications.

- Prima1y Tru·get (PTV3): Includes PTV's of prima1y tumor and the lymph nodes containing disease. The dose will be ?.70 Gy at 2 GY/ fractions.
- Secondruy Target (PTV2): Includes PTV's of area at moderate to high1isk of microscopic disease i.e. first echelon nodes. The dose will be ?. 60 Gy. This is at the treating physican discretion.
- Te1tiruy Tru·get (PTV,): Includes PTV's of areas that are at low 1isk of microscopic disease i.e. second echelon lymph nodes. The dose will be approximately ?. 46-50 Gy.

Low Neck: The midjugulru·, lo w ju gular, and supraclaviculru·nodes can be treated with IMRT or alternatively with an AP field that is beam split to the IMRT fields. Dose Volume Histograms(DVH) will be generated for each plan. Radiation doses will be as outlined above.

Treatment Planning: Either fo1ward or inverse planning can be used in order to achieve the following:

- The radiation dose will be prescribed to the isodose line that encompasses 95% of PTV.
- No more than 15% of the PTV will receive >110% of the prescribed dose.
- The maximum dose within PTV does not exceed >25% of the prescribed dose.
- No more than 1% of the tissue outside PTV will receive >110% of the prescribed dose.
- No more than 1% of any PTV will receive< 93% of the prescribed dose.
- Tissue heterogeneity co1Tection is manda to1y.
- The planning priorities include critical normal stmcture constraints followed by prescription goals.

No1mal Tissues: The appropriate n01mal organs will be contoured. Dose Volume Histograms (DVH) will be generated. An attempt will be made to keep the maximum radiation doses to the following organs as follows:

Brain Stems:	54Gy
Optic Nerve/Chiasm:	55 Gy
Spinal Cord:	45 Gy
Mandible/TM Joint:	70 Gy or 1 cc of the PTV not to exceed 75 Gy
La1ynx	70Gy

Pru·otid Glands: Attempt **will** be to achieve mean dose :'.S 26 Gy in at least one gland or at least 20cc of the combined volume of both parotid glands will receive < 20 Gy or at least 50% of the gland will receive < 30 Gy (should be achieved in at least one gland).

Other No1mal Stmcrures: Submandibular /sublingual glands, inner and middle ears, eye, lens will be considered low priority. The aim should be to decrease the doses as much as possible without compromising target.

Toxicities, and all interventions for toxicity, must be recorded on the data forms.

For patients who have undergone surgery without macroscopic residual disease a total radiation dose of up to 66 Gy will be administered (as postoperative treatment).

3.4 Supportive Care

- All supp01tive measure s consistent with optimal patient care will be given throughout the srudy. Aggressive oral and skin care and analgesics are recommended.
- Antiemetics: Patients will receive antiemetic therapy as recommended in the treatment plan.
- Concomitant Dmgs

The prophylactic use of G-CSF is recommended during induction chemotherapy (i.e. Neulasta on day 2 of each induction TPE-A cycle or Neupogen on days 2-11). If G-CSF cannot be administered for any reason, prophylactic antibiotics (e.g. ciprofloxacin 500 mg BID will be administered on days 5-14 of each cycle of TPE-A). The use of G-CSF is not allowed dming radiotherapy.

The use of erythropoietin is not allowed.

No other antitmnor agents will be given dming protocol therapy.

- The use of amifostine is not pe1mitted. Piloca rpine (Salagen) is notencouraged dming treatment but is allowed. If used, it should be recorded in the treatment fo1ms.

3.5 Gastros tomy Tubes

Prophylac tic placemen t of a gastrostomy rube before any treatment begins is recommended but is at the discretion of the treating physician. It is strongly recommended in patients with significant dysphagia and weight loss of >10-15% at baseline or poor overall nutlitional starus.

4 SAFETY REPORTING OF ADVERSE EVENTS

4.1 Definitions

Adverse event (AE) means any untoward medical occunence in a patient or subject administered a medicinal investigational dmg; the untoward medical occunence does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnonnal laborato1yfinding, for example), symptom, or disease temporally associated with the use of an investigationalmedicinal product whether or not it is considered to be related to the medicinal investigational dtug. This includes any newly occuni ng event, or a previous condition that has increased in severity or frequency since the adtninistration of study drng.
An abno1mal laborat01y value will not be assessed as an AE unless that value leads to discontinuation or delay in treatment, dose modification, therapeutic inte1vention, or is considered by the investigator to be a clinically significantchange from baseline.

Serious Adverse Event Definition

Se1ious AE (SAE) means any untoward medical occunence that at any dose:

- Results in **death.**
- Is **life-threatening.** (The telm "life-threatening"in the definition of "se1ious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event, which hypothetically lnight have caused death if it were more severe).
- Requires inpatient **hospitalization or prolongation of present hospitalization** (see cla1ification in the paragraph below on planned hospitalizations).
- Results in **persistent or significant disability/incapacity.** Disability is defined as a substantial dismption of a person's ability to conduct n01mal life functions.
- Is a **congenit al anomal y/birth defect.**
- Is a **medically important event** that may not be immediately life threatening or result in death or hospitalization but may jeopardize the patient or may require inte1vention to prevent one of the other outcomes listed in the definition above, or involves suspected translnission via a medicinal product of an infectious agent. Examples of such medical events include allergic bronchospasm requiting intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the developmentof dmg dependency or dtug abuse; any organism, vims, or infectious pruticle (e .g., prion prote in translnitt ing Translnissible Spongifo1mEncephalopathy), pathogenic or non pathogenic, is considered an infectious agent.

Cla1ification should be made between the te1ms selious and severe because they ARE NOT synonymous. The te1m seve re is often used to describe the intensity (sevetity) of a specific event (as in lnild, moderate, or severe myocardial infru·citon); the event itself, however, may be ofr elatively minor medical significance (such as a severe headache). This is NOT the same as se1ious, which is based on patient/event outcome or action c1iteria desc1ibed above and is usually associated with events that pose a threat to a patient' s life or fimctioning. A severe AE does not necessa1liy need to be considered serious. For exrunple, persistent nausea of several hours duration may be considered severe nausea but not an

SAE. On the other hand, a stroke resulting in only a minor degree of disability may be considered mild but would be defined as an SAE based on the above noted criteria. Se1iousness (not seve1ity) serves as a guide for defining regulato1y repo1ting obligations.

Unanti cipated Problem Involving Risk to Subjectsor Others (UPIRSO)

Unanticipated problem involving lisk to subjectsor others includes any incident, expelience or outcome that meets **all** of the following criteria:

(1) **unexpected** (in te1ms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRE-approved research protocol and info1med consent document; and (b) the characteristics of the subject population being studied;

(2) **related or possibly related** to paiticipation in the reseai·ch; and

(3) suggests that the research places subjects or others at a **greater risk of harm** (including physical, psychological, economic, or social ha1m) than waspreviously known or recognized.

Procedures for Recording and Rep01ting Adverse Events, Se1ious Adverse Events and UPIRSOs

All AEs spontaneously repo1ted by the patient and/or in response to an open question from study personnel or revealed by obse1v ation, physical examination, or other diagnostic procedures will be recorded on the approp1iate page of the CRF. Any clinically relevant deterioration in laborat01y assessments or other clinical finding is considered an AE and must be recorded on the approp1ia te pages of the CRF. When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event.

All SAEs, se1ious pretreatment events and UPIRSOs (as defined in Section 4.3) must be rep01ted by the investigator to the data safety monitoring boai·d (DSMB#2) (See Section 15) in addition to Genetech (See Appendix I) or designee (contact inf01mation provided below) by faxing the institutional SAE/UPIRSO Fo1m within 1 worki ng day after becoming aware of the event. In addition notification via facsimile to Genetech (See Appendix I) is required within 1 working day after becoming aware of the event. All SAEs, se1ious pretreatment events and UPIRSOs must be rep01ted whether or not considered causally related to the study mug or study procedures; however, se1ious pretreatment events that ai·e directly related to disease progression, and unrelated to study procedures, ai·e not required to be rep01ted . SAE report info1m ation and the dataprovided on the CRF must match. All SAEs should be monitored until they ai·eresolved or are cleai·ly dete1mined to be due to a patient's stable or chronic condition or intercmi:ent illness(es). The SAE rep01t must include event te1m(s), se1ious c1ite1i a, and the investigator or sub-investigator's dete1mination of both the intensity of the event(s) and the relationship of the event(s) to study drng adininistration.

Planned hospital adinissions or surgical procedures for an illness or disease that existed before the patient was enrolled in the tiial are not to be considered AEs unless the condition dete1iorated in an unexpected manner dming the tiial (e.g., surgely was perfo1med earlier or later than planned).

For both serious and nonserious AEs, the investigator must determine both the intensity of the event and the relationship of the event to study drng administration. For serious pretreatment events, the investigator must determine both the intensity of the event and the relationship of the event to study procedures.

Intensity for each AE, including any lab abnotmality, will be dete1mined using the NCI CTCAE, Version 4.0, 28 May 2009.

Monitoring of Adverse Events and Pe1iod of Observation

AEs, both nonse1ious and serious (which include all deaths), will be recorded on the CRFs. AEs will be repmted from dosing on Cycle 1, Day 1 through 30 days after the last dose of study dtug. Serious pretreatment events will be repo1ted from the time of the signing of the consent up to first dosing on study; however, serious pretreatment events that are directly related to disease progression, and unrelated to sn1dy procedure,s are not required to be reported. SAEs will be repotted from the first dose of study dtug up to and including the 30 days after administration of dtug in the study. All SAEs (which include all deaths) must also be reported to Genentech (See Appendix I) in addition to the Data Safety Monit01ing Committee (DSMC). All SAEs should be monitored until they are resolved or are clearly detennined to be due to a patient's stable or chronic condition or intercunent illness(es).

Any SAE that occurs at any time after completion of the study and the designated follow-up petiod that the investigator considers to be related to study dtug must be repmted to Genentech and the DSMB.

This is an investigator-initiated study. The ptincipal investigator, Anand Kamad, MD, who may also sometimes be referred to as the sponsor-investigator, is conducting the study and acting as the sponsor. Therefore, the legal/ethical obligations of the ptincipal investigator include both those of a sponsor and those of an investigator. In the event that this is a multisite study, the sponsor-investigator is responsible to ensure that the SAE repmts are sent to Genentech and FDA from all sites patticipating in the study. Subinvestigators must repott all SAEs to the sponsor-investigator so that the sponsor-investigator can meet his/her foregoing repmting obligations to the IRB, Genentech and FDA, unless othe1wise agreed between the sponsor-investigator and subinvestigator(s). The IRB, Genentech and FDNJllay request follow-up infotmation to a repo1ted SAE, which the sponsor-investigator will be responsible for providing.

Sponsor-investigator must also provide Genentech with a copy of all communications with applicable regulato1y auth01ities related to the sn1dyor study dtug(s), including, but not limited to, telephone conversation logs, as soon as possible but no later than 5 calendai· days of such communication.

Genentech **will** send to the sponsor-investigator a monthly listing of the SAE repmts received for SAE verification. Sponsor-investigator will be responsible for fotwarding such repmts to any subinvestigator(s).

4.2 Reporting to IRB

These events requiling rep01ting to the FDA also must be repo1ted by the Investigator to the approp1iate Institutional Review Board (IRB). The IRB cunently requires the repo1ting of serious (including life-threatening and fatal) adverse events that are unanticipated (i.e., unexpected) and felt to be associated with (i.e., possibly related or related to) the research intervention(s). Fatal and life-threatening adverse events meeting these c1ite1ia are to be rep01ted to the Univers ity IRB within 24 homs of the investigator-sponsor becolning aware of this infonnation. Se1ious adverse events meeting these c1iteria are to be reported to the University IRB within 5 days of the investigator-sponsor becolning aware of this infonnation.

MedWatch 3500a Reporting Guidelines:

In addition to completing approp1iate patient demographic and suspect medication infonnat ion, the repo1t should include the following info1mation within the Event Desc1iption (section 5) of the MedWatch 3500a fonn:

- Treatment regimen (dosing frequency, combinationtherapy)
- Protocol desc1iption (and number, if assigned)
- Desc1iption of Event, Seve1ity, Treatment and Outcome (if known)
- Suppo1tive laborat01y res ults anddiagnostics
- Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication

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

- Adding to the original MedWatch 3500a rep01t and sublnitting it as follow-up
- Adding supplemental summa1y information and sublnitting it as follow-up with the 01iginal MedWatch 3500a fo1m
- Summarizing new info1mation and faxing it with a cover letter including subject identifiers (i.e. D.O.B. initial, subject number), protocol desc1iption and number, if assigned, suspect drug, blief adverse event desc1iption, and notation that additional or follow-up inf01mation is being sublnitted (The subject identifiers are imp01tant so that the new information is added to the con ect initial repo1t)

Occasionally Genentech may contact the reporter for additional info1mation, claii fication, or cmTent stat us of the subject for whom and adverse event was repo1ted.

Assessing Causality:
Investigators ai·e required to assess whether there is a reasonable possibility that bevacizumab caused or contributed to an adverse event. The following general guidance may be used.

: if the temporal relationship of the clinical event to bevacizumab adlninistration makes a causal relationship possible, and other diugs, therapeutic inte1ventions or underlying conditions do not provide a sufficient explanation for the obse1ved event.

No: if the temporal relationship of the clinical event to bevaciZUII1ab administration makes a causal relationship unlikely, or other chu gs , therapeutic interventions or underlying conditions provide a sufficient explanation for the observed event.

5 STUDY SUBJECTS

5.1 Eligibility Ciiteria

- Patients with AJCC 7th edition stage III-IVB head and neck cancer, aU sites, including unknown primaiy tumors.
- Prior to ent:J.y in the study the resectability and alternative treatment options for each patient will be determined by a team composed of an Eai·, Nose, and Throat Surgeon, a Radiation Oncologist and a Medical Oncologist. Stage determination, optimal local t:J.·ea t:J.nent , and its timing according to this protocol will be detennined at this evaluation. The unequivocal demonst:J.·at ion of di stan t metastasis (M1) confers ineligibility.
- Histologically or cytologically confinned diagnosis of squainous cell or poorly differentiated carcinomas, or WHO types I-III of the nasopha1ynx.
- UnidimensionaUymeasurable disease is required (RECIST 1.1).
- No prior chemotherapy, biologic/moleculai·tai·geted therap y (including any prior therapy which specifically and directly tai·gets the EGFR pathway), or radiotherapy for head and neck cancer.
- Prior surgical therapy will consist only of incisional or excisional biopsy, and organ spai·ing procedures such as debulking of ailway compromising tumors or neck dissection in a patient with an existing prima1y tumor. Any non-biopsy procedure must have taken place > 4 weeks but < 3 months of initiating protocol treatment.
- ECOG perfonnance status 0-1.
- Age of :2:18 y ears.
- Inf01med consent must be obtained from all patients prior to beginning therapy. Patients should have the ability to understand and the willingness to sign a written informed consent document.
- All patients should have their tumor tissue tested for HPV (in situ hybridization and/or p16 staining by immunohistochemist:J.y), and re sults mu s t be known prior to study ent:J.y, and w ill consent to have available archival tumor samples, unstained slides or blocks from previous diagnostic or therapeutic procedures submitted for c01Telative studie s, including assessment of tai·get molecule s EGFR, VEGF and related biomarkers. Also, patients must agree to submit blood samples for co1Telative stud ies at least at baseline .
- Abso lute neu troph il count :2: 1 500 / µl , P latelet co u nt :2: 100 ,000 / µl
- Creatinine clearance 60 ml/min or higher calculated using the Cockcroft-Gault formula:

Calculated Creatinine Clearance= $\frac{\text{O40-age) X actual body wt (kg)}}{\text{72 X sernm creatinine}}$

Multiply this number by 0.85 if the patient is female

- Total bililubin within nonnal limits and AST/ALT less than 3 times the upper limit ofnonnal.
- U1ine dipstick must be < 0-1+ within 2 weeks (14 days) of randomization. If urine dipstick result is > 1+, a calculation of U1ine Protein Creatinine (UPC) ratio is requil·ed. Patients must have a

UPC ratio < 1.0 to patticipate in the study.

NOTE: UPC ratio of spot mine is an estimation of the 24-mine protein excretion - a UPC ratio of I is roughly equivalent to a 24-hour urine protein of 1 gm. UPC ratio is calculated using one of the following fo1mula:

- [mi ne protein]/[urine creatinine] - if both protein and creatinine ai·e rep 01ted in mg/DI
- [(urine protein) x 0.088]/[urine creatinine] - if urine creatinine is repo1ted in mmol/L

- Patients with a prior histo1y of squamous cell or basal carcinoma of the skin or *in situ* cervical cancer must have been curatively treated. Patients with a histo1y of other prior malignancy must have been h·eated with curative intent and must have remained disease-free for 3 years post diagnosis.
- Patients may not be receiving any other investigational agents.

5.2 Exclusion Criteria

- Histmy of severe allergic reactions ath·ibuted to docetaxel or compounds of similar chelnical or biologic composition to docetaxel, or other drugs fmmulated with polysorbate 80.
- Plior severe infusion reaction to a monoclonal antibody or known hypersensitivity to any component of bevacizumab
- Unconh·olled intercmTentillness incl uding, but not limited to, ongoing or active infection or psychiatric illness/social situations that would lilnit compliance with study requirements.
- All patients will have a baseline EKG. If abn01m alities consistent with active coron aiy ait e1y disease ai·e detected , the patient will be refen ed to a cai·diologist for approp1iate evaluation and management prior to treatment on study
- No patients with significant baseline senso1y or motor neurologic deficits (> grade I neuropathy) will be treated on this study.
- Because patients with immune deficiency ai·e at increased1isk of lethal Infections when h·eated with matTow-suppressive therapy , HIV-positive patients ai·e exc1uded from the study. Appropriate studies will be unde1taken in patients with HIV and those receiving combination anti- reh·oviral therapies when indicated.
- Patients with HPV positive tumors (P16+ by immunohistochelnishy and/or HPV+ by in situ hybridization) AND smoking histmy =<10 pack-years
- Inadequately conh·olled hype1tension (defined as systolic blood pressure >150 mmHg and/or diastolic blood pressure > 100 mmHg)
- Pi·ior histo1y of hype1tensive clisis or hype1tensive encephalopathy
- New York Hea1t Association (NYHA) Grade II or greater congestive hea1tfailure (see Appendix F)
- Histo1y of myocardial infai·ction or unstable angina within 12 months prior to Day I
- No histmy of sh·oke or h·ansient ischelnic attack within 6 months p1ior to Day I
- Significant vascular disease (e.,g. ao1tic anemy sm, requiting surgical repait·or recent pelipheral a1te1ial thrombosis) within 6 months p1ior to Day I
- Histmy of hemoptysis (1/2 teaspoon of b1ight red blood per episode) within I month prior to Day I

- Evidence of bleeding diathesis or significant coagulopathy (in the absence of therapeutic anticoagulation)
- Patients should not be on therapeutic anticoagulation therapy (prophylactic use of warfarin 1mg per day is allowed) and INR should be <1.5 at registration
- The use of anti-platelet agents (e.g. dipyridamole (Persatine), ticlopidine (Ticlid), clopidogrel (Plavix)) is allowed only if patient is not receiving aspitin or NSAID's known to inhibit platelet function.
- Major surgical procedure (including neck dissection), open biopsy, or significant traumatic injmy within 28 days prior to Day 1 or anticipation of need for major surgical procedure during the course of the study
- Core biopsy or other minor surgical procedure, excluding placement of a vascular access device, within 7 days prior to Day 1
- History of abdominal fistula or gastrointestinal perforation within 6 months prior to Day **1**
- Se1ious, non-healing wound, active ulcer, or untreated bone fracture
- Pregnant or breast-feeding women will be excluded.

