A RANDOMIZED PHASE II TRIAL OF CHEMORADIOThERAPY VERSUS CHEMORADIOThERAPY AND VANDEtanib FOR HIGH-RISK POSTOPERATIVE ADVANCED SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK

[6/8/09] vandetanib, NSC 744325, IND 103,648, supplied by AstraZeneca; cisplatin, NSC 119875, commercially available]
INDEX (2/25/10)

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RADIATION THERAPY ONCOLOGY GROUP

RTOG 0619

A Randomized Phase II Trial of Chemoradiotherapy
Versus Chemoradiotherapy and Vandetanib for High-Risk Postoperative
Advanced Squamous Cell Carcinoma of the Head And Neck

SCHEMA

<table>
<thead>
<tr>
<th>Arm 1: Chemoradiotherapy</th>
<th>Cisplatin, 100 mg/m², beginning on day 1 of RT, every 3 weeks for 3 cycles</th>
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<tr>
<td>Arm 2: Chemoradiotherapy + Vandetanib</td>
<td>Vandetanib, 100 mg, daily</td>
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**SCHEMA**

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<th>E patients:</th>
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<td>G</td>
<td>Mandatory</td>
<td>R</td>
<td>Status</td>
<td>N</td>
<td>Radiation: 5.5-6.5 weeks; total dose of 58-66 Gy</td>
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**Primary Site**

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<tr>
<th>R</th>
<th>For</th>
<th>Y</th>
<th>Oral cavity/hypopharynx</th>
<th>Z</th>
<th>Note: Vandetanib will begin 14 days prior to start of RT and no earlier than 3 weeks after surgery</th>
</tr>
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<tr>
<td>E</td>
<td>F</td>
<td>Primary Site</td>
<td>I</td>
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**HPV**

<table>
<thead>
<tr>
<th>Z</th>
<th>Cisplatin, 30 mg/m², on day 1 of RT, weekly for 6 weeks</th>
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</thead>
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<tr>
<td>E</td>
<td>Radiation: 5.5-6.5 weeks; total dose of 58-66 Gy</td>
</tr>
</tbody>
</table>

*Prior to stratification and randomization, **all patients** must consent to submission of tissue for central review. In addition, **patients with oropharyngeal carcinoma** must consent to use of the submitted tissue for required HPV analysis. **All institutions will receive a 0.5 case credit for submission of tissue for analysis.**

HPV analysis results are expected in approximately 7-10 days. At that time, patients with oropharyngeal carcinoma can be randomized. See Section 5.4 for details of registration/randomization.

**Note:** It is mandatory the treating physician determine the radiation therapy technique (3D-CRT vs. IMRT) to be used prior to the site registering the patient. See Section 5.0 for pre-registration requirements; Section 6.0 for details of radiation therapy, and Section 7.0 for details of drug therapy.

**Patient Population:** (See Section 3.0 for Eligibility)

AJCC pathological stage III or IV squamous cell carcinoma of the oral cavity, oropharynx, larynx, or hypopharynx (excluding lip, nasopharynx, or sinuses)

Complete tumor resection (with curative intent) must be completed within 3 to 6 weeks of registration, with pathology demonstrating one or more of the following risk factors:

- Histologic extracapsular nodal extension;
- Invasive cancer seen on microscopic evaluation of the resection margin, when all visible tumor has been removed.

Tonsillar cancer patients who undergo transoral excision of all gross tumor are eligible if the patient has formal neck dissection confirming histologic extracapsular nodal extension.

**Required Sample Size: 170**

RTOG 0619
_____ (Y) 1. Does the patient have a histologically or cytologically proven Stage III or IV diagnosis of squamous cell carcinoma of the oral cavity, oropharynx, larynx or hypopharynx (excluding lip, nasopharynx or sinuses)?

_____ (Y) 2. Was a gross total resection completed within 3 to 6 weeks of registration?

_____ (Y) 3. Did pathology demonstrate one or more of the following risk factors?
   • Histologic extracapsular nodal extension;
   • Invasive cancer seen on microscopic evaluation of the resection margin, when all visible tumor has been removed;
   • Clinical T4a tumors

_____ (Y/N) 4. Is the primary tonsillar cancer?

_____ (Y) If yes, was a neck dissection performed confirming extracapsular nodal extension?

_____ (N) 5. Is there any evidence of distant metastasis?

_____ (Y) 6. Were the pre-treatment radiographic studies done within 12 weeks prior to registration?

_____ (Y/N) 7. Was an EKG performed within 4 weeks prior to registration?

_____ (Y) If, yes was it within the parameters required in Section 3.1.3.4?

_____ (Y/N) 8. Is the patient receiving one of the medications listed in Appendix VII (Medications Generally Accepted by Authorities to Have a Risk of Causing Torsades De Pointes [Tdp])?

_____ (Y) If yes, is the screening QTc < 460 msec?

_____ (Y) 9. Was the Zubrod performance status 0-1 within 4 wks prior to registration?

_____ (Y) 10. Is the patient at least 18 years of age?

_____ (Y) 11. Are the pre-treatment lab values within the parameters specified in Sections 3.1.6-3.1.8.2?

_____ (Y) 12. For women of childbearing potential, was a serum pregnancy test completed within 2 weeks of registration?

_____ (Y) If yes, was the serum pregnancy test negative?

_____ (Y/NA) 13. If a male participant or a woman of child bearing potential, is the patient willing to use effective contraception while on treatment and for at least 60 days after end of treatment?