6 PATIENT REGISTRATION

Patients must not strut protoco l treatment p1ior to consent being signed and being registrru·. Treatme nt shou ld statt within fi ve working days after registration. Subjects can be emolled after eligibility criteria are met by calling the site research nurse or designee.

For questions regarding the eligibility of subjects, Anand Kamad, MD, should be contacted at (210) 450-1267.

Registration will requit·e the following infmmation: **1)** your name, telephone and page number; **2)** protocol name and number; **3)** date treatment begins; **4)** subject name; **5)** date of bitth; **6)** subject hospital medical record number; **7)** p1ima1ystudy physician; **8)** pritna1ytreatment institution; **9)** confi1mation of eligibility; **10)** copies of the info1med consent signature page; **11)** verification that the info1med consent was signed.

7 DOSE MODIFICATIONS - INDUCTION DOCETAXEL / CISPLATIN / CETUXIMAB / BEVACIZUMAB (TPE-A)

All toxicities will be graded according to NCI Common Toxicity Crite1i a AE version 4.0 (http://evs.nci.nih.gov/ftp1/CTCAE/About.html).
Patients who cannot tolerate induction chemotherapy or have delays for more than 3 weeks due to toxicity will proceed dit·ectly to chemoradiotherapy even without the completion of 3 cycles of induction.
Cetuximab or/ and Bevacizumab will NOT be held for known docetaxel and cisplatin toxicities. If docetaxel and cisplatin are held to allow for the resolution of known toxicities to these dtugs, cetuximab will be allowed to be adtninistered weekly.

7.1 Hematologic Toxicity (Docetaxel)

ANC must be 1,500/mm^3 and platelet count must be 100,000/ LLo n day **1** of each cycle.

(Reduce doses only for feb1ile neutropenia or if ANC is < 1,000 for > 5 days.)

Dose modifications on Day 1 based on nadir during previous cycle

ANC (per mm^3)		Platelets (per mm^3)	Cisplatin Dose	Docetaxel Dose
ANC >= 1000 Or <1000for <5 days	And	>75,000	100%	100%
500-1000 for >= 5 days	or	50,000- 75,000	100%	80%
<500 for >=5 days	or	<50,000	100%	70%
Febrile neut:ropenia **			100%	70%

**Neutropenic fever is defined as one reading of oral temperanire >38.5°C or tln·ee readings of oral temperanire >38.0°C in a 24-hour period.

Dose reductions for reduced ANC are NOT based on a single nadir count. The ANC must remain <1,000 for :::: 5 days before a dose reduction is made.

If docetaxel is withheld due to hematologic toxicity, cisplatin should also be withheld, and administered when the docetaxel is resumed. No dose reductions of cisplatin will be made for hematologic toxicity.

In the event that dose adjustments are needed for both ANC and platelets, patients are to receive the lower dose.

Note: prophylactic G-CSF use is recommended. Neutropenic fever is defined as one reading of oral temperature > 38.5°C or three readings of oral temperature> 38.0°C in a 24-hour period.

Treatment should be delayed for up to 2 weeks until the day I ANC is ::::1500 and the plate let count is ::::100 ,000. However , if the count s have not recovered in 3 weeks, the **patient should start radiotherapy.**

Patients and investigators need to be attentive to the possibility of fever and infection so that these complications can be promptly and appropriately managed.

- When a dose reduction is made for a decreased ANC, platelet count or febrile neutropenia and the reduced dosage results in no toxicity, an attempt should be made to gradually re-escalate the dose in subsequent courses. For example, the next course should be given at inte1mediate dose rather than full dose, e.g., if a 70% dose results in no toxicity, the next course should sta1t at 80% dose rather than 100% (i.e., 70% dose increased to 80% of dose, and 80% dose would be increased to 100%).
- If chemotherapy must be withheld due to hematologic toxicity, CBC and platelet counts should be obtained at least weekly until the counts reach the lower limits for treatment as outlined. The treatment schedule will then proceed in the usual sequence.
- No dose reductions will be made for anemia. Patients should be suppo1ted per the treating physician's discretion.

7.2 Neurologic Toxicity(Docetaxel, Cisplatin)

Docetaxel and cisplatin doses should be modified as follows for neurologic toxicity.

Grade of toxicity	Cisplatin/docetaxel doses to give
0	100%
1	100%
2	Hold treatment until patient recovers to grade O or 1 toxicity , then resume treatment at 75% dose.
3 or worse	Discontinue treatment

If patients do not recover to grade 0 or I neurotoxicity within 2 weeks, they will be taken off-study. Dose modifications made for neurotoxicity are pe1manent reductions.

7.3 Ototoxicity (Cisplatin)

Cisplatin is well known to cause high-frequency heaiing loss. Continued use of the mug does not always result in hearing loss, although it may do so. If grade 2 or worse hearing loss is noted, the patient should be presented with a discussion of the relative1isks of hea1ing loss versus the potential benefit of continuing cisplatin therapy, and a decision made on the continuation of cisplatin. Severe hea1ing loss (grades 3 or 4) is an indication to discontinue the mug.

7.4 Gastrointestinal Toxicity (Docetaxel, Cisplatin)

7.4.1 Nausea and/or Vomiting

Adequate antiemetics for acute and delayed emesis should be given. If grade 3 nausea/vomiting occurs in spite of antiemetics, the cisplatin dose should be reduced by 25% for the next course. Doses of docetaxel may be reduced by 25% in subsequent cycles **if** needed. If tolerated, increase back to 100% dose as soon as possible.

7.4.2 Stomatitis

If stomatitis is present on day I of any cycle , treatment should be withheld until stomatitis has resolved to grade 0.

If Grade 3/4 stomatitis occurs at any time, the dose of docetaxel should be given at 75% dose when the mucositis is completely cleared.

7.5 Renal Toxicity (Cisplatin)

Measurement of sernm creatinine is required before each cycle of mug. Modify the Cisplatin dose using the following pai·ametesr for calculated creatinine clearance **determined in the well-hydrated patient using the Cockcroft-Gault formula.** The actual weight will be used for the calculation of creatinine clearance.

CrCl(males) = (140-age) x weight(kg)/(creatinine x 72)

CrCl(females) = CrCl(males) x 0.85

Creatinine Clearance	Cisplatin to give	Docetaxel to give
60 mL/min	100%	100%
50-60 mL/min	50%	100%
< 50 mL/min	0%	0%

If semm creatinine is increased by 100% over baseline or is increased above upper institutional limits, a 24-hour urine collection with measurement of creatinine clearance is recommended.

If creatinine clearance is decreased such that treatment is not administered as scheduled, repeat the abnormal tests every week at least. If the serum creatinine/creatinine clearance returns to baseline (60 mL/min), cisplatin may be reinstituted at 50% of the full dose during the next cycle (permanent dose reduction).

If the creatinine clearance is between 50-60 mL/inin, docetaxel should be continued at the dose dictated by myelosuppression and should be given on schedule. If the creatinine clearance is < 50 mL/min, withhold any therapy until creatinine clearance improves. Delays in therapy should not be more than 2 weeks. If a delay of >2 weeks is necessaiy patients should be taken off study.

If semm creatinine increased at any time to 2-4 mg/dL, a permanent dose reduction of cisplatin by 20% will be applied; if semm creatinine increased at any time to >4 mg/dL, a permanent dose reduction of cisplatin by 40% will be applied.

7.6 Hepatic Toxicity (Docetaxel)

The day 1 value should be used in determining dose.

Both AST and ALT should be drawn. The more abnormal of the two values (AST or ALT) should be used in determining the dose.

Patients who develop abnormal liver function tests for any reason while on the study will have the following dose reductions:

Docetaxel Dose Modifications for Abnormal Liver Function

	AST or ALT:			
ALK PHOS:	**ULN**	**>1x but 1.5x**	**>1.5x but 2.5x**	**>2.5x ULN**
ULN	Full Dose	Full Dose	Full Dose	Hold*
>1x but 2.5x	Full Dose	Full Dose	Reduce Dose by 20%	Hold*
>2.5x but 5x	Full Dose	Reduce Dose by 20%	Hold*	Hold*
>5x ULN	Hold*	Hold*	Hold*	Hold*

*Hold until recovered, maximum 14 days, then re-treat at a reduced dose by 20%. "Recovered" is defined as meeting the study baseline eligibility criteria.

Bilirubin: Docetaxel should not be administered to patients with senun total bilirnbin >ULN. If serum total bilirnbin is >ULN on treatment day, hold docetaxel until sernm total bilirnbin is :::;; ULN (maximum 14 days), then re-treat at a reduced dose by 20%.

7.7 Hypersensitivity Reactions (Docetaxel)

See section 8.4 for management guidelines. Discontinueprotocol treatment for Grade 3 or 4 infusion related reactions or allergic reactions. There are no dose reductions for infusion related reactions or allergic reactions.

7.8 Fluid Retention (Docetaxel)

Fluid retention should be managed as outlined in section 8.5.

7.9 Other Non-Hematologic Toxicities

For any grade 3 or 4 toxicity not mentioned above, the treatment should be withheld until the patient recovers completely or to grade 1 toxicity then reinstituted (if medically appropriate). The treatment (both cisplatin and docetaxel) should then be resumed at 75% dose(permanent dose reduction).

For grade 1 and 2 toxicities, no dose reduction should be made.

8 DOSE MODIFICATIONS- RADIATION PLUS CISPLATIN / CETUXIMAB / BEVACIZUMAB (XPE-A)

Prior to initiating chemoradiation, all prior toxicities occuned during inductionchemotherapy, except alopecia and anemia should have resolved to grade 0-1.

The following criteria should be met to start chemoradiation as per protocol:

- Stomatitis should have completely resolved (grade 0)
- ANC 1500 cells/mm^3
- Platelet count of > 100,000 cells/mm^3
- Creatinine clearance 60 mL/min

If these parameters are not met, patients may strut radiation therapy alone and receive cisplatin / cetuximab / bevacizumab when these criteria are met.

If patients develop significant non-hematologic cisplatin-associated toxicities, such as ototoxicity, nausea/vomiting, and neuropathy (see 8.1.3 below), will receive carboplatin AUC 1.5 weekly instead of cisplatin dming chemoradiotherapy. Cisplatin, cetuximab and bevacizumab will only be given concunently with radiation.

Cetuximab or/and bevacizumab will NOT be held for known cisplatin toxicities. If **cisplatin is held to allow for the resolution of known cisplatin toxicities, cetuximab or/and bevacizumab will be allowed to be administered.**

Dose Modifications for Cisplatin During Chemoradiotherapy

(For cetuximab and bevacizumab dose modification see above)

8.1.1 Neutropenia

If on the day of scheduled treatment with cisplatin the absolute neutrnphil count *{ANC)* is < 1000 , hold cisplatin until ANC >= l0 00, then treat at 100% dose. Neut:ropenic fever will require pe1manent 25% dose reduction.

8.1.2 Tlirombocytopenia

If on the day of scheduled treatment with cisplatin the platelet count is < 75,000, hold treatment until platelets are 2::75 ,000 , the n treat at 100% dose. Thrombocytopenia that results in bleeding will require pelmanent 25% dose reduction.

8.1.3 Neurotoxicity

If persistent grade 2 neuropathy (>1 week), see 8.1.9 (carboplatin substitution).

If any signs of grade 3 or greater neurotoxicity occur, discontinue cisplatin. Patients developing grade 3 or 4 neuropathy will have cisplatin discontinued.

8.1.4 Renal Toxicity

Measurement of senun creatinine is required before each cycle of dtug. Modify the cisplatin dose using the following parameters for calculated creatinine clearance dete1mined in the well-hydt·atedpatient using the Cockcroft-Gault fo1mula.

CrC l(mates) = (140-age) x weight(kgy(sen un creatinine x 72)

CrCl(females)= ClCr(males) x 0.85

The actual weight will be used for the calculation of Creatinine Clearance.

Cisplatin should be adtninistered on the scheduled day of treatment using the following guidelines:

Creatinine Clearance	C isplat in Dose
2:: 60 mL / min	l00%
< 60 ml/min	0 (Substitute Carboplatin AUC 1.5 weekly)

*If at the time of treatment serum creatinine is increased by 100% or more over baseline or to above institutional upper limits of nonnal, a 24-hour mine collection with calculation of creatinine clearance is recommended.

If semm creatinine increased at any time to 2-4 mg/dL, a pe1manent dose reduction of 20% will be applied; if senun creatinine increased at any time to >4 mg/dL, carboplatin will be used instead of cisplatin on all subsequent cycles.

8.1.5 Ototoxicity

Cisplatin is well known to cause high-frequency hearing loss. Continued use of the dtug does not always result in hearing loss, although it may do so. If persistent grade 2 heating loss is noted, the patient should

be presented with a discussion of the relative risks of hearing loss versus the potential benefit of continuing cisplatin therapy, and a decision made on the continuation of cisplatin or switching to carboplatin (see 8.1.9). Severe hearing loss (grades 3 or 4) is an indication to discontinue the chu g.

8.1.6 Nausea and/or Vomiting

Adequate antiemetics for acute and delayed emesis should be given. If grade 3 nausea/vomiting occurs in spite of antiemetics, the cisplatin dose should be reduced by 25% for the next course. If tolerated, increase back to 100% dose as soon as possible.

8.1.7 In-field Toxicities During Radiation: Radiation Mucositis / Dysphagia / Dermatitis

No cisplatin dose adjustments for grade 3 or less radiation mucositis/dysphagia/de1matitis.

Grade 4 radiation mucositis / mucositis / or de1matitis that develops at any time will require pe1manent 25% dose reduction of cisplatin on all subsequent cycles. If radiation is given in the setting of grade 4 mucositis / dysphagia / de1matitis, cisplatin will be achninistered with a 25% dose reduction.

IfRT is held because ofmucositis, hold cisplatin, cetuximab and bevacizumab until RT is resumed.

8.1.8 Otller Toxicities

For any grade 3 or 4 toxicity not mentioned above (except fatigue, anorexia, weight loss, alopecia, electrolyte abn01malities that are being cotTected , and any cetuximab-related toxicity), cisplatin should be withheld tmtil the patient recovers completely or to grade 1 toxicity after discussing the case with the principal investigator. Cisplatin should then be resumed at 75% dose (pe1manent dose reduction).

For grade **1** and 2 toxicities, no dose reduction should be made.

8.1.9 Carboplatin Substitution During Chemoradiotllerapy

Patient s developing the following cisplatin-induced toxicities will discontinue Cisplatin and substitute Carboplatin, AUC 1.5, achninistered as a 30-minute infusion weekly using the following formula to calculate the total dose:

(CrCl + 25) x 1.5 = total mg dose*

- Persistent grade 2 senso1y or motor neuropathy (objective weakness or sens01y loss intetfering with function but not interfering with activities of daily living)
- Nephrotoxicity with creatinine clearance < 60 ml/min on the day of schedule chemotherapy achninistration , a 1ise in sem m creatinine to >4 mg/dL at any time, or persistent/refract01y hypomagnesemia or other electrolyte imbalances and severe kidney abnonnalities that can be atttibuted to cisplatin.
- Ototoxicity - Carboplatin may also cause ototoxicity. If hearing loss of grade 1-2 from carboplatin is noted, the patient should be presented with a discussion of the relative risks of heating loss versus the potential benefit ofreceiving cai·boplatin therap y. Severe heating loss (grades 3 or 4) is an indication to discontinue the carboplatin.
- Grade 4 nausea and vomiting despite approp1iate antiemetics

Calculation of Carboplatin Dose: The dose of Carboplatin during chemoradiotherapy will be calculated using the following f01mula (Coc kcroft-Ga ult fo1mula):

Carboplatin Dose(mg)= 1.5 x (CrC I1·2 +25)

CrClcmates) = (140-age) x weight(kg)/ (serum creatinine x 72)

CrClcremales) = CrCl(males)x 0.85

The actual weight will be used for the calculation of Creatinine Clearance.

By the end of 2010, all clinical laboratories in the US will use the new standardized Isotope Dilution Mass Spectrometly (IDMS) method to measure semm creatinine. The IDMS method appears to underestimate serum creatinine values compared to older methods when the semm creatinine values are relatively low (e.g., ~0.7 mg/dL). Measurement of serum creatinine by the IDMS-method could result in an overestimation of the Glomemlar Filtt·ation Rate (GFR) in some patients with n01mal renal function. If the total carboplatin dose is calculated based on IDMS-measured semm creatinine using the Calve1t f01mula, carboplatin dosing could be higher than desired and could result in increasedm ug-related toxicity.

The cmrnnt label for carboplatin provides safe dosing instluctions that are based on actual GFR measmements. Provided that actual GFR measurements are made to assess renal function, carboplatin can be safely dosed according to the insttuctions desc1ibed in the label.