_____ (Y) 14. Has the patient signed a study-specific consent form?

_____ (N) 15. Did the patient have any synchronous or simultaneous primaries?

_____ (Y/N) 16. Did the patient have a prior invasive malignancy?

_____ (Y) If yes, is the prior malignancy within the parameters specified in Section 3.2.2?

_____ (N) 17. Did the patient have previous systemic chemotherapy for the study cancer?

Continued on the next page
18. Did the patient have previous irradiation to the head and neck that would result in overlap in radiation fields? (N)

19. Has the patient had any major surgery within 3 weeks prior to registration? (N)

20. Does the patient have any incompletely healed surgical wounds at registration? (N)

21. Did the patient have any of the severe comorbid conditions listed in Section 3.2.6 within 3 months prior to registration that would exclude him/her from participation? (N)

22. Does the patient have any of the CTCAE v. 3.0 grade 3-4 electrolyte abnormalities specified in Section 3.2.6.11? (N)

23. Does the patient have ≥ grade 1 CTCAE v. 3.0 diarrhea as described in Section 3.2.6.12? (N)

24. Did the patient receive intravenous antibiotics for acute bacterial or fungal infection at the time of registration? (N)

25. Did the patient have an exacerbation of chronic obstructive pulmonary disease or other respiratory illness requiring hospitalization or precluding study therapy within 30 days prior to registration? (N)

26. Does the patient have hepatic insufficiency resulting in clinical jaundice and/or coagulation defects? (N)

27. Does the patient have Immune Deficiency Syndrome (AIDS) based on the current CDC definition? (N)

28. For women of childbearing potential, is the patient lactating? (N/NA)

29. Does the patient have a prior history of allergic reaction to cisplatin, vandetanib, or derivatives similar to these drugs? (N)

30. Has the patient received any investigational agents other than vandetanib within 30 days prior to registration? (N)

31. Has the patient used known potent inducers of CYP3A4 (rifampicin, phenytoin, carbamazepine, barbiturates, St. John’s Wort) within 2 weeks prior to registration? (N)

The following questions will be asked at Study Registration:

IMRT CREDENTIALING IS REQUIRED BEFORE REGISTRATION.

(N/Y) Specify use of IMRT (Question 25)

1. Name of institutional person registering this case?

Continued on the next page
2. Has the Eligibility Checklist (above) been completed? 
3. Is the patient eligible for this study? 
4. Date the study-specific Consent Form was signed? (must be prior to study entry) 
5. Patient’s Initials (First Middle Last) [May 2003; If no middle initial, use hyphen] 
6. Verifying Physician 
7. Patient’s ID Number 
8. Date of Birth 
9. Race 
10. Ethnic Category (Hispanic or Latino; Not Hispanic or Latino; Unknown) 
11. Gender 
12. Patient’s Country of Residence 
13. Zip Code (U.S. Residents) 
14. Method of Payment 
15. Will any component of the patient’s care be given at a military or VA facility? 
16. Calendar Base Date 
17. Registration date: This date will be populated automatically. 
18. Medical Oncologist’s name 
19. Have you obtained the patient’s consent for his or her tissue to be kept for use in research to learn about, prevent, treat, or cure cancer? 
20. Have you obtained the patient’s consent for his or her blood to be kept for use in research to learn about, prevent, treat, or cure cancer? 
21. Have you obtained the patient’s consent for his or her tissue to be kept for use in research about other health problems (for example: causes of diabetes, Alzheimer’s disease, and heart disease)? 
22. Have you obtained the patient’s consent for his or her blood to be kept for use in research about other health problems (for example: diabetes, Alzheimer’s disease, or heart disease).
23. Have you obtained the patient's consent to allow someone from this institution to contact him or her in the future to take part in more research?

24. Specify Zubrod Performance Status (0 vs. 1)

25. Will oropharynx tissue be submitted for HPV analyses?

26. Specify Primary Site (oral cavity/hypopharynx; larynx; oropharynx)

The Eligibility Checklist must be completed in its entirety prior to web registration. The completed, signed, and dated checklist used at study entry must be retained in the patient's study file and will be evaluated during an institutional NCI/RTOG audit.

Completed by ________________________________ Date ____________________________
1. Name of institutional person registering this case

__________  (Y/N)  2. Is the patient going to receive protocol treatment?

__________  3. If no, specify the reason the patient cannot continue to Step 2: 1) progression of disease; 2) patient refusal; 3) physician preference; 4) failure to submit tissue assay; 5) other

__________  4. Patient's Initials

__________  5. Verifying Physician

__________  6. Patient's ID number

__________  7. Calendar Base Date (for Step 2)

__________  8. Randomization Date (for Step 2)

Completed by ___________________________________________  Date ___________________________
1.0 INTRODUCTION

1.1 Treatment of Head and Neck Squamous Cell Carcinoma

Of the approximately 43,000 cases of head and neck squamous cell carcinoma (HNSCC) diagnosed annually in the United States, two thirds of these patients will present with advanced disease (Stage III or IV) [Forastiere 2001; Vokes 1993]. The primary treatment options for patients presenting with locally advanced HNSCC include: 1) The use of accelerated radiation, combination chemoradiation approaches, and improved radiation delivery techniques designed to spare critical organs such as the major salivary glands; (Ang 1997; Ang 1998; Withers 1988; Fu 2000; Bourhis 2006; Vokes 2000; Mendenhall 2006) or 2) Surgical resection followed by postoperative radiation therapy with or without chemotherapy (Bauchaud 1996; Cooper 1998; H & N Contracts Program 1987; Laramore 1992; Ang 2001). Despite the latter approach, many patients still succumb to locoregional disease recurrence which also can be a harbinger of distant metastasis.

Recent efforts to improve locoregional control and survival have centered on the use of combined chemoradiation for patients deemed at high risk for failure after surgery (approximately one third of resected patients). The two most important studies, conducted through the RTOG and EORTC cooperative groups in a phase III setting have demonstrated significant improvements in locoregional control. Both studies (RTOG 95-01 and EORTC 22931) randomized patients with high-risk pathologic features to postoperative radiation alone or radiation in combination with cisplatin chemotherapy (Cooper 2004; Bernier 2004). These two randomized trials yielded positive results for their respective endpoints but contrasting results for overall survival.

The EORTC trial enrolled 334 patients and identified a clear benefit in locoregional disease control, disease free survival (primary endpoint), and overall survival for those patients receiving cisplatin chemotherapy concurrent with radiation. The RTOG trial enrolled 459 patients and identified a clear benefit in locoregional disease control (primary endpoint) but not for overall survival with the addition of cisplatin. Both trials confirmed greater acute and overall toxicity with the addition of cisplatin chemotherapy. A recent re-analysis of both trials suggested that virtually all of the benefit of chemoradiation was observed in patients with positive margins or extracapsular extension (Bernier 2005). As such, the criterion, two or more positive lymph nodes, will no longer be considered a high-risk factor for this study.

1.2 Epidermal Growth Factor Receptor

Epidermal growth factor receptor (EGFR) signaling has been implicated as an important prognostic marker for patients with head and neck cancer. High levels of EGFR expression are associated with reduced local control and survival (Ang 2002). Importantly, preclinical studies have shown that EGFR expression is inversely related to radiation response (Akimoto 1999). Corroborating these observations are recent studies that have demonstrated a correlation between outcomes and duration of therapy based on low or high levels of EGFR expression. A multitude of preclinical studies have demonstrated that perturbation of the EGFR signaling pathway using either anti-EGFR antibodies such as C225 (cetuximab) or small molecule tyrosine kinase inhibitors (gefitinib, erlotinib) results in enhanced radiation cytotoxicity, reduced angiogenesis, and an increase in apoptosis (Huang 1999; Huang 2000; Harari 2000; Milas 2000; Bianco 2000; Bianco 2002; Huang 2002; Chinnaiyan 2005).

Recently, the addition of C225 to radiation was shown to significantly improve locoregional control, disease free survival, and overall survival when compared to radiation alone in a randomized phase III setting for patients with locally advanced HNSCC (Bonner 2006). RTOG 0234, a protocol designed to examine the toxicity and outcomes with the addition of C225 to an adjuvant chemoradiation therapy regimen for patients with high-risk features, was closed on 12/1/06 as it met its accrual objective. In this phase II trial, C225 was combined with radiation in conjunction with either weekly cisplatin or weekly docetaxel. RTOG 0234 was amended to allow for the use of intensity modulated radiation (IMRT), which substantially increased the accrual rate.

EGFR inhibition when combined with radiotherapy has demonstrated a tumor control and survival benefit (10-15%) in patients with advanced HNSCC cancers. Although there was a significant improvement in local control at 3 years with the addition of cetuximab to radiation (47% vs. 34%) in the Bonner trial (2006), local failure rates still were greater than 50%, leaving considerable
room for improvement. Thus, combining radiation with chemotherapy and biologics or attacking additional pathways that drive cancer cells are important to consider.

To put this proposed study into perspective, we reviewed ongoing trials (accessible in public domains and by personal contacts) for patients with head and neck carcinomas. Many relatively small phase I-II trials are ongoing to address the combinations of radiation +/- chemotherapy plus either cetuximab (8 trials), gefitinib (12 trials), erlotinib (6 trials), or panitumumab (1 trial). Five other studies test the combinations of radiotherapy plus either chemotherapy and celecoxib, chemotherapy and bevacizumab, or lapatinib (+/- cisplatin).

RTOG has completed accrual to a randomized phase II trial (mentioned above) evaluating the safety and preliminary efficacy of the combination of radiation + cisplatin + cetuximab in comparison to radiation + docetaxel + cetuximab in the post-operative adjuvant setting. This trial enrolled 238 patients with high-risk surgical pathologic features. Thus far, this is the largest study that has completed patient accrual testing the combination of radiation, chemotherapy, and molecular therapeutics in head and neck carcinoma. The results of this trial will not be available until 2009. Currently, the most logical extension seems to be to test the concept of combining radiotherapy with chemotherapy while inhibiting two signaling pathways, since the prognosis of the patient population is rather poor (5-year survival even with adjuvant radiation-chemotherapy is approximately 40%). The most appealing option in our view is to target the VEGFR pathway in addition to EGFR signaling as outlined below.

1.3 Angiogenesis

Another aspect of tumorigenesis that has been under investigation for several decades is the process of angiogenesis. Studies suggested that tumor cells could actually stimulate new blood vessel formation, a process known as angiogenesis. This field has evolved considerably over the last 20 years to the point where tumors are no longer considered separately from their stromal environment. The growth of tumors is dependent on their ability to parasitize their host, recruiting blood vessels to allow them to utilize host nutrients and oxygen to grow and metastasize.

It was hypothesized many years ago that therapeutic approaches that target the process of angiogenesis will be relatively specific for pathological angiogenesis in tumors (Folkman 1972). Thus, tumor cells, endothelial cells, and the stromal matrix define at least three compartments that represent potential targets for cancer therapy. Therefore, research has been aimed at developing inhibitors of this process; for example, VEGF is a key proangiogenic factor that stimulates endothelial cell proliferation and migration and promotes endothelial cell survival (Ferrara 1997). The vascular endothelial growth factor (VEGFR) family comprises three receptor tyrosine kinases: VEGFR-1 (Flt-1), VEGFR-2 (KDR), and VEGFR-3 (Flt-4) [Eskens 2004]. Of these, VEGFR-2 is considered the most important receptor for mediating the angiogenic effects of VEGF. Therefore, inhibition of VEGFR-2–mediated tumor angiogenesis has become an important therapeutic target.