(http://dailymed.nlm.nih.gov/dailymed/dtu ginfo.cfm ?id= l 3328)

If a patient's GFR is estimated based on semm creatinine measurements by the IDMS method, as recollllllended by the FDA, physicians should consider capping the dose of carboplatin for desired exposure (AUC) to avoid potential toxicity due to overdosing. Based on the Calve1tf01mula described in the carboplatin label, the maximum doses can be calculated as:

Total Carboplatin Dose (mg) = (target AUC) x (GFR +25) [Calve1t fo1mula]

Maximum Carboplatin Dose (mg) = target AUC (mg•min/mL) x (150 mL/min)

The maximum dose is based on a GFR estimate that is capped at 125 mL/min for patients with n01mal renal function. No higher estimated GFR values should be used.

For a target AUC = 6, the maximum dose is 6 x 150 = 900 mg

For a target AUC = 5, the maximum dose is 5 x 150 = 750 mg

For a target AUC = 4, the maximum dose is 4 x 150 = 600 mg

8.1.10 Carboplatin DoseModifications

Carboplatin will only be given concmrnntly with radiation.

- Carboplatin will be administered if platelets are 75,000 cells/llllll^3 or above and ANC is 1000 cells/tmn^3 or above. Treatlnent will be delayed until the above clitelia are met.
- No carboplatin dose adjustlnents for grade 3 or less mucositis/dysphagia/den natitis. Grade 4 mucositis/ dysphagia/de1matitis that develops at any time will require a pe1manent dose reduction

of carboplatin to an AUC of 1 on all subsequent cycles. If radiation is given in the setting of grade 4 mucositis/dysphagia/de1matitis, carboplatin will be given at a reduced dose of AUC of 1.

- If in the previous cycle of carboplatin, patients developed grade 4 thrombocytopenia or grade 4 neutropenia or neutropenic fever, or grade 3 or 4 non-hematologic toxicities with the exception of mucositis/dysphagia/de1matitis, carboplatin dose will be reduced to AUC of 1 in all subsequent administrations.
- Ifneuropathy worsens to a grade 3 (impailment of function) after treatment with carboplatin, then patients may discontinue chemotherapy for reasons of toxicity at the discretion of the treating physician, based on seve1ity of function loss.
- Patients developing grade 3 or 4 neuropathy will have carboplatin discontinued.

8.2 Management of Cetuximab Adverse Reactions and Dose Modifications

Cetuximab will NOT be held for known docetaxel, cisplatin and bevacizumab toxicities. If **docetaxel, cisplatin and bevacizumab are held to allow for the resolution of known toxicities to these drugs, cetuximab will be allowed to be administered weekly**

Cetuximab will be held or its dose reduced to dose level **-1** or -2 (see below) for the following toxicities (see 8.2.2 to 8.2.4).

Cetuximab will **NOT** be held or reduced for hematologic toxicities.

Dose levels for cetuxilnab are as follows:

Cetuximab Dose Levels

	Weel-dy Cetuxi mab dose
Staiting dose	250 mg/m2
Dose Level -1	200 mg/m2
Dose Level -2	150 mg/m2

There will be no dose level reductions below a weekly dose of 150 mg/m^2.

8.2.1 Management of Infusion Reactions

Severe infusion reactions requil·ethe ilnmediate interruption of cetuximab therapy and pe1manent discontinuation from further treatment. Appropriate medical therapy including epinephrine, c01ticosteroids, intravenous antihistainines, bronchodilators, and oxygen should be available for use in the treatment of such reactions. Patients should be carefully obse1ved until the comp lete resolution of all signs and symptoms.

In clinical trials, lnild to moderate infusion reactions were managed by slowing the infusion rate of cetuximab and by continued use of antihistainine pre-medications (eg, diphenhydrainine) in subsequent doses. If the patient experiences a lnild or moderate (Grade 1 or 2) infusion reaction, the infusion rate should be pe1manently reduced by 50%. For grade 1 or 2 reactions manifesting only as delayed drng fever, see below in Section 8.2.2.

Cetuximab should be immediately and permanently discontinued in patients who experience severe (Grade 3 or 4) infusion reactions.

8.2.2 Treatment of Isolated Drug Fever

In event of isolated dmg fever, the investigator must use clinical judgment to detennine if the fever is related to the study dmg or to an infectious etiology.

If a patient experiences isolated dmg fever, for the next dose, pre treat with acetaminophen or non-steroidal anti-inflammat01y agent (investigator discretion), repeat antipy:retic dose 6 and 12 hours after cetuximab infusion. The infusion rate will remain unchanged for future doses.

If a patient expe1iences recun:entisolated dmg fever following premedication and post-dosing with an approp1iate antipy:retic, the infusion rate for subsequent dosing should be 505 of previous rate. If fever recurs following infusion rate change, the investigator should assess the patient's level of discomfo1t with the event and use clinical judgment to dete1ruine if the patient should receive further cetuximab.

8.2.3 Management of Pulmonary Toxicity

In the event of acute onset (grade 2:2) or wo rsening pu lmonaly symptoms which are not thought to be related to underlying cancer, cetuximab therapy should be intenupted and a prompt investigation of these symptomsshould occur. If ILD is confirmed, cetuximab should be discontinued and the patient should be treated appropriately.

8.2.4 Management of Dermatologic Toxicity

Patients developing de1m atologic toxicities while receiving cetuximab should be monitored for the development of inflammatmy or infectious sequelae, and approp1iate treatment of these symptoms initiated. Dose modifications of any future cetuximab infusions should be instituted in case of severe (grade 3) acneifonn rash. Treatment with topical and/or oral antibiotics should be considered; topical corticosteroids are not recommended.

If a patient expe1iences severe acneifonn rash, cetuximab treatment adjustments should be made according to the following table. In patients with mild and moderate skin toxicity, treatment should continue without dose modification.

Cetuximab Dose Modification Guidelines

Grade 3 Acneform Rash	Cetuximab	Outcome	Cetuximab Dose Modification
1st occunence	Delay infusion 1 to 2 weeks	Improvement	Continue at 250 mg/m^2
		No Improvement	Discontinue cetuximab
2nd occmTence	Delay infusion 1 to 2 weeks	Improvement	Reduce dose to 200 mg/m^2
		No Improvement	Discontinue cetuximab
3rd occmTence	Delay infusion 1 to 2 weeks	Improvement	Reduce dose to 150 mg/m^2
		No Improvement	Discontinue cetuximab
4th occmTence	Discontinue cetuximab		
Intolerable Persistent Grade 2 (only during maintenance)	Delay infusion 1 to 2 weeks	Improvement	Dose reduction by one dose level
		No improvement	Discontinue

8.2.5 In-field Toxicities During Radiation: Radiation Mucositis / Dysphagia/ Dermatitis

No cetuximab dose adjustments for grade 3 or less radiation mucositis, dysphagia, dennatitis.

Grade 4 radiation mucositis/dysphagia or de1matitis that develops at any time will require pe1manent dose reduction of cetuximab by one dose level on all subsequent cycles. If radiation is given in the setting of grade 4 radiation mucositis/dysphagia/de1matitis, cetuximab will be administered with a dose reduction by one dose level.

If RT is held because of in-field toxicities, hold cisplatin and cetuximab until RT is resumed.

8.2.6 Retreatment Criteria/or Cetuximab

Cetuximab may only be administered if all the following criteria are met regardless of cycle, providing no criteria for discontinuation are met:

- Acne-like rash is grade 2 or less
- All grade 3 or 4 non-hematologic out-of-field toxicities (except fatigue, anorexia, alopecia, and dianhea, and any cisplatin/carboplatin or docetaxel-associated toxicities of any grade) have resolved to grade 1 or 0.
- Patients with hypomagnesemia and other electrolyte abnormalities can be treated on schedule and without a dose reduction if the abno1mality can be con-ected (e.g. intravenous magnesium is given for con-ection of hypomagnese mia).
- Cetuximab can be administered in the setting of any grade hematologic toxicities.
- For in-field toxicities see 8.1.7.

8.3 Bevacizumab Dose Modification and Toxicity Management

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

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

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

Anaphylaxis Precautions: Anaphylaxis precautions should be observed during bevacizumab administration. The patient' s blood pressure and heait rate should be monitored during the infusion. Emergency agents including oxygen, oral and endotracheal ailways, intubation equipment, epinephrine, antihistatninesand colticosteroids should be available. fu the event of a suspected anaphylactic reaction dming bevacizumab infusion, stop the bevacizumab infusion and apply a tomniquet proximal to the injection site, if possible, to slow systemic absorption of bevacizumab. Administer antihistamines, epinephrine, or other medications at the investigatorsdiscretion.

fufusion Reaction: fufusion of bevacizumab should be intenupted for subjects who develop dyspnea or clinically significant hypotension. Subjects who experience a NCI CTCAE v. 4.0 Grade 3 or 4 allergic reaction / hypersensitivity, adult respirato1y distress syndrome, or bronchospasm (regai·dless of grade) will be discontinued from bevacizumab treatment.

The infusion should be slowed to 50% or less or intenupted for subjects who expe1ience any infusion-associated symptoms not specified above. When the subject's symptoms have completely resolved, the infusion may be continued at no more than 50% of the rate prior to the reaction and increased in 50% increments eve1y 30 minutes if well tolerated. fufusions may be restaited at the full rate dming the next cycle.

Adverse events requiling delays or pennanent discontinuation of bevacizumab are listed in the table below.

If **bevacizumabis held for any reason, the other study drugs will be given on time assuming parameters for their continuation are met and the patient will remain on study.**

Bevacizumab Dose Management Due to Adve1·seEvents

Event	Action to be Taken
Hypertension No dose modifications for grade 1/2 events	
Grade 3	If not controlled to 150/100 mmHg with medication, discontinue bevacizumab.
Grade 4 (includinghypertensive encephalopath)y	Discontinue bevacizumab

Hemorrhage No dose modifications for grade 1/2 non-pulmonary and non-CNS events	
Grade 3 Non-puhnomuyand non-CNS hemorrhage	Subjects who are also receiving full-dose anticoagulation will be discontinued from receiving bevacizumab. All other subjects will have bevacizumab held until all of the following criteria are met: The bleeding has resolved and hemoglobin is stable. There is no bleeding diathesis that would increase the risk of therapy. There is no anatomic or pathologic condition that significantly increases the risk of hemorrhage recmTence. Subjects who experience a repeat Grade 3 hemorrhagic event will be discontinued from receiving bevacizumab.
Grade4 non- puhnonruy or non -CNS hemorrhage	Discontinue bevacizumab
Grade 1 pulmonary or CNS hemorrhage	Subjects who are also receiving full-dose anticoagulation will be discontinued from receiving bevacizumab. All oilier subjects will have bevacizumab held until all of the following criteria are met: TI1e bleeding has resolved and hemoglobin is stable. There is no bleeding diatl1esis that would increase the risk of therapy. There is no anatomic or pathologic condition that significantly increases the risk of hemorrhage recmTence.
Grade 2, 3, or 4 puhnonary or CNS hemoll"hage	Discontinue bevacizumab
Venou s Tirrombosis No dose modifications for grade 1/2 events	
Grade 3 or 4	Hold study drug treatment. If tlie planned duration of full-dose anticoagulation is < 2 weeks, bevacizumab should be held until the full-dose anticoagulation period is over. Iffue planned duration of full-dose anticoagulation is > 2 weeks, bevacizumab may be resmned during tl1e period of full-dose ru1ticoagulation if all of tl1e following c1iteria are met: The subject must have an in-range INR (usually between 2 and 3) if on warfarin; LMWH, warfarin, or other anticoagulant dosing must be stable prior to restarting bevacizumab treatment. TI1esubject must not have had a Grade 3 or 4 hemorrhagic event while on anticoagulation.
Alteri.al Tirromboembolic event (New onset, worsening, or unstable angina myocru-dial infru·ction, transien t ischemic attack , cerebro vascular accident , and any oilier arterial thromboembolic event)	
Ally grade	Discontinue bevacizumab
BevaciZllllllab Dose Managemen t due to Adverse Events	
Congestive Heart Failure (Left. ventriculru·systolic dysfi.mction) No dose modifications for grade 1/2 events	
Grade 3	Hold bevacizumab until resolution to Grade:::; 1
Grade4	Discontinue bevacizumab
Proteintlfia Nodose modifications for grade 1/2 events	
	[Proteinuria should be monitored by mine analysis for mine protein creatinine (UPC) ratio ptior to every other dose of bevacizumab]

UPC Ratio <3.5 or 24-h mine protein <3.5 gm	Continue bevacizumab.
UPC ratio;::3.5 or 24-h urine protein 2:._3 . 5 gm	Hold bevacizumab until UPC recovers to< 3.5, or 24-h mine protein < 3.5 gm Discontinue bevacizumab if urine protein does not recover to < 3.5 after 8 weeks or bevacizumab intem.1ption.
Nephrotic syndrome	Discontinue bevacizumab
Fistula	
Any grade (TE fistula)	Discontinue bevacizumab
Grade 4 fistula	Discontinue bevaciZll!nab
Bowel Obstmction Grade 1	Continue patient on study for partial obstruction NOT requiring medical inte1vention.
Grade 2	Hold bevacizumab for partial obstmction requiring medical intervention. Patient may restart upon completeresolution.
Grade 3/4	Hold bevacizumab for complete obstmction. If surge1y is necessaiy, patient may restait bevacizumabaft.er full recovery from surgery, and at investigator's discretion.
Wound dehiscence Any grade (requiring medical or smgical therapy)	Discontinue bevacizmnab
Perforation (GI, or at1y other organ)	Discontinue bevacizmnab
Reversible Poste1i or Leukoencephalopathy	
Any grade (confirmed by MRI)	Discontinue bevaciztunab
Other Unspecified Bevaci.Zll!nab -Rela ted Adverse Events	
Grade3 Grade4	Hold bevaciztunab until recove1y to :5Grade 1 Discontinue bevaciztunab

8.4 Docetaxel-Associated Hypersensitivity Reactions

Treatment should be discontinued for Grade 3 or 4 hypersensitivity reactions.

There are no dose reductions for hypersensitivity reactions.

Management of Acute Hypersensitivity

Severity of Symptoms	Treatment Guidelines
Mild symptoms: localized cutaneous reactions such as mild pn ni tus, flushing, rash	Consider decreasing the rate of infusion until recove1y from symptoms, stay at bedside and monitor patient then, complete Docetaxel infusion at the initial planned rate
Moderate symptoms: any symptom that is not listed above (mild symptoms) or below (severe symptoms) such as generalized pnni tus, flushing, rash, dyspn,ea hypotension with systolic	• intem1pt Docetaxel infusion • give diphenhydramine 50 mg IV with or without dexamethasone 10 mg IV; monitor patient until resolution of symptoms • resmne Docetaxel infusion after recove1y of symptoms; depending on the physician' s assessment of the patient,

BP > 80 mm Hg	Docetaxel infusion should be resumed at a slower rate, then increased incrementally to the initial planned rate, *(eg. infase at a 8-hour rate for 5 minutes, then at a 4-h rate for 5 minutes, then at a 2-h rate for 5 minutes, then finally, resume at the Ih infusion rate).* • depending on the intensity of the reaction observed, additional oral or *N* premedication with an antihistamine should also be given for the next cycle of treatment, and the rate of infusion should be decreased initially and then increased back to the recommended 1-hour infusion, *(eg. infuse at a 8-hour rate for 5 minutes, then at a 4-h rate for 5 minutes, then at a 2-h rate for 5 minutes, and finally, administer at thel -h infi,1sion rate).*
Seve re symptoms: any reaction such as bronchospasm, generalized urticaria, systolic BP 80mm Hg, angioedema	• immediately discontinue Docetaxel infusion • give diphenhydramine 50 mg *N* with or without dexamethasone 10 mg *N* and/or epinephrine as needed; monitor patient until resolution of symptoms the same treatment guidelines outlined under moderate symptoms (i.e. the third and fourth bullets) should be followed.
Grade 3 or 4 infusion related reactions or allergic reactions	DISCONTINUE PROTOCOL TREATMENT* In the case of a severe life-threatening anaphylactic reaction, docetaxel will not be re-administeredand hence docetaxel will be discontinued. Following an infusion related reaction or allergic reaction, and depending on its severity, additional oral or *N* premedication with an antihistarnine should be given p1ior to the next administration and the rate of the infusion should be increased gradually to the recommended I-hour infusion rate (e.g. at an 8 hour rate for 5 rninutes , then a 4 hour rate for 5 minutes, then at a 2-hour infusion rate for 5 minutes, then finally, resume at the I-hour infusion rate). *In case of prolonged or recmTent infusion reactions or allergic reactions, following initial improvement, or if hospitalization is indicated for clinical sequelae, or **if** life-threatening consequences; urgent intervention is indicated.

8.5 Fluid Retention Syndrome

There are no dose reductions for fluid retention.

Patients developing new onset edema, progression of existing edema, or another sign of fluid retention (eg. 2 pound weight gain) are to be treated with oral diuretics. Regimens found to be effective in the management of fluid retention due to Docetaxel are listed below.

- Tliamterene/hydrochlorothiazide one capsule po qd up to tid.
- Furosemide 40 mg po daily if edema progresses despite Triamterene/hydrochlorothiazide therapy. Potassium supplementation should be given as needed.
- If after a two-week tlial, furosemide 40 mg po qd is ineffective, the patient may be t1·eated with furosemide20 mg po daily plus metolazone 2.5 mg po daily with potassium supplementation as needed.

Fmih er therapy should be customized depending upon the clinical situation. The clinical tolerance of the patient, the overall tumor response and the medical judgment of the investigator will detennine if it is in the patient' s best interest to continue or discontinue treatment.

8.6 Hyperlacrimation

The excessive lacrimation (epiphora) seen in some patients receiving Docetaxel appears to be related to cumulative dose (median 300 mg/m^2) and resolves rapidly after treatmentcessation.

Excessive lac1imation seems to be the result of a chemical conjunctivitis and/or chemical inflammation (with edema) of the lac1imal duct epithelium (producing a reversible lac1imal duct stenosis). Consequently, investigators in clinical trials have treated such patients with (a) artificial tears and/or (b) saline eyewash and/or (c) steroid based eye drops.

It is suggested that the following approach be taken for patients expe1iencing clinically significant hyperlaclimation:

- Withhold Docetaxel treatment for 2 weeks,
- Recommend frequent instillation of aitificial teai·s,
- Prescribe a steroid ophthalmic solution (eg. prednisolone acetate) 2 gtts each eye bid for 3 days stai·ting the day before Docetaxel administration in patients **without** a hist01y of herpet ic eye disease .

9 DURATION OF THERAPY / WITHDRAWAL FROM STUDY

Patients will receive a maximum of 3 cycles of induction chemotherapy followed by chemoradiotherapy as specified in the study design.

Patients will remain and be followed per protocol even if bevacizumab is discontinued.

Patients who progressed locoregionally post induction may proceed onto chemoradiotherapyas per protocol or have salvage surge1yat the discretion of the multidisciplina1yteain.

10 DRUG FORMULATION AND PROCUREMENT

10.1 Docetaxel

10.1.1 Other Names

Taxotere®, RP56976

10.1.2 Classification

Docetaxel is an antimicrotubule agent that belongs to the taxane family.

10.1.3 Mode of Action

Docetaxel acts plincipallyby binding to free tubulin and promoting the assembly of tubulin into stable microtubules while simultaneously inhibiting their disassembly. As a result, bundles of microtubules accumulate and intelfere with cell division causing cell cycle anest in M-phase, which ultimatelyleads to cell death. In addition, the taxanes have other biological effects, including induction of apoptosis, and inhibition of angiogenesis.

10.1.4 Storage a11d Stability

Docetaxel vials should be stored between 2 and 25oc(36 and 77° F). Retain in the 01iginal package to protect from blight light. Freezing does not adversely affect the product.

Docetaxel infusion solution, if stored between 2 and 25°C (36 and 77°F) is stable for 4 hours. Fully prepared docetaxel infusion solution (in either 0.9% Sodium Chl01ide solution or 5% Dextrose solution) should be used within 4 hours (including the **1** hour i.v. administration).

10.1.5 Dose Specifics

Docetaxel will be administered at a dose as per 3.**1.** The BSA will be calculated with the patient's actual weight.

10.1.6 Preparation and Administration

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

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

Docetaxel for Injection Concentrate requires two dilutions p1ior to administration. Please follow the preparation instruct ions provided below. Note: Both the docetaxel for Injection Concentrate and the diluent vials contain an ove1ftll.

10.1.6.1 Preparation of the Initial Diluted Solution

- Gather the appropriate number of vials of docetaxel 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.
- Aseptically withdraw the contents of the approp1iate diluent vial into a syringe and tr·ansfer it to the appropriate vial of docetaxel for Injection Concentrate. **If the procedure is followed as described, an initial diluted solution of 10mg docetaxel/mL will result.**
- Mix the initial diluted solution by repeated inversions for at least 45 seconds to assure full mixture of the concentr·ate and diluent. Do not shake.

- The initial diluted docetaxel 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 dissipates p1ior to continuing the preparation process. The initial diluted solution may be used immediatelyor stored either in the refrigerator or at room temperature for a maximum of 8 hours.

10.1.6.2 Preparation of the Final Dilution for Infusion

- Aseptically withdraw the required amount of initial diluted docetaxel solution (10 mg docetaxel/mL) with a calibrated syringe and inject into a 250 mL infusion bag or bottle of either 0.9% Sodium Chlo1ide solution or 5% Dextrose solution to produce a final concentration of 0.3 to 0.74 mg/mL. If a dose greater than 200 mg of docetaxel is required, use a larger volume of the infusion vehicle so that a concentration of 0.74 mg/mL docetaxel is not exceeded.
- Thoroughly mix the infusion by manual rotation.
- As with all parenteral products, docetaxel should be inspected visually for paiticulate matter or discoloration p1ior to administration whenever the solution and container pennit. If the docetaxel for Injection initial diluted solution or final dilution for infusion is not cleai· or appeai·s to have precipitation, these should be discai·ded. The final docetaxel dilution for infusion should be administered intravenously as a I-hour infusion under ambient room temperature and lighting conditions. Contact of the docetaxel concentrate with plasticized PVC equipment or devices used to prepai·e solutions for infusion is not recommended. In order to minimize patient exposure to the plasticizer DEHP (di-2-ethylliexyl phthalate), which may be leached from PVC infusion bags or sets, the final docetaxel dilution for infusion should be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets.

10.1.7 Route of Administration

Docetaxel will be administered as a 60-minute infusion in saline or D5W through an administration set that does not contain phthalate plasticizers along the fluid pathway that is connected to the patient's vasculai· access catheter.

10.1.8 Incompatibilities/Interactions

Contact of the undiluted concentrate with plasticized PVC equipment or devices used to prepai·e solutions for infusion should be avoided. Diluted docetaxel solution should be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets.

The metabolism of docetaxel may be modified by the concomitant administration of compounds that induce, inhibit, or are metabolized by cytochrome P450 3A4, such as cyclosp01ine, terfenad ine, ketoconazole, elythromycin, and troleandomycin. Caution should be exercised with these mugs when treating patients receiving docetaxel, as there is a potential for a significant interaction.

10.1.9 Availability

Docetaxel (Taxotere®)is commercially available by Aventis.

Docetaxel 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 strnngths are available:

DOCETAXEL 80 MG (NOC 0075-8001-80)

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

DOCETAXEL 20 MG (NOC 0075-8001-20)

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

Handling and Disposal: Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published. There is no general agreement that all of the procedures recommended in the guidelines ai·e necessa1y or approp1iate

10.1.JO Side Eff ects

Cardiac: a rrhythmias, pe1icardial effusions (due to fluid retention). Hypotension may occur in 3% of patients. Clinically meaningful events such as hea1t fa ilure, sinus tachycai·dia, atti al flu tter, dysrhythmia, unstable angina, pulmona1y edema, and hyp e1tension occur rai·ely.8.1% of metastatic breast cancer patients receiving docetaxel 100 mg/m ^{2} in a rando1nized trial and who had se1ial left ventricular ejection fractions assessed developed dete1ioration of LVEF by 2:_1 0% assoc iated wit h a drop below the institutional lower litnit of n01mal.

Hematolo gic: d ose -re lated neutropen ia , thro mbocytope n ia , and anetnia. Neutt·openia (< 2000 neutrophils/1Ilill^3) occurs in virtually all patients given 60-100 mg/m ^{2} of docetaxel and grade 4 neutt·openia (< 500 cells/1Ilill^3) occ urs in 85% of p atien ts given 100 mg/m ^{2} and 75% of patients given 60 mg/m^2. Febrile neutt·openia occurs in 12% of patients given 100 mg/m^2 but is uncolilillon in patients given 60 mg/m^2. The median time to nadir is 7 days, while the median duration of grade IV neutropenia is 7 days. Patients with abn01mal ities in liver function tests have an increased 1isk for severe neutropenia, and neutt·openic fever, as well as severe thrombocytopenia. Neutropenia and thrombocytopenia are significantly reduced with weekly schedules of adtninistration.

Gastrointestinal: nausea and votniting, diaiThea, and mucosi tis, whic h ai·e generally tnild to moderate. Severe gastrointestinal reactions occur in 5% of patients.

Neurologic: severe neurosens01y symptoms (dysesthesias, pai·esthesias, or pain) occur in up to 6% of patients, whereas severe motor neuropathy develops in 4% of patients.

Hypersensitivity: Severe hypersensitivity reactions chaiacte1ized by hypotension and/or bronchospasm, or generalized rash/e1ythema occurs in 2% of patients premedicated with 3-day c01ticostero ids. Patients with a histo1yof life-threatening hypersensitivity reactions should not be rechallenged with docetaxel.

Fluid retention: Severe fluid retention occurs in 7% of patients despite use of a 3-day dexamethasone premedication regimen. It is characterized by one or more of the following events: poorly tolerated peripheral edema, generalized edema, pleural effusion requiring mgent drainage, dyspnea at rest, cardiac tamponade, or pronounced abdominal distention due to ascites. Fluid retention may be cumulative and is less likely to develop with weekly regimens.

Dermatologic: alopecia, reversible rash, nail changes, and infusion site reactions. Infusion site reactions were generally mild and consisted of hyperpigmentation, inflammation, redness or dryness of the skin, phlebitis, extravasation, or swelling of the vein. Severe nail changes with hypo- or hype1pigmentation and occasionallyonycholysis and pain may also occur.

Hepatic: In patients with normal liver function tests at baseline, an elevation in bilimbin occms in 9% of cases. Increases in AST or ALT > 1.5 times the ULN, or alkaline phosphatase > 2.5 times ULN, are observed in 19% and 7% of patients, respectively.

Other: asthen ia , dysgeusia , anorex,ia conjunctivitis, epiphora, aithralgia, myalgias.

Toxicities with 100 mg/m^2 of docetaxel (patients with normal LFTs)		
Adverse Events		%
Neutropenia <2000 cells/mm3		95.5
<500 cells/mm3		75.4
Thrombocytopenia <100,000 cells/mm3		8.0
Anemia <8 g/dL		8.8
Febrile Neutropenia		11.0
Septic Death		1.6
Infections	(Severe)	6.1
Hype1·sensitivity rea ct.ion	(An y)	21.0
	(Severe)	4.2
With 3-day Premedication	(Severe)	2.2
Fluid retention	(Any)	47.0
	(Severe)	6.9
With 3-day Premedication	(Any)	64.1
	(Severe)	6.5
Neurosensory	(Any)	49.3
	(Severe)	4.3
Cutaneous	(Any)	47.6
	(Severe)	4.8
Nail changes	(Any)	30.6
	(Severe)	2.5
Any Gastrointestinal	(Severe)	4.7
Nausea		38.8
Vomiting		22.3
Diarrhea		38.7

St.omatit is	(Any)	41. 7
	(Severe)	5.5
Alo pecia		75.8
Asthenia	(Any)	61.8
	(Severe)	12.8
Myalgia	(Any)	18.9
	(Severe)	1.5
Arthralgia		9.2
Infusion Site Reactions		4.4
(Table modified from Docetaxel Prescribing Information (Aventis). PDR 2000.)		

10.1.11 Nursing Implications

- Monitor CBC with differential and platelet count plior to mug adininistration.
- Symptom management of expected nausea, vomiting, and mucositis.
- Advise patients of possible hair loss.
- Patients should be observed closely for hypersensitivity reactions, especially during the first and second infusions.
- Resuscitation equipment and medications to treat hypersensitivity reactions should be available dming docetaxel administration.
- Monitor liver function tests.
- Evaluate site regularly for signs of infiltration.
- Monitor for symptomsand signs of fluid retention, and pe1ipheral neuropathy.

10.1.12 References

- Docetaxel presc1ibing information (Aventis). PDR 2003.
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- Tomiak, E., Piccait M.J., Kerger, S., et al. Phase I study of docetaxel administered as a I-hour inti·avenous infusion on a weekly basis. JCO 1994;12:1458.
- Hainswo1th JD, Bunis HA, Erland JB, Thomas M, Greco FA. Phase I trial of docetaxel adininistered by weekly infusion in patients with advanced refractmy cancer. J Clin Oncol 1998; 16:2164-8.
- Hainswmth JD, Bm i s HA, Litchy, S. et al. Weekly docetaxel in the treatmentof elderly patients

with advanced non-small-cell lung cancer: A Minnie Pearl Cancer Research Network phase II trial, Cancer 2000;89:328-33.

10.1.13 Taxotere Reimbursement Program (PACT+)

Website: http://www.taxotere.com/hcp/index.asp

PACT+ offers toll-free support at 1-800-996-ONCO(6626) Monday through Friday, from 8:30 AM to 6:00 PM Eastern Time, to answer questions about reimbursement, uninsured patients, andm u g inf01mation . Messages can be left 24 hours a day. You can also send electronic messages to the PACT+ Program at ePACT@access2health.com.

In addition to calling The Aventis Oncology PACT+ Program, healthcare professionals and patients can fax info1mation requests to the PACT+ Program fax number: 1-800-996-6627

10.2 Cisplatin (Cis-diaminedichloroplatinum, CDDP)

10.2.1 Formulation

Each vial contains 10 mg or 50 mg of CDDP. Vialsare reconstituted with sterile water. The pH range will be 3.5 to 4.5. Cisplatin is also commercially available in solution.

10.2.2 Storage and Preparation

Vials of cisplatin are stored at room temperature. When reconstituted as directed, the solution is stable at room temperature for 20 hours. When fmther diluted to 0.5 mg/ml with nom1alsaline, it is stable for 72 hours at room temperature. Cisplatin 10 mg/vial and 50 mg/ml should be reconstituted with 10 and 50 ml of sterile water, respectively, resulting in a **1** mg/ml solution. The desired dose of cisplatin is fiuther diluted with 250 ml or more of 0.45%-0.9% NaCl and 5% dextrose, or n01mal saline .

10.2.3 Administration

Intravenous over 1-2 hours (see treatment plan)

10.2.4 Mechanism of Action

The mechanism of action of cisplatin has not been clearly elucidated. However, preliminaiy studies have indicated that the most likely mechanism of antitumor 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 DDP binds to DNA and produces inter-strand cross-links. Also DDP is not phase-sensitive and its cytotoxicity is similar in all phases of the cell cycle.

10.2.5 Toxicology

The major effects in humans have been renal toxicity manifested by BUN and sernm creatinine elevation, tinnitus and audiologic impailment in the high frequency range *(4000 to 8000 Hz),* nausea and vomiting, hypem1icemia,mild to moderate anemia, peripheral neuropathy, and electrolyte abno1malities.

10.2.6 Incompatibilities

Cisplatin may react with aluminum which is found in some syiin ge needles or IV sets f01ming a black precipitate. Cisplatin is less stable in solutions that do not contain chloride ions (e.g. 5% dextrose).

10.2.7 Supplier

C01mnerciallyava ilable.

10.3 Carbopl atin

10.3.1 Other names

Paraplatin

10.3.2 Supply and Preparation

Carboplatin is available in vials containing 50 mg. 150 mg or 450 mg. The content of each vial must be reconstituted with either Sterile Water for Injection, D5W, or 0.9% Sodium Chloride. Five mL of the diluent should be added to the 50 mg vial, 15 mL to the 150 mg vial and 45 mL to the 450 mg vial for a resulting concentration of 10 mg/mL. Carboplatin can be further diluted to concentrations as low as 0.5 mg/mL with D5W or 0.9% Sodium Chlo1ide.

10.3.3 Storage and Stability

Unopened vials of carboplatin are stable for the life indicated on the package when stored at controlled room temperature 15°-30°C (59° 86° F), and protected from light. When prepared as directed, carboplatin solutions are stable for 8 hours at room temperature (25° C) or for 24 hours refrigerated (2-8° C).

10.3.4 Mode of Action

Alkylating agent

10.3.5 Dose and Administration

Carboplatin will be administered intravenously (see Treatment plan).

10.3.6 Availability

Commercially available.

10.3. 7 Side Effects

Hematologic: Bone marrow suppression is the dose-limiting toxicity of carboplatin. (1) Thrombocytopenia, with platelet counts below 50,000/mm^3, occurs in 25% of the patients (35% of pretreated ovarian cancer patients), (2) neutropenia, with granulocyte counts below 1,000/mm^3, occurs in 16% of the patients (21% of pretreated ova1ian cancer patients) and, (3) leukopenia, with WBC counts below,2 000/mm^3, occurs in 15% of the patients (26% of pretreated ovalian cancer patients). The nadir usually occurs about day **21** in patients receiving single agent therapy. By day 28, 90% of patients have platelet counts above 100,000/mm^3; 74% have neutrophil counts above 2,000/mm^3; 67% have leukocyte counts above 4,000/mm^3. Mairnw suppression is usually more severe in patients with impaired kidney function. The hematologic effects, although usually reversible, have resulted in infectious or hemorrhagic complications in 5% of the patients treated with cai·boplatin. Fever has also been reported in patients with neutropenia. Anemia with hemoglobin less than 11 g/dL has been observed in 71% of the patients who staited therapy with a baseline above that value. The incidence of anemia increases with increasing exposure to carboplatin. Transfusions have been administered to 26% of the patients treated with carboplatin (44% of previously treated ovaiian cancer patients).

Gastrointestinal: Vomiting occurs in 65% of the patients (81% of previously treated ovarian cancer patients) and in about one-third of these patients it is severe. Nausea alone occurs in an additional 10 to 15% of patients.

Neurologic: Peripheral neuropathies have been observed in 4% of the patients receiving carboplatin (6% of pretreated ovarian cancer patients) with mild paresthesias occun ing most frequently. Carboplatin therapy produces significantly fewer and less severe neurologic side effects than does therapy with cisplatin. However, patients older than 65 years and/or previously treated with cisplatin appear to have an increased 1isk (10%) for peripheral neuropathies. Clinical ototoxicity and other sens01y abn01malities such as visual disturbances and change in taste have been rep01ted in only 1% of the patient. Although the overall incidence of peripheral neurologic side effects induced by carboplatin is low, prolonged treatme,nt particularly in cisplatin-pretreated patients, may result in cumulative neurotoxicity.

Renal: Development of abno1mal renal function test results is unco1mnon despite the fact that carboplatin, unlike cisplatin, has usually been administered without high-volume fluid hydration and/or forced diuresis. The incidences of abn01mal renal function tests reported are 6% for serum creatinine and 14% for blood urea nitrogen (10% and 22%, respectively, in pretreated ovarian cancer patients). Most of these repo1ted abnonnalities have been mild and about one half of them were reversible.

Hepatic: The incidences of abnonnal liver function tests in patients with nonnal baseline values were repo1ted as follows: total bilirnbin, 5%; SGOT, **15%;** and alkaline phosphatase, 24%; (5%, 19%, and 37%, respectively, in pretreated ovarian cancer patients). These abn01malities have generally been mild and reversible in about one-half of the cases, although the role of metastatic tumor in the liver may complicate the assessment in many patients.

Electrolytes: The incidences of abn01mally decreased serum electrolyte values reported were as follows: sodium, 29%; potassium, 20%; calcium, 22%; and magnesium, 29%; (47% 28%, 31%, and 43%, respectively, in pretreated ovaiian cancer patients).

Allergic reactions: Hypersensitivity to carboplatin has been reported in 2% of the patients. These allergic reactions have been similar in nature and seve1ity to those rep01ted with other platinum-containing compounds, i.e., rash, mticaria, e1ythema prnritus, and rarely bronchospasm and hypotension. These reactions have been successfully managed with standard epinephtine, co1ticosteroid, and antihistamine therapy.

Other events: Pain and asthenia were the most frequently repo1ted miscellaneous adverse effects; their relationship to the tumor and to anemia was likely. Alopecia was repo1ted (3%). Card iovascular , respirat01y, genitouri na1y , and mucosal side effects have occmrnd in 6% or less of the patients.