1.4 Rationale for Blocking Both EGFR and Angiogenic Signaling

Attacking different aspects of the cancer cell environment and signaling cascade is an appealing approach in head and neck cancer. EGFR activation can lead to increases in VEGF signaling. Radiation also has been shown to induce both VEGF and EGFR expression. In addition, cancer cells that become resistant to EGFR inhibitors express amplified VEGF (Vilora-Petit 2001). Thus, blocking both EGFR and VEGF signaling may improve tumor control even further and optimize outcomes. This has been demonstrated in a variety of pre-clinical models (Shaheen 2001; McCarty 2004; Yokoi 2005; Park 2005). A number of clinical studies are evaluating this sort of strategy with the combination of EGFR inhibitors, such as erlotinib, with anti-angiogenic inhibitors, such as bevacizumab, a monoclonal antibody targeting vascular endothelial growth factor (VEGF), in recurrent HNC (Vokes 2005). The Phase I part of the study utilized fixed doses of erlotinib (150 mg orally daily) with escalating doses of bevacizumab delivered every 3 weeks. Encouraging results were reported with 5 patients experiencing either a complete or partial response as well as stabilization of disease in 31/44 evaluable patients. A median progression-free survival of 127 days was reported at ASCO in 2005 with a median overall survival of 226 days. A phase I trial combining AZD2171, an inhibitor of VEGFR-2 tyrosine kinase activity, with gefitinib resulted in diarrhea (14/16 patients), rash (nine of 16), abdominal pain (nine of 16), and hypertension (eight of 16). Hypertension and diarrhea were the most commonly reported CTC grade 2 adverse events considered to be related to treatment. These are typical side effects observed with anti-angiogenic and EGFR inhibition respectively; however, no major bleeding
episodes were reported (Van Cruijsen 2005). Building on this strategy is a recently initiated Phase I trial at Duke University that combines either erlotinib or bevacizumab with chemoradiation for patients with locally advanced HNC. An additional cohort combines both erlotinib and bevacizumab with chemoradiation. Of the 10 patients accrued at the time of this report, no major bleeding episodes had been reported and there were no untoward wound healing issues or enhanced mucositis over expected events (Brizel 2006).

1.5 Vandetanib (ZD6474) [Zactima™] (6/8/09)

1.5.1 Properties
Vandetanib is an orally bioavailable potent inhibitor of the tyrosine kinase activity of kinase insert domain-containing receptor (KDR), an endothelial cell receptor for vascular endothelial growth factor (VEGF) and also possesses activity against epidermal growth factor receptor (EGFR). VEGF is a humoral mediator of endothelial cell proliferation, and is one of the primary growth factors responsible for the initiation of new blood vessel growth. This process, termed angiogenesis, is essential for the growth and dissemination of tumors. By specifically targeting angiogenesis, it is hoped that the growth of tumors will be controlled, with relative sparing of normal tissues.

1.5.2 Activity in Preclinical Models (6/8/09)
Vandetanib has shown excellent inhibition of tumor cell growth in a broad range of pre-clinical models, including lung cancer xenografts (Calu-6 and A549). Regression of established tumors (PC-9 lung cancer and PC-3 prostate cancer) in animals was observed following oral administration. Vandetanib was considered to have an acceptable pre-clinical toxicology profile for the proposed therapeutic indication. Vandetanib also inhibits epidermal growth factor (EGF) stimulated cell proliferation, though at a concentration (the molar concentration of a compound required to produce 50% inhibition of a biological effect; IC50=170 nM) approximately 3-fold higher than that required for the inhibition of VEGF-stimulated cell proliferation (60 nM).

Vandetanib has demonstrated inhibition of both vascular endothelial growth factor receptor (VEGFR) and EGFR tyrosine kinases in vitro, and pre-clinical models have shown activity against non-small cell lung cancer (NSCLC) xenografts. AstraZeneca has conducted clinical studies in patients with NSCLC. In the Japanese Phase I study (TVE-15-11), 4 of 9 patients with NSCLC had confirmed partial responses (PRs). Subsequently, 2 randomized Phase II studies (6474IL/0003 and 6474IL/0006) were performed in patients with NSCLC refractory to first-line therapy. Vandetanib demonstrated an advantage in progression-free survival (PFS) compared with gefitinib in study 6474IL/0003, and in combination with docetaxel compared with docetaxel alone in study 6474IL/0006. The results of these Phase II studies led to the designs of 4 Phase III studies. Two studies investigated vandetanib in combination with chemotherapy (study D4200C00032 with docetaxel and study D4200C00036 with pemetrexed), and 2 studies investigated vandetanib as monotherapy (study D4200C00057 compared to erlotinib and study D4200C00044 compared to best supportive care in patients who have previously received an EGFR inhibitor). In the 2 combination studies, the addition of vandetanib to docetaxel provided a statistically significant advantage in PFS compared to docetaxel alone; in the smaller study with pemetrexed, there was a positive trend for PFS in favor of the addition of vandetanib. Study D4200C00057 did not meet the goal of demonstrating superiority in PFS compared to erlotinib, but the efficacy of the 2 drugs was equivalent. Study D4200C00044 was still ongoing at the time of edition 11 of the Investigator’s Brochure (IB). The most common side effects associated with vandetanib are rash and diarrhea. In addition to the studies of vandetanib in NSCLC, several other Phase I and II studies are ongoing in other tumors, and a Phase III study in patients with medullary thyroid cancer is also ongoing (Vandetanib IB, 2009).

1.5.3 Radiation Sensitization in Preclinical Models
Important in the context of this proposed trial, pre-clinical work has also shown a cooperative benefit to combining vandetanib with radiation in a variety of tumor models including gliomas (Damiano 2005), NSCLC (Williams 2004), and HNSCC (Gustafson 2004). Both sequential and concomitant administration of vandetanib have been shown to improve tumor response to radiation in NSCLC and HNSCC models when combined with radiation (Williams 2004; Gustafson 2004). A recently published study showed that the combination of vandetanib and RT is active in both EGFR+ and EGFR- HNSCC tumor xenografts, but vandetanib alone only has significant activity in EGFR+ xenografts (Gustafson 2008). The response of EGFR+ tumor to vandetanib and RT was independent of treatment sequencing, but concomitant treatment was better than sequential regimen in EGFR- tumors. The anti-tumor effects of vandetanib were also examined in a human colorectal cancer xenograft model (HT29), either alone or
combined with RT (Brazelle 2006). Irrespective of sequencing, combination therapy resulted in a significantly greater growth delay than either RT or vandetanib treatment alone.

In contrast to vandetanib, data seem to suggest that the activity of some other anti-angiogenic agents is more schedule-dependent and certain timing could even result in tumor protection.

In the NCI-H441 human lung adenocarcinoma model, vandetanib was found to be more effective than paclitaxel when combined with radiation in inducing apoptosis of tumors and surrounding endothelium, reducing endothelial proliferation, inhibiting local tumor growth, and reducing metastatic spread to the mediastinal nodes, pleural cavity, and vertebral bodies (Shibuya in press).

Data on the combination of vandetanib with radiation and chemotherapy also are emerging. For example, vandetanib (30 mg/kg daily) given with combination of radiotherapy and temozolomide resulted in the greatest tumor growth inhibition in an intracerebral rat BT4C glioma model (Sandstrom 2008). Similar cooperative effects were seen in pancreatic xenografts treated with combination of vandetanib, gemcitabine and radiation (Bianco 2006).

1.5.4 Clinical Development

Two Phase I studies were conducted in the West and in Japan, which demonstrated a maximum tolerated dose of 300 mg, with common adverse events (AEs) being diarrhea, rash, hypertension, and QTc prolongation.

Vandetanib monotherapy (300 mg/day) has shown clinical activity in a phase II trial in patients with advanced medullary thyroid carcinoma (Wells 2007). Other phase II development includes studies have been conducted in NSCLC, breast cancer, and multiple myeloma with vandetanib monotherapy at 100, 200, or 300 mg/day. In addition, a randomized double blind study was conducted to compare the efficacy of vandetanib at 100 mg or 300 mg in combination with docetaxel relative to that of docetaxel plus placebo. Study ZD6474IL/0003 (the largest monotherapy study conducted thus far) and Study ZD6474IL/0006 (combination with docetaxel) demonstrated that vandetanib prolonged progression-free survival (PFS) in patients with NSCLC (Natale 2006; Heymach 2006). Of interest to this proposed study is the finding that patients treated at the 100 mg dose level with docetaxel had slightly superior outcomes compared to patients treated at the 300 mg dose level with docetaxel. In addition, a Phase II randomized trials in pancreatic cancer and Phase III trials in lung cancer and medullary thyroid cancer are ongoing.

Many investigators consider the combination of radiotherapy with concurrent cisplatin a non-surgical standard of care for patients with locally advanced head and neck cancer. A phase II trial (RTOG 99-14) testing the combination of concomitant boost radiotherapy with concurrent cisplatin in this subset of patients (Ang 2005) showed a complete response rate of 83% and a 2-year disease-free survival rate of 53.5%. These results are encouraging, which lead to the subsequent completion of a Phase III trial (RTOG 0129). However, the data also show that there is still room for further improvement. Therefore, University of Colorado Cancer Center in conjunction with the University of Chicago and MD Anderson Cancer Center are currently conducting a Phase I study combining vandetanib (starting at 100 mg) with radiotherapy alone (for T1-2) or combined with weekly 30 mg/m² cisplatin (T3-4). So far, the data are encouraging, and patient accrual is ongoing.

1.6 Summary of Adverse Events (AEs) in Vandetanib Phase I and Phase II Studies (6/8/09)

The events below are discussed regardless of causality to vandetanib. Some of these events may reflect symptoms of cancer, effects of chemotherapy or radiation, or concomitant medical illness. Events that are thought likely to be causally related to vandetanib are listed in the Emerging Safety Profile below. This summary of adverse events was taken from Vandetanib I/B, Edition Number 10, March 2000.

Skin and Subcutaneous Tissue Disorders

The events, organized by MedDRA preferred term, that were categorized under this system organ class include rash, acne, maculo-papular rash, dry skin, night sweats, pruritus, acniform dermatitis, exfoliative dermatitis, contusion, rash photosensitivity, photosensitivity reaction, desquamation, erythema, erythematous rash, macular rash, pruritic rash, pustular rash, follicular rash, skin eruption, hyperhidrosis, nail discoloration, skin ulcer, urticaria and alopecia.
Most of these skin disorders happened in the first 4 weeks of treatment and were CTC/CTCAE grade 1-2. There was a tendency for dose-dependent increase in incidence of drug-related adverse events. At least 2 distinct types of rash related to vandetanib therapy have been described, namely, a macular erythema in some patients and a follicular (acneform) rash in others. Also, photosensitive rash has been reported in some of these patients. When vandetanib was combined with pemetrexed, 10 patients developed skin rash; 7 of the events were considered to be vandetanib-related. None of the cases was reported to be CTCAE Grade 3 or higher. The majority of the events developed within the first 6 weeks of treatment and some of them within the first week of vandetanib exposure.

**Gastrointestinal System**

Events included diarrhea, nausea, vomiting, constipation, abdominal pain, upper abdominal pain, abdominal discomfort, abdominal distention, flatulence, dry mouth, dry lip, mouth ulceration, dyspepsia, dysphagia, gastroesophageal, stomatitis, aphthous stomatitis, acquired esophageal stenosis, and gingival bleeding. Most of these adverse events were CTC/CTCAE grade 1 or 2 and did not need interruption of study treatment. Routine anti-diarrheal agents also are recommended. Abdominal pain has been seen in Phase I, but was not common in Phase II studies.