10.3.8 Incompatibilities

Fo1ms a precipitate when in contact with aluminium

10.3.9 Nursing Implications

Monitor CBC with differential and platelet count p1ior to drng administration.

Symptom management of expected nausea and vomiting.

10.4 Cetuximab(C225, ERBITUX)

Cetuximab is an anti-EGFR human-to-murine chime1ic antibody. Cetuximab is expressed in SP2/0 myeloma cell line, grown in large scale cell culture bioreactors and pmified to a high level purity using several pmification steps including protein A chromatography, ion exchange chromatography, low pH treatment and nanofiltration. Cetuximab is not known to be a vesicant.

10.4.1 Supplier/How Supplied

The product is a sterile, clear, colorless liquid of pH 7.0 to 7.4, which may contain a small amount of easily visible, white, amorphous cetuximab pa1ticulates. Each single-use 50-mL vial contains 100 mg of cetuximab at a concentration of2 mg/mL and is f01mulated in a preservative-free solution containing 8.48 mg/mL sodium chlo1ide, 1.88 mg/mL sodium phosphate dibasic heptahydrate, 0.42 mg/mL sodium phosphate monobasic monohydrate, and Water for injection, USP.

10.4.2 Packaging and Labeling

Cetuximab for injection will be in single-use, ready-to-use 50-mL vials containing 2 mg/mL of product.

10.4.3 Handlingand Dispensing of Cetu.ximab

Cetuximab must be dispensed only from official study sites by authorized personnel according to local regulations. Cetuximab should be stored in a secme area according to local regulations. It is the responsibility of the Investigator to ensure that study dtug is only dispensed to study patients.

10.4.4 Storage RequiremenVStability

Store vials under refrigeration at 2° C to 8° C (36° F to 46° F). DO NOT FREEZE. Increased paiticulate fo1mation may occur at temperatures at or below 0°C. This product contains no prese1vatives. Prepai·aitons of cen1ximab in infusion containers are chemically and physically stable for up to 12 hours at 2° C to 8° C (36° F to 46° F) or up to 8 hours at controlled room temperature (20° C to 25° C; 68° F to 77° F). Discai·dany remaining solution in the infusion container after 8 hours at controlled room temperature or afier 12 hours at 2° to 8° C. Discai·dany unused po1tion of the vial.

10.4.5 Preparationand Administration

Cetuximab must not be adtninistered as an IV push or bolus.

Cetuximab must be adtninistered with the use of a low protein binding 0.22-micrometerin-line filter.

Cetuximabis supplied as a 50-mL, single-use vial containing 100 mg of cetuximab at a concentration of 2 mg/mL in phosphate buffered saline. The solution should be clear and colorless and may contain a small amount of easily visible white amo1phous cetuximab pa1ticulates. DO NOT SHAKE OR DILUTE.

Cenlx.imab can be admini stered via infusion pump or syiinge pump.

Infusion Pump:

- Draw up the volume of a vial using a ste1ile syi·inge atta.ched to an appropriate needle (a vented spike or other approp1iate transfer device may be used).
- Fill cetuximab into a sterile evacuated container or bag such as glass containers, polyolefin bags (eg, Baxter Intravia), ethylene vinyl acetate bags (eg, Baxter Clintec), DEHP plasticized PVC

bags (eg, Abbott Lifeca.re), or PVC bags.

- Repeat procedure until the calculated volume has been put in to the container. Use a new needle for each vial.
- Administer through a low protein binding 0.22-micrometer in-line filter (placed as proximal to the patient as practical).
- Affix the infusion line and prime it with cetuximab before sta1ting the infusion.
- Maximum infusion rateshould not exceed 5 mL/min.
- Use 0.9% saline solution to flush line at the end of infusion.

SVIinge Pu mp:

- Draw up the volume of a vial using a ste1ile syringe attached to an appropriate needle (a vented spike may beused).
- Place the syringe into the syiinge diiver of a syiinge pump and set the rate.
- Administer through a low protein binding 0.22-micrometer in-line filter rated for syringe pump use (placed as proximal to the patient aspractical).
- Connect up the infusion line and strut the infusion after pliming the line with cetuximab.
- Repeat procedure until the calculated vohune has been infused.
- Use a new needle and filter for each vial.
- Maximum infusion rate should not exceed 5 mL/min.
- Use 0.9% saline solution to flush line at the end of infusion.
- Cetuximab should be piggybacked to the patient' s infusion line.

Following the cetuximab infusion, a I-hour observation pe1iod is recommended.

10.4.6 Availability

Commerc ially available.

10.4.7 Safety Precautions

Appropriate mask, protective clothing, eye protection, gloves, and Class II ve1tical-lamina.r-airflow safety cabinets are recommended dming prepai·ation and handling. Opened vials must be disposed of at the investigational center as chemotherapy or biohazardous waste provideddocumentedproceduresfor destmction ai·e in place.

Cetuximab therapy should be used with caution in patients with known hypersensitivity to Cetuximab, mmine proteins, or any component of this product.

It is recommended that patients weai·sunscreen and hats and limit sun exposure while receiving cetuximab as sunlight can exacerbate any skin reactions that may occur.

10.5 Bevacizumab

10.5.1 Other Names

RhuMAb VEGF, Avastin

10.5.2 Classification

Recombinant humanized monoclonal antibody

10.5.3 Molecular Weight

Approximate molecular weight is 149,000 daltons

10.5.4 Mode of Action

Bevacizumab blocks the binding of vascular endothelial growth factor (VEGF) to its receptors resulting in inhibition of angiogenesis.

10.5.5 Description

Bevacizumab is a recombinant humanized anti-VEGF monoclonal antibody, consisting of93% human and 7% murine amino acid sequences. The agent is composed of human IgG framework and mmine antigen-binding complementarity-detennining regions.

10.5.6 How Supplied

Bevacizumab is a clear to slightly opalescent, colorless to pale brown, sterile liquid concentrate for solution for intravenous (IV) infusion. Bevacizumab may be supplied in 5-cc (I00-mg) and 20-cc (400-mg), glass vials containing 4 mL, and 16 mL, respectively (all at 25 mg/mL). Vials contain bevacizumab with phosphate, trehalose, polysorbate 20, and Sterile Water for Injection (SWFI), USP. Vials contain no preservative and are suitable for single use only. The monoclonal antibody (bevacizumab) being administered is intended for use only in clinical trials.

10.5.7 Preparation

Vials contain no preservatives and are intended for single use only. The calculated dose should be placed in a sterile, empty IV bag and diluted with a sufficientamount of 0.9% sodium chloride for injection to obtain a final volume of I00 mL.

10.5.8 Storage

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

Opened vials must be used within 8 hours. VIALS ARE FOR SINGLE USE ONLY. Vials used for I subject may not be used for any other subject. Once study drng has been added to a bag of ste1ile saline, the solution must be administered within 8 hours.

10.5.9 Stability

Shelf-life studies ofrhuMAb VEGF are ongoing. The ste1ile single use vials contain no antibacte1ial preservatives. Therefore, vials should be discarded 8 hours after initial entty.

Once diluted in 0.9% sodium chloride, solutions of bevacizumab must be administered within 8 hours.

10.5.10 Route of Administration

Intravenous

All conventional chemotherapy dtugs, including Bevacizumab, are adtninistered according to institutional practices. It is the practice of the Cancer Therapy and Research Center (CTRC) and University Hospital (UH) to give Bevacizumab in 30 minutes beginning with the first dose. Safety data published in the

Journal of Clinical Oncology and elsewhere have shown that bevacizmnab is safe with few hypersensitivity reactions and thus has been adopted as cmrnnt policy at CTRC and UH[80 81]. The investigators recognize this policy is different from the FDA label for bevacizmnab. All patients are monitored for potential reactions. Vital signs at CTRC are recorded on study specific flowsheets pre- and post-bevacizumab infusion. Vital signs at UH are recorded pre-bevacizumab infusion and then eve1y 4 hours while patient is in the clinic for treatment. See Section 3.1.1 Treatment and Premedications. To insure complete delive1y of bevacizmnab, the IV infusion line must be flushed with 0.9% sodium chloride. The following are two recommended methods for flushing the bevacizmnab IV infusion line:

- When the bevacizmnab infusion is complete, add an additional 50mL of 0.9% sodium chl01ide for injection to the bevacizumab infusion bag. Continue the infusion until a volume equal to that of the volume contained in the tubing has been administered.
- Replace the empty bevacizmnab infusion bag with a 50mL bag of 0.9% sodium chloride for injection and infuse a volume equal to the volume contained in the tubing.

NOTE: The flush is not included in the total recommended infusion times.

10.5.11 Availability

The bevacizmnab will be supplied by Genentech.

10.5.12 Patient Care Implications

Measurement of blood pressure and dipstick mi nalysis should be pe1fo1med p1ior to each dose of bevacizumab. Hypertension will be monitored through routine evaluation of blood pressure prior to each bevacizumab treatment. Optimal control of blood pressure according to standard public health guidelines is recommended for patients on treatment with or without bevacizumab. Discontinuation of therapy should be considered if the patient expe1iences uncontrolled hype1tension.

Proteinmi a will be monitored by mine protein: creatinine (UPC) ratio or dipstick at least eve1y 6 weeks .

Monitor patient closely dming infusion, for infusion related events and for bleeding.

Instrnct patient to monitor and repo1tsigns of bleeding, increased cough, swelling.

Treat pain, aithralgias, etc. with acetaminophen, or other pain relief strategies that do not inte1fere with the clotting cascade.

10.5.13 Side Effects

Allergy/Immunology: Allergic reaction/hypersensitivity. Infusion-related reactions.

Blood/Bone Marrow: Leukopenia, neutropenia, thrombocytopenia.

Cardiac: Hype1tension/hypertensivec1isis,cai·diacischelnia/ infarction,supraventriculai·anhythlnia,left ventriculai·dysfunction (congestive heait failure), hypotension, syncope.

Constitutional symptoms: Asthe nia, fever, 1i gors/chills, weight loss.

Dermatologylslan: Exfoliative delmatitis, complications with wound healing, rash, skin ulceration, urticai·ia

Gastrointestinal: GI perforation and wound dehiscence, sometimes complicated by intra-abdominal abscesses. Lru·ge bowel leakage, GI fistula, intestinal obstruction, intestinal necrosis, mesenteric venous occlusion, colitis, mucositis/stomatitis, nausea, vomiting, anorexia, constipation, diruThea, hea1tbum /dyspepsia , dty mouth , taste disturbance.

Hemorrhage/Bleeding: Life -threatenin g or fatal puhnona1y hemotThage (primarily in lung cancer patients), CNS bleeding, GI hemotThage, subarachnoid hemo tThage , hemotThagic stroke, epistaxis (nose bleeds), vaginal bleeding, gum bleeding.

In fection : Infection with normal ANC.

Metabolic/Laboratorv: Increased: alkaline phosphatase, ALT (SGPT), AST (SOOT), Bilirnbin, senun creatinine.Hyponatremia and hypokalemia.

Neurology: Cerebrovasculru·ischemia, dizziness, abnonnal gait, confusion.

Ocular: Excessive lacrimation.

Pain: Abdominal pain, chest/thoracic pain, headache, ruthralgias, myalgias, generalized.

Pulmonarv/Upper Respiratorv: Dyspnea , cough, bronchospasm/wheezing, voice changes (hoarseness).

Renal/Genitourinarv Pro tein mi, a nephrotic syndt·ome.

Reversible Posterior Luekoen-cephalopathy Syndrome: Possible blindness , stro ke sy mpt oms, stro ke .

Vascular: Life-threatening and potentially fatal a1te1ial thromboembolic events: cerebral infarction, transient ischemic attacks, myocardial infru·ction and angina. Venous thromboembolic events: deep vein thrombosis, intra-abdominal thrombosis.

11 CLINICAL AND LABORATORY EVALUATIONS

11.1 Evaluations at Screening / Baseline

(Perfo1med within 4 weeks of registration unless othe1wise indicated)

- Histmy and physical examination, including vital signs, weight and perfo1mance status dete1mination (within 1 week ofr egistration).
- Complete blood counts, including platelets and INR (within I week of registration).
- Blood chemistty studies, including creatinine, electrolytes (K+, Na+ , CJ-, C O 2), calc ium , Mg (within 1 week of registration) and liver function tests including bilirnbin, AST (SGOT) ALT (SGPT), and alkaline phosphatase (within I week ofr egistt·ation).
- If urine dipstick result is > 1+, a calculation of Utine Protein Creatinine (UPC) ratio is required. Patients must have a UPC ratio < 1.0 to pruticipate in the study.
- Pregnancy test (when applicable, within 3 days prior to treatment initiation)
- PET/CT scans and CT of the chest and other imaging studies as indicated for staging and baseline tumor measurements. Any scans or x-rays used to document measurable disease should be done as close to study entty as possible and within 4 weeks p1ior to registt·ation.
- Dental evaluation (within 6 weeks ofregistration)
- ENT evaluation/endoscopy (within 6 weeks ofr egistration)

- Swallowing assessment (within 6 weeks ofregistration)
- Audiometly (within 6 weeks of registi·ation)
- Quality of life questionnaire (complete FACTHN questionnaire in Appendix F)
- Blood samples for research purposes
- Obtain archival tumor sample of unstained slides
- Tumor biopsies at baseline (optional) for con elative studies
- EKG (All patients will have a baseline EKG. If abnonnaliti es consistent with active coromuy a1tery disease are detected, the patient will be refe1rnd to a cardiologist for approp1iate evaluation and management p1ior to treatlnent on study.)

11.2 Evaluation During Treatment

11.2.1 Induction - Prior to Each Treatment Cycle, Day 1

- Histo1y and physical examination, including vital signs, weight and perfo1mance status dete1mination
- Hype1tension **will** be monitored through routine evaluation of blood pressure prior to each bevacizumab treatlnent. Optimal control of blood pressure according to standard public health guidelines is recommended for patients on treatment with or without bevacizumab.
- Toxicity assessment
- Complete blood counts, including platelets
- Blood chemistty studies, including creatinine, electrolytes (K +, Na+, er-, CO 2), c a++, Mg++, and liver function tests, including bilirnbin, AST (SGOT), ALT (SGPT), and alkaline phosphatase
- Urine for protein: creatinine ratio (and 24 hour collection if indicated). Proteinuria should be monitored by mine dipstick prior to eve1y other dose of bevacizumab. If urine dipstick is > I+ then UPC ratio should be dete1mined.
- Blood samples for con elatives studies (p1ior to cycle 2)
- Tumor biopsies on cycle I, day 21 (plus/minus 2 days) (optional) for correlative studies

11.2.2 Induction- after cycle 3

- Evaluations as after cycle I and 2 (see above)
- ENT evaluation/endoscopy
- PET/CT scan
- CT scan of chest
- Response assessment by clinical and by radiographic evaluation (repo1ted separate ly) in prima1y and lymph nodes
- QOL questionnaire
- Swallowing assessment
- Blood samples for con elativesstudies (p1ior to staiting radiation therapy)
- Urine for protein: creatinine ratio (and 24 hour collection if indicated). Proteinuria should be monitored by mine dipstick prior to eve1y other dose of bevacizumab. If urine dipstick is > I+ then UPC ratio should be dete1mined.

11.2.3 Cllemoradiotherapy - weekly and 2 weeks after completion

- Hist01y and physical examination. A focused evaluation of toxicities on a weekly basis will be

performed at a minimum. A complete histmy and physical examination is needed at least eve1y 3 weeks.

- Hype1tension will be monitored through routine evaluation of blood pressure prior to each bevacizumab treatment. Optimal control of blood pressure according to standard public health guidelines is recommended for patients on treatment with or without bevacizumab.
- CBC, platelets and creatinine/electrolyteswill be pe1fo1med at the time of cisplatin administration at a lninimum.
- Vitals signs will be checked eve1y time cetuximab is administered.
- Urine for protein: creatinine ratio (and 24 hour collection if indicated). Proteinuria should be monitored by urine dipstick prior to eve1y other dose of bevacizumab. If urine dipstick is > 1+ then UPC ratio should be dete1mined.

11.2.4 Evaluation After Completion of Radiation (8 weeks after)

- Histmy and physical examination
- Complete blood counts, including platelets
- Blood chemistly studies, including creatinine, electrolytes (K+, Na+, er-, C O 2), c a++, Mg++ , and liver function tests, including bilirnbin, AST (SGOT), ALT (SGPT), and alkaline phosphatase
- ENT evaluation/endoscopy
- PET/CT scan
- CT scan ofchest
- Response assessment by clinical and by radiographic evaluation (repo1ted separate ly) in prima1y and lymph nodes
- Blood samples for co1Telati ves studi es
- Urine for protein: creatinine ratio (and 24 hour collection if indicated). If urine dipstick is > 1+ then UPC ratio should be dete1mined.

11.3 Evaluations at Follow Up

Staiting 8 weeks after completion of radiation, patients will be followed eve1y 3 months for 2 yeai·s and then eve1y 6 months for 3 years, and subsequently annually for a total of 10 yeai·s. (Follow up evaluation will include assessment of late toxicities, such as dysphagia, G-tube feedings requirements, xerostomia, and others.)

Quality of life assessments will be repeated at 3 months and 12 months after radiation completion.

Tumor assessments will be perfo1med 8 weeks after completion of radiotherapy. Subsequently, repeat imaging with CT scan of neck/chest will be perfo1med eve1y 3 months x 2 times, and then eve1y 6 months for the first 3 years. Subsequent scans eve1y 6 months until the 5th year and then annually ai·e recommended but not required.

Swallowing assessments **will** be perfonned as standard practice at baseline and 3 months post chemoradiotherapy and then as indicated.

Blood samples will be collected for co1Telat ive s 6 m ont h s after completion of radiation.