**General Disorders and Administration Site Conditions**

Fatigue, pyrexia and peripheral edema were observed, as were asthenia, rigors, chest pain, chest tightness, mucosal inflammation, abnormal gait, and lethargy. Most of the adverse events were CTC/CTCAE grade 1-2; grade 3 was rare.

**Vascular Disorders**

Hypertension is considered to be a class effect for VEGF pathway inhibitors, and was a DLT for studies 6474IL/0001 and TVE-15-11. Pulmonary thrombosis and deep vein thrombosis have been observed so far. One instance of pulmonary hemorrhage after cavitation also was observed in a study of vandetanib combined with docetaxel (6474IL/0006.) It is unclear whether deep vein thrombosis and pulmonary hemorrhage may be related to vandetanib or reflect the underlying cancer or co-morbid conditions.

**Respiratory System**

Cough and dyspnea were common adverse events but are common symptoms of lung cancer. Other reported adverse events included pharyngolaryngeal pain, epistaxis, dysphonia, hiccups, respiratory alkalosis, rhinorrhea, pulmonary embolism, and pulmonary artery thrombosis.

**Other Adverse Events**

Other commonly reported AEs included nervous system disorders (lethargy, neuropathy peripheral, headache and dysesthesia), blood and lymphatic system disorders (neutropenia and thrombocytopenia), and metabolism and nutrition disorders (hypokalemia).

**QT/QTc Prolongation**

**Phase I studies**

Prolongation of the ECG corrected QT interval was initially observed in Phase I and II studies, and no patients experienced symptoms definitely related to QTc prolongation. On rare occasions, patients with QTc prolongation have experienced cardiac arrhythmias; however, all patients had confounding factors that were much more likely to be the cause.

**Phase II studies**

Prolongation of the QTc interval, using Bazett's correction, was seen in Phase II studies. No significant changes in heart rate were observed across any of the doses studied. No patient developed symptomatic ventricular arrhythmias, although 1 patient with pneumonia and QTc greater than 600 ms was noted to have a non-sustained run of ventricular tachycardia while in a monitored hospital setting (see below). Using extensive ECG monitoring to assess the QTc prolongation more closely, at a dose of 300 mg/day, QTc prolongation resulting in dose reduction has been seen in approximately 5% of patients, and at a dose of 100 mg in combination with chemotherapy in < 2% of patients.
Phase III studies
In the Phase III studies, the incidence of prolongation of the ECG QTc interval was seen in 1.9% of patients treated with vandetanib 100 mg plus docetaxel and in 0.4% of patients treated with vandetanib 100 mg plus pemetrexed. No patients receiving vandetanib 100 mg experienced torsade de pointes or other arrhythmia attributed to prolongation of the QTc interval. In study D4200C00057, 5% of patients receiving vandetanib 300 mg experienced prolongation of the QTc interval, and there was 1 case of reversible, non-fatal torsade de pointes. The QTc prolongation was managed by dose interruption followed by dose reduction. A non-linear relationship between QTc and vandetanib plasma concentration has been determined using pharmacokinetic/pharmacodynamic modelling.

Emerging Safety Profile
Vandetanib produces repolarisation abnormalities in human myocardium that are consistent with blockade of the IKR (potassium) channel. The most consistent electrophysiologic effects are a change in T-wave morphology (flattening, broadening or notching) and prolongation of the QT interval, both of which occur more commonly as the dose is increased. Vandetanib can cause rash, diarrhea and hypertension, all of which appear to be dose-related and are likely to be related to the pharmacologic activity of vandetanib (Vandetanib IB, 2009).

The drug-related AEs seen with vandetanib monotherapy also are expected to occur in combination with chemotherapy. All drug-related AEs expected to occur in association with the concomitant chemotherapeutic agent(s) [as defined and listed in the package insert(s)] will be expected to occur when used in combination with vandetanib. The relevant product information for the concomitant chemotherapy should be used to determine these expected, drug-related AEs.

Reported adverse events that may be related to vandetanib are listed below by body system:

**Cardiovascular**
- Abnormal ECG (with or without QT prolongation; i.e. either T-wave or ST-segment changes consistent with repolarization abnormalities), torsade-de-pointes and ventricular tachycardia (both at 300 mg daily dose) and hypertension.
- Cardiac failure (300 mg daily dose) [See Appendix III for the New York Heart Association (NYHA) Cardiac Classifications].

**Central Nervous System**
- Headache
- Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

**Digestive**
- Constipation
- Diarrhea
- Nausea
- Vomiting

**Hematologic and Lymphatic**
- Ecchymosis
- Thrombocytopenia

**Investigations:** Elevated liver function tests (generally CTC/CTCAE grade 1-2, weight loss

**Metabolic and Nutritional**
- Dehydration
- Hypokalemia
- Hypomagnesemia
- Hypophosphatemia

**Skin and Appendages**
- Acneform rash
- Pruritus
- Macular or macupapular rash (generalized or localized)
- Localized and generalized erythema
- Photosensitivity reaction
- Sweating.
On occasion (especially when given with chemotherapy) these have progressed to more serious conditions to include exfoliative dermatitis, skin desquamation, erythroderma, toxicodermia, toxic epidermal necrolysis, erythema multiforme

**Respiratory**
- Interstitial lung disease (ILD)

A very small number of patients with lung cancer receiving vandetanib have developed shortness of breath and cough due to inflammation or scar tissue formation in the lungs (although this could be due to the underlying lung cancer)

**Renal**
- Proteinuria
- Hematuria

**Vascular:** Arterial ischemic events (including myocardial infarction, stroke, peripheral ischaemia)

**Psychiatric:** Mood disorders (anxiety, depression, insomnia). It is possible that these events are not direct effects of vandetanib, but rather are secondary to symptoms of cancer or to other effects of vandetanib (rash, etc.).

**General**
- Asthenia
- Fatigue

For additional details on vandetanib, please refer to the current vandetanib IB.

### 1.7 Rationale for Translational Study of Human Papillomaviruses (HPV)

A major change in the landscape of head and neck cancer research over the past decade has been the recognition of the increased incidence of HPV-related oropharynx cancer. HPV (mostly HPV 16) DNA can be detected in many human oropharyngeal SCC specimens, and strong evidence suggests that it is a causative agent. HPV related oropharynx SCCHN is probably arises as a consequence of integration of HPV early viral oncoproteins E6 and E7 into the genome of mucosal cells in the oropharynx; these oncoproteins dysregulate normal cell proliferation via the p53 and p16/Rb pathways (Gillison 2000).

An emerging body of literature suggests that HPV-related SCCHN (oropharynx cancer) has a number of important biologic and clinical differences compared with traditional SCCHN. Retrospective analysis revealed that HPV associated oropharynx SCCHN has a better prognosis than non-HPV associated disease, possibly due to improved responsiveness to RT +/-chemotherapy (Gillison 2000; Capone 2001; Schwartz 2001).

The above data strongly suggests that it is important to account for HPV in large scale clinical trials that include oropharynx cancer. Most notably, it is probably necessary to stratify for HPV-related cancer (yes vs. no) in order to assure that treatment arms are well balanced (An imbalance could very likely result in improved outcomes in the treatment arm that has more patients with HPV-related cancer). Thus, one of the stratifications in our study will be for HPV-related SCC of the oropharynx. Since HPV is not typically associated with non-oropharynx SCCHN, this will only specifically be done for oropharynx cancer. To avoid possible bias in randomization of patients to the study, the patient’s physician or institution cannot request the patient’s HPV status from RTOG Headquarters until the patient has completed study treatment.

There is still controversy regarding the best method for determining whether or not an oropharynx cancer is HPV-related. The probable gold standard is to perform DNA analysis using PCR techniques; however, that is likely to be unwieldy for a large multicenter cooperative group trial at this time. Another technique is to perform immunohistochemical staining for the p16 protein (which is generally overexpressed in HPV-positive oropharynx cancer). However, there is not yet a standardized antibody/technique for routine analysis of p16; also, p16 overexpression may be associated with cellular dysregulations other than HPV. Thus, we propose to analyze HPV via in situ hybridization (ISH), as performed in the studies by Gillison, et al. at Johns Hopkins (Gillison 2000; Schwartz 2001). All samples will undergo HPV16 ISH, given that 90-95% of HPV-positive SCCHN patients are HPV16 positive. HPV16 negative cases will undergo further analysis by use of a probe cocktail for high risk HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68. This technique, used in the previous retrospective analysis, was found to be highly sensitive and specific for HPV-infected oropharynx SCC.

### 1.8 Rationale for the Proposed Trial (6/8/09)

The rationale for this particular proposal is based on the desire to improve upon current locoregional control, disease-free survival, and overall survival outcomes in patients with high-risk
HNSCC treated with surgery and post-operative chemoradiation. RTOG 95-01, using radiation with concurrent high dose cisplatin (100 mg/m2 every 3 weeks), demonstrated a local failure rate of ~19% with a disease free survival of ~40% at 60 months (Cooper 2004). We hope to improve outcomes by combining vandetanib, an oral small molecule tyrosine kinase inhibitor, with activity against both angiogenic and epidermal growth factor signaling, with a less toxic chemotherapy regimen plus IMRT in patients with high risk HNSCC in the post-operative setting with a control arm using the best arm from RTOG 95-01.

The main reasons for selecting vandetanib in the experimental arm are: (1) encouraging single-agent activity in many preclinical models; (2) strong preclinical data on its efficacy in sensitizing a variety of tumors to radiotherapy; and (3) no bleeding episodes observed in clinical trials. Other advantages of vandetanib include the lack of hypersensitivity reaction associated with antibodies (which can be substantial in certain geographic regions), ease of administration, and lower overall cost of therapy.

The rationale for using a lower dose of cisplatin in the experimental arm is based on the following: In 1996, Bachaud evaluated weekly cisplatin at 50 mg per week with RT, demonstrating a significant survival advantage over radiotherapy alone in the post-operative setting for high risk patient, which included ECE in metastatic lymph nodes. The LRC (77%) and DFS at 5 years (45%) were similar to what was reported in RTOG 95-01 and EORTC 22931. In addition, the German ARO 693 study compared cisplatin at 20 mg/m2, albeit with 5-FU, on days 1-5 and 29-33 to RT alone and again, demonstrated a LRC and DFS advantage with results similar to every 3 week cisplatin in the RTOG and EORTC studies (Feitkau 2006). RTOG 97-03 utilized weekly cisplatin (Arm 3) with Taxol® in a randomized phase II design, and the outcomes with this approach appear superior to historical RTOG studies using radiation alone. (Of note, Arm 2 with Hydrea and 5-FU with no cisplatin had similar results to Arms 1 and 3 with cisplatin in the treatment regimen.)

A recent article by Ho and colleagues (2008) points out the issues with delivering high dose versus low dose CDDP with RT: “More patients received a higher cumulative dose of at least 240 mg/m(2) if given weekly Cisplatin 40 mg/m(2) or 3-weekly Cisplatin 80 mg/m(2) compared with those receiving Cisplatin 3-weekly 100 mg/m(2) (p=0.04). Maximum cumulative dose achievable in the latter group was only 200 mg/m(2) and none achieved the full 3 cycles.” This is a common problem with the delivery of cisplatin at 100 mg/m². The Bonner trial (2006) used no cisplatin, and when compared by Bernier, Bonner, and others to randomized clinical trials with cisplatin, outcomes appear similar. RTOG 95-01 was quite toxic to patients, with grade 4 toxicity seen in approximately 25% of patients. RTOG 0234 also implemented lower dose cisplatin or docetaxel in conjunction with C225 and RT as a means of studying less dose intensive chemotherapy with the addition of cetuximab. Preliminary analysis revealed no exacerbation of acute toxicity and perhaps more encouraging tumor control outcome, particularly for the docetaxel arm. Taken together, these data provide rationale for using a less dose intensive, weekly cisplatin in Arm 2 of this randomized phase II trial.