STUDY PARAMETERS TABLE

	Baseline	Prior to Each Treatment Cycle, Day 1	After 3 Cycles of induction	During CRT Weekly and 2 weeks post RT	8 weeks after CRT	Off therapy Follow-Up
History and physical exam	X	X	X	X •	X	X
Height	X					
Weight	X	X	X	X •	X	
Vital signs	X	X	X	X •		
T oxicity assessment		X	X	X	X	X
Perfonnance Status	X	X	X	X •	X	
CB,C Differential, Platelets[1]	X	X	X	X •	X8	
Creat inine, Electrolytes (K'", Na • , er-, CO,,) Mg • +,c a++	X	X	X	X •	X8	
Liver enzymes '	X	X	X		X	
Chest X-ray (optional)	X					
Urine for protein (every2 bevacizumab infusions) [11]	X		X	X	X	
Pregnancy test'	X					
PET/CT scan	X		X		X	
CT scan of the neck/chest (can be part of PET/CT)	X		X		X	X •
Bonescan,if clinically indicated	X					
Tumor measurements•	X		X		X	X•
Swallowing assessment '	X		X			X
Dental evaluation	X					
QOL assessment (FACT-HN)'	X		X			X
Audiometry	X					
Pathology materials6	X					
Blood samples [7]	X	X	X		X	X
ENT evaluation/endoscopy	X		X		X	

	Baseline	Prior to Each Treatment Cycle, Day 1	After 3 Cycles of induction	During CRT Weekly and 2 weeks post RT	8 weeks after CRT	Off therapy Follow-Up
EK<f	X					
Tumor biopsies (optional)'"	X	X				

All patients should be seen by a Medical Oncologist, an ENT surgeon, and a Radiation Oncologist prior to initiating therapy. Unresectability should be determined by a multidisciplinary team.

NOTE: For H+P required on every cycle day 1, patients can be seen the previous day (due to long duration of drug infusions on cycle day 1).

1 Complete blood counts with differential and platelet count should be performed< 24 hours prior to chemotherapy administration (with the exception of baseline CBC). In the event of grade 3 or 4 hematologic toxicity, follow-up CBC ,vith differential and platelet count will be obtained every 1-3 days until there is evidence of hematologic recovery. During CRT, CBC will be performed on the day of cisplatin administration at a minimum.

2 Liver fimction tests should include: Bilirubin, AST (SOOT), ALT (SGPT), and alkaline phosphatase should be performed <24 hours prior to chemotherapy administration

3 All females of childbearing potential must have a negative pregnancy test done within 3 days of initiation of treatment to rule out pregnancy

4 Tumor measurements will be made using physical examination, including endoscopic examination (clinically) and PET/CT scans (radiographically). Clinical and radiographic assessments will be reported separately. Response in the primary and the neck will be reported separately as well. Tumor assessments will be performed after 3 cycles of induction and 8 weeks after completion of chemoradiotherapy using PET/CT. Subsequently no specific tumor measurements are required. Patients will be categorized as having progression of disease or not. A repeat imaging with CT scan of neck/chest will be performed every 3 months for 2 years, and then every 6 months for 3 years. Subsequent scans every 6 months until the 5th year and then annually are recommended but not required.

5 QOL assessments (FACT-H&N, version 4) will be performed at baseline, after completion of induction therapy, at 3 months, and 12 months post chemoradiotherapy. Swallowing assessments will be performed at baseline, 3 months follow up, and if problems persist at 12, 24, 36, 48, and 60 months follow up.

6 The following materials will be submitted (optional studies): paraffin-embedded tumor specimens for i.nnnunohistochemistry and molecular studies.

7 Blood samples for DNA/RNA and EGFR studies will be obtained a) at baseline, b) prior to cycle 2, c) after 3 cycles of induction, d) 8 weeks after completion of chemoradiotherapy (see section 13.0 for details). Samples will be forwarded as specified in the correlative study section (13).

8 During chemoradiotherapy and in the i.nnnediate 2 week period following RT completion, patients need a focused evaluation of toxicities on a weekly basis. However, a complete history and physical examination is only needed every 3 weeks. CBC and electrolytes/creatini.ne will be performed at the time of cisplatin administration at a minimum and will also be repeated 2 weeks post completion of radiation. Vitals signs will be checked every time cetuximab is administered.

9 EKG (All patients will have a baseline EKG. 1f abnormalities consistent with active coronary artery disease are detected, the patient will be referred to a cardiologist for appropriate evaluation and management prior to treatment on study.)

10 Tumor biopsies at baseline (optional) and on cycle 1, day 21 (plus/minus 2 days)(optional)

11 UPC ra tio is requi red for patients with dipstick > 1+.

CRT=chemoradiotherapy

12 SUBJECT DISCONTINUATION

Subjects who cannot receive one of the drugs will still remain on study and be followed per protocol unless they withdraw consent. C1iteria for removal from study are:

- Disease progression
- Study closure
- Unacceptable adverse event(s) as defined in dose modification or other unacceptable AEs
- Patient decision to withdraw from the study, or
- In the judgment of the investigator, fmt her treatment would not be in the best interest of the patient.

The following will require discontinuationof bevacizumab:

- If the patient develops anaphylaxis to bevacizumab
- Grade 4 hype1tension or Grade 3 hype1tension not controlled with medication
- Nephrotic syndrome
- Grade 2 pulmonary or CNS hemoIThage ; any Grade 4 hemorrhage
- Symptomatic Grade 4 venous thromboembolic event requiring full dose warfrui n or eq uiva lent (i .e ., unfract ionated or low molec u lar we ight hepru"in)
- Any grade rut erial thromboembo lic event
- Grade 4 congestive herut failure
- Gastrointestinal perforation
- Tracheoesophageal fistula (any grade) or Grade 4 fistula
- Grade 1 bowel obstrnction that has not fully recovered despite medical or surgical intervention
- Wound dehiscence requiting medical or surgical intervention
- Unwillingness or inability of subject to comply with study requil·ements
- Determination by the investigator that it is no longer safe for the subjectto continue therapy
- All Grade 4 events thought to be related to bevacizumab by the investigator

Patients who have an ongoing bevacizumab-related Grade 4 or se1iou s ad ve1·se event at the time of discontinuation from study treatment will continue to be followed until resolution of the event or until the event is considered irreversible.

NOTE: Patients will remain and be followed per protocol even if bevacizumabis discontinued.

13 STATISTICAL METHODS

13.1 Sample Size

The Simon's optimal two- stage design will be used to test whether the administration of induction with cisplatin, docetaxel, cetuximab and bevacizumab followed by cisplatin, cetuximab, bevacizumab and radiation yields a complete response rate that is of clinical interest. The histo1ical control is our previousstudy (UPCI 05-003) in which the complete response (CR) rate after TPE was 21% (by PET). We assume that the CR rate with TPE plus Avastin will be significantly higher. This design will test the null hypothesis that the trne CR rate is less than or equal to 21% versus the alternative hypothesis that it exceeds 40%. The sample size of 30 response-evaluable patients (Subjects that complete the induction phase of the study and at least have staited the concmTent chemo-radiation pa1t before discontinuing therapy) will provide 81% power to reject the null hypothesis when the hue response rate is 40%, with the type I e1mr rate at 7.6%. The

regimen will be considered of clinical interest if there are 10 or more complete responders out of the total of 30 response-evaluable patients.

The following Simon's optimal two-stage design uses 30 patients to test the null hypothesis that the tme CR rate is at most 21% versus the alternative hypothesis that it exceeds 40%.

Stage 1: Enrollment will be placed on hold after the first 3 patients strut the study treatment. They will be evaluated for any unexpected toxicities until completion of study treatment. A repott will be subtnitted to the DSMC and IRB prior to continuing study accrnal. Toxicities will also be assessed in the first 13 patients. If 1 grade 5 or unexpected toxicities occur compared to UPCI 05-003, the study will be reviewed by the DSMC. The trial regimen will also be assessed after the first 13 evaluable patients. If 2 or fewer patients have a complete response (CR), the ttial will be tenninated for insufficient efficacy and the accrnal of patients will be stopped. If 3 or more patients have a CR, then accrnal will continue in the second stage oft his tt·ial.

Stage 2: Enter an additional 17 evaluable patients to the tti al. Thus, a total of 30 patients will be studied. If the total number responding is less than or equal to 9 in the total 30 evaluable patients, the tt·ial tt·eatment will be not concluded effective. If 10 or more CRs are observed in the total 30 evaluable patients, then this treattnent will be considered protnising in this patient population and will be evaluated futt her in future studies.

A minimum of 2 cycles of induction is required for response assessment. Response-Evaluable patients ru·e s tu dy - eligible patien ts (i.e. , those meeting all of the protocol inclusion/exclusion c1ite1ia) who complete a tninimum of 2 cycles of induction. Determination of evaluability will be done by the laborato1y and the study principal investigator. It can be assumed that some patients will not be evaluable for response. Thus, more than 30 patients may need to be enrolled to obtain 30 response-evaluable patients. Assutning a 10% inevaluability rate, a total of about 33 patients will be enrolled.

13.2 Analyses

The CR rate will be estimated by the numberof CR dividedby the total number of evaluable patients. Confidence intervals for the ttue CR rate will also be calculated.

Smvival data will be analyzed using Kaplan-Meier analysis. The median, 2-ye,ar 3-year, 5-yeru·overa ll smvival and the c01Tespond ing 95% confidence inte1val will also be repmted.

The maximum grade for each type of toxicity will be recorded for each patient, and frequency tables will be reviewed to determine toxicity patterns. Point estimation and Confidence Interval estimation will be done for toxicities.

Statistical analyses will also be done for the following: 1) local/regional and distant failme rates, point estimation and Confidence Inte1val estimation; 2) acute and late QOL changes associated with tt·eattnent with induction docetaxel/cetuximab/cisplatin followed by cisplatin plus cetuximab given concmTen tly with standard radiotherapy. Longitudinal QOL analysis will be pe1fo1med to compru·e FACT -HN scores before and after therapy. The first site of recurrence will be recorded and used as the reference point for the calculation of the time to locoregional or distant progression.

13.3 Definition of response

Response c1iteria will as previously used by Passero et al (Annals of Oncology 2010;21:2278-83).[79] CR by PET is defined as complete disapperu·ance of FDG activity attiibutable to malignancy, without regard to the degree of CT response, assessed on combined PET-CT. Patients without CR on PET (non-CR) will be categorized as having either abnonnal

findings but unlikely to be malignant or abnormal findings likely to represent residual malignancy with recommendations to undergo tissue sampling as clinically appropriate.

Patients will have PET-CT at baseline, after induction and after completion of RT. Beyond this third PET-CT scan no specific Tumor Measurements are required. We will categorize to either progression or no progression.

14 CORRELATIVE STUDIES

14.1 Background and Methods

We plan to collect tissue and blood samples for potential future studies. A panel of candidate biomarkers including markers of proliferation, apoptosis and activation of EGFR and VEGF signaling pathways as well as HPV will be evaluated. Analysis ofbiomarkers will be explorato1y.

14.2 Material Submission

14.2.1 Tissue Biomarker Studies

14.2.1.1 Sample Submission Schedule

Paraffin-embedded specimens will be used.

These studies will be perfo1med at baseline , p1ior to treatment initiation and after first cycle, day 21 (± 2 days as an optional tumor biopsy for patient who provide info1med consent for it). Specimens that have been already collected for diagnosis will be generally used.

14.2.1.2 Sample Preparation Guidelines

A representative paraffin block of the 01iginal diagnosis and all repeat biopsies, if available, will be subtnitted. If blocks cannot be submitted, 10 unstained slides of 4 micron section mounted on positively-charged glass slides are acceptable.

If you have any questions regarding sample collection, processing, and shipping contact:

Jennifer S. Carew, PhD or Steffan T. Nawrocki, Ph.D.
Co-Director, Preclinical Research
CTRC Institute for Drng Development
Assistant Professor
Depa1t ment of Medicine/Division of Hematology and Medical Oncology
University of Texas Health Science Center at San Antonio
7979 Wurzbach Road, MC 8232
RoomG437
San Antonio, TX 78229
Phone: 210-450-3894
Email: Nawrocki@uthscsa.edu
Email: Carew@uthscsa.edu

14.2.1.3 Shipping Procedures

Specimens will be shippedovernight. DO NOT SHIP ON FRIDAY OR BEFORE A HOLIDAY. Ship to Dr. Carew or Dr. Nawrocki at the above address.

14.2.1.4 Methods

Methods will include but not limited to immunohistochemishy, FISH, and detection of HPV16 using in-situ hybridization. Immunohistochemistiy for the determination of biomarkers will be perfo1med using commercial antibodies. Prin::taiy antibody incubation, secondaiy antibody detection complex using Dako Envision plus, followed by DAB. Heat induced antigen rehieval will be applied. Tissue microairnys will be constiu cted, if feasible.

14.2.2 BloodBiomarker Studies

Blood samples (about 5mL each) **will** be collected for co1Telatives at the following tin::te point s (p1ior to treatment that day unless othe1wise indicated): a) baseline prior to cycle 1, day **1**, b) prior to cycle 2, c) cycle 3, plior radiation, d) 8 weeks after completion of radiation, e) 6 months after completion of radiation.

14.3 Banking

The residuals and/or derivatives of samples collected and submitted for studies associated with this protocol will be retained by the Principal Investigator for possible use in future studies. If future use is denied or withdrawn by the patient, the samples will be removed from consideration for use in any future study.

14.4 Blood Correlatives for Lavender Top and Serum Red Top Tubes

Blood samples (34 cc) will be collected at each tin::te po int as li ste d above.

Sample Collection Methods

- Before venipuncture, the phlebotomist prepares two ?ml lavender top tubes and two red top plastic 5 ml blood collection tube **(red top #1 and #2)** and affixes a label to each blood collection tube. Info1mation to be encoded on the label includes the clinical tI"ial study n umber, subject's unique identification (ID) number and date. The tubes ai·e placed in a test tube rack, in order of collection (lavendertops, then red tops).
- The phelobotomist uses standard venipuncture techniques. Approxin::tate blood volume to be collected in each tube is as follows: 7 mL in each lavender tube and 5 ml in each red top tube.
- The phlebotomist affixes the Subject ID on to the blood collection f01m.
- The phlebotomist uses the blood collection fo1m to record duration of fast before phlebotomy date and time of phlebotomy, approximate amount of blood collected into each tube, complications from phlebotomy, and staff initials.

14.5 Methods

Instructions for blood processing protocols for lavender top tubes #1, #2 and red top tube #1 and #2 are outlined below. CTRC Pharmacokintetic laboratory personnel will can y out these procedures.

LavenderTop Tubes (PBMC)

- Samplesshould be processed as soon as possible after receipt.
- Allowblood to equilibrate to room temperatur.e
- Centrifuge lavender top tubes #1 and #2.
- Transfer separated plasma and aliquot into 1 ml volumes in 1.8 ml cryovials labeled with specimen number, contents of tube (plasma), volume and date.
- Freeze plasma at -80° C.
- Replace plasma with an equal volume of PBS and mix blood by inversion.

- Aliquot blood mixture into 15 ml tubes containing 1.5 ml per each tube.
- Add 7.5 ml EL buffer (Qiagen #79217,) vortex, and place on ice for 10 minutes
- After 10 minutes, the blood should be transparent. If not, replace on ice for an addition 10 minutes
- Centrifuge tubes containing blood at 1,300x *g* for 10 minutes at room temperature.
- Aspirate and discard the supernatant.
- Resuspend the pellet in 3mls of EL buffer, place in 3 ml cryovial, and centrifuge for 10 minutes at 1,300 x *g* at room temperature
- Carefully aspirate supernatant.
- Add 0.6 ml RNA Later (Qiagen #76106) to the pellet and label the tube with the specimen number, "1.5 ml blood PBMC", and date.
- Store samples at -80°C
- RNA, DNA and protein will be subsequently isolated using All Prep DNA/RNA/Protein mini kit (Qiagen #80004).
- Deliver to Steffan Nawrocki (Nawrocki@uthscsa.edu) or Claudia Espitia Olaya (Espitia@uthscsa.edu).

Red Top Tubes (Serum)

- To allow clot fmmation, red top tubes sit at room temperature (22° to 25° C) for at least 30 to 45 minutes.
- If futther processing cannot be accomplished immediately after clot retraction, red top tubes should be placed at 40 C.
- Centr ifuge r ed t op tu bes. If futt her processing can not be accomplished within 5 minutes after completing centrifugatio n, red top tubes should be placed at 4° C.
- Inspect and record if serum shows signs of hemolysis, ictems, and/or turbidity Transfer serum into labeled freezer tubes. Aliquot 1ml of sera per 1.8ml c1yovial.
- Info1mation to be encoded on each tube includes the specimen number con esponding to the sample collection, the contents of the freezer tube (sernm), volume and date.
- Freeze and store at -80° C until shipment to Dr. Nawrocki or Dr. Carew.

Anticipated aliquot distribution

Collection tube	Contents of fre ezer tube	Number of aliquots per tube
Lavender #1 & #2	PBMC	
Red top #1 & #2	Serum	4-5
Total		11

14.6 SWpping

The ce ll pellet from the CPT collection tubes and the sernm c1yovials are to be delivered to:

Jennifer S. Carew, PhD,
Steffan T. Nawrocki, Ph.D. (or Claudia Espitia Olaya)
Co-Director, Preclinical Research

CTRC Institute for Dmg Development
Assistant Professor
Department of Medicine/Division of Hematology and Medical Oncology
University of Texas Health Science Center at San Antonio
7979 Wurzbach Road, MC 8232
Room G437
San Antonio, TX 78229
Phone: 210-450-3894
Email: Nawrocki@uthscsa.edu
Email: Carew@uthscsa.edu
Email: espitia@uthscsa.edu

Please send e-mail notification to the above laborat01y contacts to ensure someone is there to receive samples. Include patient's initials, date and cycle drawn and time sample drawn.

15 DATA SAFETY MONITORING

Data and Safety Monitoring Oversight

A Data and Safety Monit01ing Plan is required for all an individual protocols conducted at CTRC. All protocols conducted at CTRC are covered under the auspices of the CTRC Institutional Data Safety Monit01ing Plan (DSMP).

The CTRC Institutional DSMP global policies provide individual ttials with:

- Institutional policies and procedures for institutional data safety and monitoring,
- An institutional guide to follow,
- Monitoring of protocol accmal by the CTRC Protocol Review Committee,
- Review of study forms and orders by the Fonns Committee,
- Independent monitoring and source data ve1ification by the CTRC QA Monitor/Auditor
- Tools for monitoring safety events,
- Monitoring of UPIRSO's by the Director of Quality Assurance and DSMC,
- Detennining level of 1isk (Prio1ity of Audit Level Score - PALS),
- Oversight by the Data Safety Monit01ing Committee (DSMC), and
- Ve1ification of protocol adherence via annual audit for all Investigator Initiated Studies by the CTRC Quality Assurance Division.

Monitoring Safety

Due to the risks associated with participation in this protocol, the CTRC Data Safety Monitoring Board (DSMB) #2 in conjunction with the Plincipal Investigator will pelf01m assessment of adverse events, adverse event trends and tt·eatment effects on this study. The CTRC DSMB #2 acts as an independent DSMB for Investigator Initiated Studies (ITS) cond u cted at CTRC. The CTRC DSMB #2 will monitor data throughout the duration of a study to dete1mine if continuation of the study is approp1iate scie ntifically and ethically. The CTRC DSMC who will review the DSMB's qua1terly rep01ts provides an additional layer of review.

Baseline events and adverse events will be captured using the CTRC Master Adverse Events Document for each patient using CTCAE V4.0 for the grading and atttibution of adverse events. Usage of the CTRC Master Adverse Events Docl.lIIlent centt·ally docl.lIIlents:

- The event and grades the seriousness of the event,

- If the event was a change from baseline,
- The detennination of the relationship between the event and study intervention,
- If the event was pait of the nom1al disease process, and
- What actions were taken as a result of the event?

Reporting Requirements

For this study the Master Adverse Events Documents collected on patients for this protocol will be reviewed by the Principal Investigator on a monthly basis to determine if a serious safety problem has emerged that result in a change or eai·ly tennination of a protocol such as:

- Dose modification,
- Suspending enrollment due to safety or efficacy, or
- Termination of the study due to a significant change in risks or benefits.

The PI will provide the DSMB #2 with the monthly findings for discussion and review dming their meetings.

As per the CTRC DSMP, any protocol modifications, problematic safety repo1ts, unanticipated problelllS, and suspension or eai·ly tennination of a tiial must be rep01ted to the DSMB #2 and all members of the reseai·ch team . Suspension and early termination of a ti·ial must also be rep01ted immediately to the Director of Quality Assmance who will promptly notify the sponsor and the UTHSCSA IRB.

The PI will review the Master Adverse Events documents to detemline the significance of the reported events and will provide findings to the DSMB #2 after the third patient completes ti·eatment for which toxicity analyses will also be performed, after an additional 10 patients are accmed and completed ti·eatment, eve1y 6 months, at the end of study, and as necessaiy should significant adverse events ai·ise. The DSMB #2 will review the infonnation provided by the PI and repo1t to the CTRC DSMC on a bi-annual basis unless an emergent issue has been identified. The Investigator Initiated Study DSMC Repo1t F01m includes infonnation on adverse events, cunent dose levels, number of patients enrolled, significant toxicities per the protocol, patient status (morbidity and mortality), dose adjustments with observed response, and any intelim findings. Any trend consisting of three or more of the same event will be repo1ted to the CTRC DSMC for independent review outside of the bi-annual reporting cycle, which begins three months following protocol sta1t up. DSMB #2 will also provide its findings to the CTRC's Regulato1yAffairs Division so that it may be provided to the UTHSCSA IRB with the protocol's annual progress repo1t. Conflict of interest is avoided by the independent reviews of the CTRC DSMB #2, CTRC DSMC and by ongoing independent review ofUPIRSO's by the Director of Quality Assmance.

All SAE and UPRISO' s will be rep01ted following CTRC and UTHSCSA institutional guidelines.

UTHSCSA SAE/UPRISO REPORTING REQUIREMENTS		
Type Event	Report to	Timeframe
All AE, SAE and UPIRSO	Regulato1y Affairs and DQA	Same as other notification timeframes except for SAE/AE which should be reported on Monday for tl1e prior week
SAE	Clinical Trial Sponsor	Within 24 hours

AE/SAE	UTHSCSA IRB	Annually
UPIRSO - all	Clinical Trial Sponsor	Within 24 hours of the PI determining a UPIRSO exists
UPIRSO - life threatening	UTHSCSAIRB	Within 48 hours of the PI determining a UPIRSO exists
UPIRSO - non-life threatening	UTHSCSAIRB	Within 7 days of the PI determininga UPIRSO exists

Expedited Reporting for Phase II and III **Studies (including hospitalization.:.**

U NEXPECTED EVENT		**EXPECTED EVENT**	
GRADES2 - 3 Attribution of Possible, Probable or Definite	**GRADES4 - 5 Regardless of Attribution**	**GRADES 1 - 3**	**GRADES 4 - 5 Regardless of Attribution**
Expedited report within 10 working days **Grade 1** - Adverse Event Expedited Reporting NOT required.)	Rep011 by phone to IDB within 24 hrs. Expedited rep011to follow within 10 working days. This includes all deaths within 30 days of the last dose of treatment with an investigational agent regardless of attribution. Any late death attributed to the agent (possible, probable, or definite) should be rep011ed within 10 working days.	Adverse Event Expedited Reporting NOT required.	Expedited repo11 including Grade 5 Aplasia in leukemia patients, within 10 working days. This includes all deaths within 30 days of the last dose of treatment with an investigational agent regardless of attribution. Any late death attributed to the agent (possible, probable, or definite) should be rep011ed within 10 working days. Grade 4 Myelosuppression or other Grade 4 events that do not require expedited rep011ing will be specified in the protocol.

* For Hospitalization Only - Any medical event equivalent to CTC Grade 3, 4, 5 which precipitated hospitalization (or prolongation of existing hospitalization) must be repmted regardless of requirements for Phase of study, expected or unexpected and attribution.

Expedited repo1ting may not be appropriate for specific expected adverse events for ce1tain later Phase II and Phase III protocols. In those situations the adverse events that will not have expedited repo1ting must be specified in the text of the approved protocol. An expected Grade 3 event that is definitely related to the investigational agent is only to be repo1ted if the patient is hospitalized using the generic repo1ting criteria. For instance, in a trial of an investigational agent where Grade 3 dianhea requiring hospitalization is expected, only dian hea requiring ICU care (Grade 4) might be designated for expedited repo1ting.

Setious adverse events on NCI sponsored trials utilizing a commercially available agent (with no IND's involved)will additionally be rep01ted via the FDA's Medwatchprogram.

AssU1ing Com pli ance with Protocol and Data Accuracy

As with all studies conducted at CTRC, the PI has ultimate responsibility for ensuring protocol compliance and data accuracy/integrity. Protocol compliance, data accuracy and repo1ting of events is finther ensured by an annual audit conducted by the Data Safety Officer, whose audit report is shared with the PI, the research team and will be reviewed by the CTRC DSMC.

CTRC DSMB Membership

The CTRC has two DSMB's with a prima1yset of members specific to the histology of the study consisting ofUTHSCSA faculty and staff. This Protocol will utilize DSMB#2.

DSMB #2 **(for Solid Tumors)**
C. Richard Meier, MD
Melissa Nashawati, MPA
YuanYuan Liang

As per NCI guidelines and to eliminate conflict of interest (financial, intellectual, professional, or regulato1y in nature), the CTRC DSMB specific to this study will not treat patients on this protocol. Usage of the DSMB specific to the histology has been created to ensure that expe1ts in that histology are represented on the DSMB assembled for this protocol, but may be expanded, at the PI's discretion, to include other members which may include:

- Expe1ts in the fields of medicine and science that are applicable to the study (if not CU1Tently represented on the DSMB),
- Statistical expe1t s,
- Lay representatives,
- Multidisciplina1y representation, from relevant specialties including expe1ts such as bioethicists , biostatisticians and basic scientists, and
- Others who can offer an unbiased assessment of the study progi·es.

Additional or alternate membership of in the DSMB is selected by the DSMC chair, in conjunction with the PI of this protocol.

CTRC DSMB Chaiter and Responsibilities

TheCTRCDSMBwillprovideinf01mationonthemembershipcomposition,includingqualificationsandexpe1iencetoboth the UTHSCSA IRB and CTRC PRC for review. The CTRC DSMB for this study will act as an independent adviso1y board to the PI and will repo1t its findings and recommendationsto the PI, the UTHSCSA IRB and the CTRC DSMC. CTRC DSMB repo1ts will utilize the Investigator Initiated Study DSMC Rep01t F01m and meetings will occur on a monthly basis to review any updates from the p1ior mee ting.

Once the protocol is activated, if not afready established elsewhere in the protocol the CTRC DSMB will establish and provide:

- Procedures for maintaining confidentiality;
- Statistical procedures including monitoring guidelines, which will be used to monitor the identified prim.my, seconda1y, and safety outcome valiables;
- Consider factors external to the study when relevant infonnation becomes available, such as scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the study;
- Plans for changing frequency of interim analysis as well as procedures for recommending protocol changes;
- Recommendation of dose escalation, MTD recommendation of eat"ly terminat ion based on efficacy results;
- Recommendation of tennination due to unfavorable benefit-to-risk or inability to answer study questions;
- Recommendation of continuation of ongoing studies;
- Recommend modification of sample sizes based on ongoing assessment of event rates; and
- Review of final results and publications.

16 RETENTION OF RECORDS

- In addition to the regulat· hospital chatt, a sepat·ate patient folder will be kept which includes:
  - The patient's signed, dated and witnessed consent
  - Pathologic documentation of squamous cell cat·cinoma of the head and neck
  - TheCompleted Patient Registration Fo1m and all other study fo1ms
  - Completed Patient Registration Fo1m. Eligibility clite1ia will be cleat·ly stated.
  - Baseline info1mation will include: age, gender, race, feeding tube placement, smoking and alcohol hist01y, pe1f01mance status, TNM staging, sites of disease involvement, and quality of life assessments.
  - Flow Sheet (see Appendix)reflectingpretreatment test results and the first therapy.
  - Measurement Fonn showing baseline measurement (measurable disease patients).
  - Pathology Repo1t (pathologic confum ation of disease.)
  - Signed, dated and witnessed Patient Infol mation and Consent Fo1m.
  - Evaluat ion f01ms after induction therapy (3 cycles) and after completion of chemoradiotherapy. Clinical and radiographic response will be repo1t ed. Also, response in the prima1yand lymph nodes will be reported sepat·ately.Measurement Fo1ms: after each lesion measurement or evaluation, whichever is less frequent. Measurement fo1m s must give se1ial measurements or evaluatio ns as required by protocol to assess disease response to therapy. Follow-up fo1m s will repo1t the presence of feeding tube and late toxicities.
  - A final Treatment Summaty Form is to be sublnittedwhen the patient progresses, dies, or goes off study for any other reason. Any subsequent head and neck surge1y will be rep01ted.
  - Follow-Up Fo1m is sublnitted at the time the patient goes off study at any time plior to treatment completion as scheduled and thereafter, eve1y 3 months for the first 2 years, then eve1y 6 months for the next 3 yem·,sand subseq uently ann ually for a total of 10 years.
  - Death must be rep01ted, using the Follow-Up F01m

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APPENDIX A: ECOG PERFORMANCE STATUS

Grade	ECOG
0	Fully active, able to canyon allpre-diseasepe1fo1mance without restiiction
1	Restiicted in physically strenuous activity but ambulat01y and able to cany out work of a light or sedentaiy nature, e.g., light house work, office work
2	Ambulato1y and capable of all selfcare but unable to cany out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot cany on anyselfcare.Totally confined to bed or chair
5	Dead

APPENDIX B: PROCEDURE FOR OBTAINING A URINE PROTEIN / CREATININE RATIO

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

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

Protein and creatinine concentrations should be available on standard reports of urinalyses, not dipsticks. If protein and creatinine concentrations are not routinely repo1ted at an Institution, their measurements and repo1ts may need to be requested.

APPENDIX C: NCI COMMON TOXICITY CRITERIA (CTCAE V 4.0)

See: http://evs.nci.nih.gov/ftp1/CTCAE/About.html

APPENDIX D: FDA MEDWATCH 3500A FORM

See: www.fda.gov/medwatch/safety/FDA-3500A_fillable.pdf

APPENDIX E: NEW YORK HEART ASSOCIATION (NYHA) GUIDELINES

NYHA Classification

Excerpted from Oxford Textbook of Medicine. Vol 2, p.2228. Oxford Press.1997.

Class	Description
I	Subjects with cardiac disease but without resulting limitations of physical activity. Ordinruy physical activity does not cause undue fatigue, palpitation, dyspnea, or angina}pain.
II	Subjects with cru·diac disease resulting in slight limitation of physical activity. They ru·e comfortable at rest. Ordinruy physical activity results in fatigue, palpitation, dyspnea, or angina} pain.
III	Subjects with cru·diac disease resulting in mru·ked limitation of physical activity. They are comfortable at rest. Less than ordina1y physical activity causes fatigue, palpitation, dyspnea, or anginal pain.
IV	Subjects with cru·diac disease resulting in inability to canyon physical activity without discomf01t. Symptoms of cardiac insufficiency or of the angina}syndrome may be present event at rest. If any physical activity is unde1taken, discomfo1t is increased.

APPENDIX F: FACT - H&N

Quality of Life, Pe1fo1mance and Patient Prio1ities

1) Patient Name: _____

2) Patient ID #: /_ /_/ -/_ /_ /_ /

3) Date: /_ /_ /_ /_ /_ /_ /

4) Assessment Point: / /

1 = baseline

2 = post induction

3 = 3 months follow-up

4 = 12 months follow-up

FACT - H&N (Version 4)

Below is a list of statements that other people with your illness have said are imp01t ant. **By circling one number per line, please indicate how true each statement has been for you during the past 7 days.**

PHYSICALWELL-BEING	not at all	a little bit	some-what	quite a bit	very much
GPl I have a lack of energy	0	1	2	3	4
GP2 I have nausea	0	1	2	3	4
GP3 Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4 I have pain	0	1	2	3	4
GP5 I am bothered by side effects of treatment	0	1	2	3	4

GP6 I feel ill	0	1	2	3	4
GP7 I am forced to spend time in bed	0	1	2	3	4

SOCIAL/FAMILY WELL-BEING	not at all	a little bit	some-what	quite a bit	very much
GSI I feel close to my fiiends	0	1	2	3	4
GS2 I get emotional support frommy family	0	1	2	3	4
GS3 I get suppo11from my fiiends	0	1	2	3	4
GS4 My family has accepted my illness	0	1	2	3	4
GS5 I am satisfied with family communication about my illness	0	1	2	3	4
GS6 I feel close to my partner (or the person who is my main supp01t)	0	1	2	3	4
Regardless of your CllITent level of sexual activity, please answer the following question. If you prefer not to answer it, please check the box below and go to the next section. □					
GS7 I am satisfied with mysex life	0	1	2	3	4

EMOTIONALWELL-BEING	not at all	a little bit	some-what	quite a bit	very much
GEi I feel sad	0	1	2	3	4
GE2 I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3 I am losing hope in the fight against my illness	0	1	2	3	4
GE4 I feel nervous	0	1	2	3	4

GE5 I wony about dying	0	I	2	3	4
GE6 I wony that my condition will get worse	0	I	2	3	4

FUNCTIONALWELL-BEING	not at all	a little bit	some-what	quite a bit	very much
GFI I am able to work (include work at home)	0	I	2	3	4
GF2 My work (include work at home) is fulfilling	0	I	2	3	4
GF3 I am able to enjoy life	0	I	2	3	4
GF4 I have accepted my illness	0	I	2	3	4
GF5 I am sleeping well	0	I	2	3	4
GF6 I am enjoying the things I usually do for fun	0	I	2	3	4
GF7 I am content with the quality of my life right now	0	I	2	3	4

ADDITIONAL CONCERNS	not at all	a little bit	some-what	quite a bit	very much
H&Nl I am able to eat the foods that I like	0	I	2	3	4
H&N2 My mouth is dty	0	I	2	3	4
H&N3 I have trouble breathing	0	I	2	3	4
H&N4 My voice has its usual quality and strength	0	I	2	3	4
H&N5 I am able to eat as much food as I want	0	I	2	3	4

H&N6	I am unhappy with how my face and neck look	0	I	2	3	4
H&N7	I can swallow naturally and easily	0	I	2	3	4
H&N8	I smoke cigarettes or other tobacco products	0	I	2	3	4
H&N9	I drink alcohol (e.g. beer, wine, etc.)	0	I	2	3	4
H&NIO	I am ab le to communicate with others	0	I	2	3	4
H&Nl I	I can eat solid foods	0	I	2	3	4
H&Nl2	I have pain in my mouth, throat or neck	0	I	2	3	4

APPENDIX G: AJCC STAGING SYSTEM, 7TH E DITIO N

1) LIP AND ORAL CAVITY

Patient Name/Information .....

pec

Tumor Size .....

Histology olog

Laterality Bilateral Left Right

DEFINITIONS:

Ptimaiy Tumor (T)

TX	Ptima1y tumor cannot be assessed
TO	No evidence of prima1y tumor
Tis	Carcinoma in situ
Tl	Tumor 2 cm or less in greatest dimension
T2	Tumor more than 2 cm but not more than 4 cm in greatest dimension
T3	Tumor more than 4 cm in greatest dimension
T4a	(Lip) Tumor invades through co1tical bone, infe1ior alveolai·nerve, floor of mouth, or skin of face, i.e., chin or nose(l)
T4a	(Oral Cavity) Tumor invades through co1tical bone, into deep [extlinsic] muscle of tongue (genioglossus, hyoglossus, palatoglossus, and styloglossus), maxilla1y sinus, or skin of face
T4b	Tumor involves masticator space, pte1ygoid plates, or skull base and/or encases internal cai·otid aitely

Regional Lymph Nodes (N)

NX	Regional lymph nodes cannot be assessed
NO	No regional lymph node metastasis
NI	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dnnension
N2	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dnnension; or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension; or in bilateral or conti·alateral lymph nodes, none more than 6 cm in greatest dnnension
N2a	Metastasis in single ipsilateral lymph node more than 3 cm but not more than 6 cm in greatest dnnension
N2b	Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
N2c	Metastasis in bilateral or contralateral lymphnodes, none more than 6 cm in greatest dnnension

N3 Metastasis in a lymph node more than 6 cm in greatest dimension

Distant Metastasis (M)

MX Distant metastasis cannot be assessed

MO No distant metastasis

M1 Distant metastasis

Biopsy of metastatic site perfo1med y **N**

Source of pathologic metastatic specimen

Stage Grouping

0	Tis	NO	MO
I	Tl	NO	MO
II	T2	NO	MO
III	T3	NO	MO
	Tl	**Nl**	MO
	T2	**Nl**	MO
	T3	**Nl**	MO
IVA	T4a	NO	MO
	T4a	**Nl**	MO
	Tl	N2	MO
	T2	N2	MO
	T 3	N2	MO
	T4a	N2	MO
IVB	AnyT	N3	MO
	T4b	AnyN	MO
IVC	AnyT	AnyN	Ml

Histologic Grade (G)

GX Grade cannot be assessed
Gl Well differentiated
G2 Moderately differentiated
G3 Poorly differentiated
G4 Undifferentiated

Residual Tumor (R)
RX Presence of residual tumor cannot be assessed

RO No resid ual tumor
RI Microscopic residual tumor
R2 Macroscopic residual tumor (continued)

Additional Descriptors

For identification of special cases of TNM or pTNM classifications, the "m" suffix and "y," "r," and "a" prefixes are used. Although they do not affect the stage grouping, they indicate cases needing separate analysis.

m suffix indicates the presence of multiple prima1y tumors in a single site and is recorded in parentheses: pT(m)NM.

y prefix indicates those cases in which classification is perfo1med dming or following initial multimodality therapy.

The cTNM or pTNM categ01y is identified by a "y" prefix. The ycTNM or ypTNM categ01izes the extent of tumor actually present at the time of that examination. The "y" categorization is not an estimate of tumor plior to multimodality therapy.

r prefix indicates a recmTent tumor when staged after a disease-free interval and is identified by the "r" prefix: rTNM.

a prefix designates the stage dete1mined at autopsy: aTNM.

Prognostic Indicators (if applicable)

Notes

Superficial erosion alone of bone/tooth socket by gingival primaiy is not sufficient to classify as T4.

Additional Desc1iptors
- Lymph-Vascular Invasion (LVI)
- Lymph-Vascular Invasion Not Present (absent)/Not Identified
- Lymph-Vasculai·Invasion Present/Identified
- Not Applicable
- Unknown/Indete1minate

Physician's Signatme _____ Date _ _ _ _ _ _ _ _ _ _ _ _

2. PHARYNX (INCLUDING BASE OF TONGUE, SOFT PALATE, AND UVULA)

Patient Name/Information .....

Type of Specimen .....

Tumor Size .....

Histopathologic Type _____

Laterality Bilateral Left Right

DEFINITIONS:

Prima1y Tumor (T)

TX Primaiy tumor cannot be assessed

TO No evidence of prima1y tumor

Tis Carcinoma in situ

Nasophaiynx

Tl Tmnor confined to the nasophaiynx or tumor extends to oropharynx and/or nasal cavity without pai·apha1yngeal extension

T2 Tumor with pai·aphaiyngeal extension

T3 Tumor involves bony stmctmes of skull base and/or pai·ansaal sinuses

T4 Tmnor with intracranial extension and/or involvement of cranial nerves, hypoprhaiynx, orbit, or with extension to the infratemporal fossa/masticator space

Orophatynx

Tl Tmnor 2 cm or less in greatest dimension

T2 Tumor more than 2 cm but not more than 4 cm in greatest dimension

T3 Tumor more than 4 cm in greatest dimension

T4a Moderately Advanced Disease

Tumor invades the la1ynx, extrinsic muscle of tongue, medial pte1y goid, hai·d palate , or mandible

T4b Vety Advanced Disease

Tumor invades lateral pte1ygoid muscle, pte1ygoid plates, lateral nasophaiynx, or skull base or encases cai·otid a1tery

Hypopha1ynx

Tl Tumor limited to one subsite of hypophaiynx and 2 cm or less in greatest dimension

T2 Tmnor invades more than one subsite of hypophaiynx or an adjacent site, or measmes more than 2 cm but not more than 4 cm in greatest diameter without fixation of hemila1ynx

T3 Tumor measures more than 4 cm in greatest dimension or with fixation of hemilaiynx

T4a Moderately Advanced Disease

Tumor invades thyroid/cricoid cru.tilage , hyoid bone, thyroid gland, esophagus or central compru.tm ent soft tissue(2)

T4b Vely Advanced Disease

Tmnor invades prevertebral fascia, encases carotid ru.te1y , o r in vo lves mediastinal strnctures

Regional Lymph Nodes (N)

Nasophru.ynx

NX Regional lymph nodes caJ.lllot be assessed

NO No regional lymph node metastasis

Nl Unilateral metastasis in ce1vical lymph node(s), 6 cm or less in greatest dimension, above the supraclavicular fossa(3) (continued)

2. PHARYNX (INCLUDING BASE OF TONGUE, SOFT PALATE, AND UVULA) (continued)

N2 Bilateral metastasis in cervical lymph node(s), 6 cm or less in greatest dimension, above the supraclaviculru.· fossa(3)

N3 Metastasis in a lymphnode(s) >6 cm and/or to supraclaviculru·. fossa

N3a Greater than 6 cm in dimension

N3b Extension to the supraclavicular fossa(3)

Orophru.ynx and H ypop h a1ynx

NX Regional lymph nodes cannot be assessed

NO No regional lymph node metastasis

NI Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension

N2 Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension, or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension, or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension

N2a Metastasis in a single ipsilateral lymph node more than 3 cm but not more than 6 cm in greatest dimension

N2b Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension

N2c Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension

N3 Metastasis in a lymph node more than 6 cm in greatest dimension

Distant Metastasis (M)

MX Distant metastasis cannot be assessed

MO No distant metastasis

Ml Distant metastasis

Biopsy of metastatic site perfonned y **N**

Source of pathologic metastatic specimen

Stage Grouping: Nasopharynx

0	Tis	NO	MO
I	Tl	NO	MO
II	Tl	**N I**	MO
	T2	NO	MO
	T2	NI	MO
III	Tl	N2	MO
	T2	N2	MO
	T3	NO	MO
	T3	**N I**	MO
	T3	N2	MO
IVA	T4	NO	MO
	T4	**N I**	MO
	T4	N2	MO
IVB	AnyT	N3	MO
IVC	AnyT	AnyN	Ml

Stage Grouping: Oropharynx and Hypopharynx

0	Tis	NO	MO
I	Tl	NO	MO
II	T2	NO	MO
III	T3	NO	MO
	Tl	NI	MO
	T2	NI	MO
	T3	NI	MO
IVA	T4a	NO	MO
	T4a	NI	MO
	Tl	N2	MO
	T2	N2	MO
	T3	N2	MO
	T4a	N2	MO
IVB	T4b	AnyN	MO
	AnyT	N3	MO
IVC	AnyT	AnyN	Ml

Histologic Grade (G) (Oropha1ynx Hypopha1ynx)

GX	Grade cannot be assessed
GI	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated
G4	Undifferentiated

Residual Tumor (R)

RX	Presence of residual tumor cannot be assessed
RO	No res idual tumor
RI	Microscopic residual tumor (continued)
R2	Macroscopic residual tumor

Additional Descriptors

For identification of special cases of TNM or pTNM classifications, the "m" suffix and "y," "r," and "a" prefixes are used. Although they do not affect the stage grouping, they indicate cases needing separate analysis.

m suffix indicates the presence of multiple p1imaiy tumors in a single site and is recorded in parentheses: pT(m)NM.

y prefix indicates those cases in which classification is perfonned during or following initial multimodality therapy.

The cTNM or pTNM catego1y is identified by a "y" prefix. The ycTNM or ypTNM categorizes the extent of tumor actually present at the time of that examination. The "y" categorization is not an estimate of tumor prior to multimodality therapy.

r prefix indicates a recmrnnt tumor when staged after a disease-free interval, and is identified by the "r" prefix: rTNM.

a prefix designates the stage detennined at autopsy: aTNM.

Prognostic Indicators (if applicable)

Notes

1. Paraphruyngeal extension denotes posterolateral infiltration of tumor beyond the pha1yngobasilar fascia.

2. Central compa1tment soft tissue includes prelruyn geal strap muscles and subcutaneous fat.

3. Midline nodes are considered ipsilateral nodes.

Additional Descriptors
Lymph-Vasculru· Invasion (LVI)

- o Lymph-Vasculru·Invasion Not Present (absent)/Not Identified
- o Lymph-Vasculru·In vasion Present/Identified
- o Not Applic able
- o Unkn own/Indete1minate

Physician's Signature _____ Date _ _ _ _ _ _ _ _ _ _ _ _

3. LARYNX

Patient Name/Information .....

Type of Specimen .....

Tumor Size .....

Histopathology

Laterality Bilateral Left Right

DEFINITIONS:

Primaiy Tumor (T)

TX Primaiy tumor cannot be assessed
TO No evidence of prima1y tumor
Tis Carcinoma in situ

Supraglottis

Tl Tmnor limited to one subsite of supraglottis with normal vocal cord mobility
T2 Tmnor invades mucosa of more than one adjacent subsite of supraglottis or glottis or region outside the supraglottis (e.g., mucosa of base of tongue, vallecula, medial wall of pyrifmm sinus) without fixation of the laiynx
T3 Tumor limited to laiynx with vocal cord fixation and/or invades any of the following: postcricoid ai·ea, pre-epiglottic tissues, pai·aglottic space, and/or minor thyroid caitilage erosion (e.g., inner cmtex)
T4a Moderately Advanced Local Disease
Tumor invades through the thyroid ca1tilage and/or invades tissues beyond the la1ynx (e.g., trachea, soft tissues of neck including deep extiinsic muscle of the tongue, strap muscles, thyroid, or esophagus)
T4b Ve1y Advanced Local Disease
Tumor invades preve1tebral space, encases carotid a1te1y, or invades mediastinal strnctures

Glottis

Tl Tumor limited to the vocal cord(s) (may involve ante1ior or posterior commissure) with nom1almobility
Tl a Tumor limited to one vocal cord
Tl b Tumor involves both vocal cords
T2 Tumor extends to supraglottis and/or subglottis, or with impaired vocal cord mobility
T3 Tumor limited to the laiynx with vocal cord fixation, and/or invades paraglottic space, and/or minor thyroid ca1tilage erosion (e.g., inner co1tex)
T4a Moderately Advanced Local Disease
Tumor invades through the thyroid ca1tilage and/or invades tissues beyond the la1ynx (e.g., trachea, soft tissues of neck including deep extiinsic muscle of the tongue, strap muscles, thyroid, or esophagus)
T4b Ve1y Advanced Local Disease
Tumor invades preve1tebral space, encases carotid a1te1y, or invades mediastinal strnctures

Subglottis

Tl	Tumor limited to the subglottis
T2	Tumor extends to vocal cord(s) with n01mal or impaired mobility
T3	Tumor limited to laiynx: with vocal cord fixation (continued)
T4a	Moderately Advanced Local Disease
	Tumor invades cricoid or thyroid caitilage and/or invades tissues beyond the la1ynx: (e.g., trachea, soft tissues of neck including deep extrinsic muscles of the tongue, strap muscles, thyroid, or esophagus)
T4b	Ve1y Advanced Local Disease
	Tumor invades prevertebral space, encases cai·otid ait e1y or invades mediastinal stm ctures

Regional Lymph Nodes (N)

NX	Regional lymph nodes cannot be assessed
NO	No reg ional lymph node metastasis
NI	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
N2	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension, or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension, or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N2a	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension
N2b	Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
N2c	Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N3	Metastasis in a lymph node, more than 6 cm in greatest dimension

Distant Metastasis (M)

MO	No distant metastasis
Ml	Distant metastasis
	Biopsy of metastatic site pe1f01med y **N**
	Source of pathologic metastatic specimen

Stage Grouping

0	Tis	NO	MO
I	Tl	NO	MO
II	T2	NO	MO
III	T3	NO	MO
	Tl	**NI**	MO
	T2	**NI**	MO
	T 3	**NI**	MO
IVA	T4a	NO	MO
	T4a	**NI**	MO
	Tl	N2	MO
	T2	N2	MO
	T3	N2	MO
	T4a	N2	MO
IVB	T4b	AnyN	MO
	An y T	N3	MO
IVC	An y T	AnyN	Ml

Histologic Grade (G)

GX Grade cannot be assessed
GI Well differentiated
G2 Moderately differentiated
G3 Poorly differentiated
G4 Undifferentiated

Residual Tumor (R)

RX Presence of residual tumor cannot be assessed
RO No residual tumor
RI Microscopic residual tumor
R2 Macroscopic residual tumor

Additional Descriptors

For identification of special cases of TNM or pTNM classifications, the "m" suffix and "y," "r," and "a" prefixes are used. Although they do not affect the stage grouping, they indicate cases needing separate analysis.

m suffix indicates the presence of multiple prima1y tumors in a single site and is recorded in parentheses: pT(m)NM.

y prefix indicates those cases in which classification is performed during or following initial multimodality therapy.

The cTNM or pTNM catego1y is identified by a "y" prefix. The ycTNM or ypTNM catego1izes the extent of tumor actually present at the time of that examination. The "y" categorization is not an estimate of tumor p1ior to multimodality therapy.

r prefix indicates a recmTent tumor when staged after a disease-free interval, and is identified by the "r" prefix: rTNM.

a prefix designates the stage detennined at autopsy: aTNM.

Prognostic Indicators (if applicable)

Notes

Additional Desc1iptors

Lymph-Vascular Invasion (LVI)

- Lymph-Vascular Invasion Not Present (absent)/Not Identified
- Lymph-Vascular Invasion Present/Identified
- Not Applicable
- Unknown/Indeterminate

Physician's Signature _____ Date _ _ _ _ _ _ _ _ _ _ _ _ _

4. NASAL CAVITY AND PARANASAL SINUSES

Patient Name/Information .....

TypeofSpecimen_____

Histopathology

Lateral Bilateral Left Right

DEFINITIONS:

Primaiy Tumor (T)

Maxillaiy SinusTl Tumor limited to the maxillaiy sinus mucosa with no erosion or destluction of bone

T2 Tumor causing bone erosion or destmction including extension into the haid palate and/or middle nasal meatus, except extension to posterior wall of maxillaiy sinus and pte1ygoid plates

T3 Tumor invades any of the following: bone of the posterior wall of maxilla1y sinus, subcutaneous tissues, floor or medial wall of orbit, pte1ygoid fossa, ethmoid sinuses

T4a Moderately Advanced Local Disease

Tumor invades anterior orbital contents, skin of cheek, pte1ygoid plates, infratemporal fossa, cribrifo1mplate, sphenoid or frontal sinuses

T4b Ve1y Advanced Local Disease

Tmnor invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial ne1ves other than maxillaiy division oftiigeminal nerv e V2 , nasopha1ynx , or cliv us

Na sa l Cavity and Ethmoid Sinus

TX Primaiy tumor cannot be assessed

TO No evid en ce of pri ma1ytmnor

Tis Carcinoma in situ

Tl Tmnor restricted to any one subsite, with or without bony invasion

T2 Tmnor invading two subsites in a single region or extending to involve an adjacent region within the nasoethmoidal complex, with or without bony invasion

T3 Tmnor extends to invade the medial wall or floor of the orbit, maxillaiy sinus, palate, or cribriform plate

T4a Tumor invades any of the following: anterior orbital contents, skin of nose or cheek, minimal extension to anterior cranial fossa, pterygoid plates, sphenoid or frontal sinuses

T4b Tumor invades any of the following: orbital apex, dura, brain, middle cranial fos,sa cranial nerves other than V2, nasopha1ynx, or clivus

Regional Lymph Nodes (N)

NX Regional lymph nodes cannot be assessed

NO No reg ional lymph node metastasis

NI Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension

N2 Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension, or in multiple ipsilateral lymph nod,es none more than 6 cm in greatest dimensio,n or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension

N2a Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension

N2b Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
N2c Metastasis in bilateral or contralateral lymphnodes, none more than 6 cm in greatest dimension
N3 Metastasis in a lymphnode, more than 6cm in greatest dimension

Distant Metastasis (M)
MO No distant metastasis
Ml Distant metastasis
Biopsy of metastatic site perfmmed y N
Source of pathologic metastatic specimen

Stage Grouping

0	Tis	NO	MO
I	Tl	NO	MO
II	T2	NO	MO
III	T3	NO	MO
	Tl	**Nl**	MO
	T2	**Nl**	MO
	T3	**Nl**	MO
IVA	T4a	NO	MO
	T4a	**Nl**	MO
	Tl	N2	MO
	T2	N2	MO
	T 3	N2	MO
	T4a	N2	MO
IVB	T4b	AnyN	MO
	AnyT	N3	MO
IVC	AnyT	AnyN	Ml

Histologic Grade (G)
GX Grade cannot be assessed
G1 Well differentiated
G2 Moderately differentiated
G3 Poorly differentiated
G4 Undifferentiated

Residual Tumor (R)
RX Presence of residual tumor cannot be assessed
RO No residual tumor
Rl Microscopic residual tumor
R2 Macroscopic residual tumor

Additional Desc1iptors
For identification of special cases of TNM or pTNM classifications, the "m" suffix and "y," "r," and "a" prefixes are used. Although they do not affect the stage grouping, they indicate cases needing separate analysis.
m suffix indicates the presence of multiple primaiy tumors in a single site and is recorded in parentheses: pT(m)NM.

y prefix indicates those cases in which classification is perfo1med during or following initial multimodality therapy. The cTNM or pTNM categ01y is identified by a "y" prefix. The ycTNM or ypTNM categorizes the extent of tumor actually present at the time of that exalnination. The "y" categorization is not an estimate of tumor prior to multimodality therapy.

r prefix indicates a recun ent tumor when staged after a disease-free interval, and is identified by the "r" prefix: rTNM.

a prefix designates the stage detennined at autopsy: aTNM.

Prognostic Indicators (if applicable)

Notes

Additional Descriptors

Lymph-Vascular Invasion (LVI)

- o Lymph-Vascular Invasion Not Present (absent)/Not Identified
- o Lymph-Vascular Invasion Present/Identified
- o Not Applicable
- o Unknown/Indete1minate

Physician's Signature _____ Date _ _ _ _ _ _ _ _ _ _ _ _

APPENDIX H: GENENTECH SAFETY REPORTING FAX COVER SHEET

Genentech

BIO NCOLOGY

SAFETY REPORTING FAX COVERSHEET
Investigator SponsoredTrials

SAE FAX No: (650) 225-4682
Alternate Fax No: (650) 225-5288

Study Number (Genentech studv number}	
Principal Investigator	
Site Name	
Reporter name	
Reporter Telephone #	
Reporter Fax #	

I nitial Report Date (DD/MON/YYYY)	____/ ____/ _
Follow-up Report Date (DD/ MON/ YYYY)	_/ /____

Subject Initials (**Please** enter a dash If the patienthasno middle name	____ ____ ____

PLEASE PLACE MEDWATCH REPORT or SAFETY REPORT BEHIND THIS **COVERSHEET**

Please contact Genentech Safety for any questions regarding SAE or Safety reporting at **(888) 835-2555**