2.0 OBJECTIVES

2.1 Primary Objective (6/8/09)
To screen for an indication that the addition of vandetanib to chemoradiotherapy may prolong disease-free survival as compared to a combination of chemoradiotherapy in patients with resected, high-risk head and neck squamous cell carcinoma

2.2 Secondary Objectives

2.2.1 To determine whether this treatment regimen can be delivered safely and successfully following surgical resection for advanced head and neck cancer;

2.2.2 (6/8/09) To estimate the local-regional control, distant metastasis, and overall survival rates for patients treated with this regimen;

2.2.3 (6/8/09) To examine the distribution of selected biomarkers that may include but are not limited to EGFR (total and phosphorylated), E-cadherin, pMAPK, pAKT, Stat-3, Ki-67, COX-2, ERCC1, and cyclin B1 expression in this group of patients and to explore the potential correlation between these markers with the ultimate treatment outcome.
### 3.0 PATIENT SELECTION

**NOTE: PER NCI GUIDELINES, EXCEPTIONS TO ELIGIBILITY ARE NOT PERMITTED**

#### 3.1 Conditions for Patient Eligibility

<table>
<thead>
<tr>
<th>3.1.1</th>
<th>Pathologically (histologically or cytologically) proven AJCC pathological stage III or IV (note that the preoperative clinical stage may be I-IV) diagnosis of squamous cell carcinoma of the oral cavity, oropharynx, larynx, or hypopharynx (excluding lip, nasopharynx, or sinuses);</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.1.2</td>
<td>(2/25/10) Gross total resection (with curative intent) must be completed within 3 to 6 weeks of registration, with pathology demonstrating one or more of the following risk factors:</td>
</tr>
<tr>
<td></td>
<td>▪ Histologic extracapsular nodal extension (ECE);</td>
</tr>
<tr>
<td></td>
<td>▪ Invasive cancer seen on microscopic evaluation of the resection margin, when all visible tumor has been removed;</td>
</tr>
<tr>
<td></td>
<td>▪ Clinical T4a tumors (e.g., oral cavity primaries invading through the cortical bone, pharyngeal cancers invading the larynx, extrinsic muscles of the tongue [and/or pterygoids], or laryngeal-hypopharyngeal carcinomas extending through the thyroid or cricoids cartilages) are eligible after total resection in the absence of microscopic positive margin or ECE. (The NCI Steering Committee designated reviewers considered these patients to be at higher risk for relapse and hence recommended their exclusion from RTOG 0920).</td>
</tr>
</tbody>
</table>

Surgical resection of the microscopic involved margin is **NOT** permitted (see Section 8.1). **Note:** Tonsillar cancer patients who undergo transoral excision of all gross tumor are eligible if the patient has formal neck dissection confirming histologic extracapsular nodal extension.

#### 3.1.3 Appropriate stage for protocol entry, including no distant metastases, based upon the following minimum diagnostic workup:

| 3.1.3.1 | History/physical examination within 4 weeks prior to registration; |
| 3.1.3.2 | (6/8/09) Pre-operative CT, CT-PET, or MRI of the primary tumor and neck for clinical staging within 12 weeks prior to registration; |
| 3.1.3.3 | Chest x-ray or thoracic CT scan within 12 weeks prior to registration; |
| 3.1.3.4 | (6/8/09) Screening electrocardiogram (EKG) within 4 weeks prior to registration; **Note:** The screening EKG is performed once unless the initial EKG demonstrates a QTc with Bazett's correction unmeasurable or > 480 msec; If a patient demonstrates a QTc interval > 480 msec, then 2 additional EKGs should be done at least 24 hrs apart and the average QTc from the three screening EKGs must be ≤ 480 msec in order for the patient to be eligible for the study. |

In addition, if the patient is receiving one of the medications that has a risk of QTc prolongation prior to study entry (see Appendix VII) [but where the risk of Torsades is not clear] and the medication(s) cannot be discontinued before study entry, then the screening QTc must be < 460 msec.

| 3.1.4 | Zubrod Performance Status 0-1 within 4 weeks prior to registration; |
| 3.1.5 | Age ≥ 18 |
| 3.1.6 | Adequate bone marrow function, defined as follows: |
| 3.1.6.1 | Absolute neutrophil count (ANC) ≥ 2,000 cells/mm³ based upon CBC/differential obtained within 2 weeks prior to registration; |
| 3.1.6.2 | Platelets ≥ 100,000 cells/mm³ based upon CBC/differential obtained within 2 weeks prior to registration; |
| 3.1.6.3 | Hemoglobin ≥ 8.0 g/dl based upon CBC/differential obtained within 2 weeks prior to registration (Note: The use of transfusion or other intervention to achieve Hgb ≥ 8.0 g/dl is acceptable.) |
| 3.1.7 | Adequate hepatic function, defined as follows: |
| 3.1.7.1 | Total bilirubin must be within normal institutional limits within 2 weeks prior to registration; |
| 3.1.7.2 | AST or ALT ≤ 2 x the upper limit of normal within 2 weeks prior to registration; |
| 3.1.7.3 | Alkaline phosphatase (ALP) ≤ 2.5 x ULN within 2 weeks prior to registration; |
| 3.1.8 | Adequate renal function, defined as follows: |
| 3.1.8.1 | Serum creatinine must be ≤ 1.5 within 2 weeks prior to registration; |
| 3.1.8.2 | Creatinine clearance (CC) ≥ 60 ml/min within 2 weeks prior to registration determined by 24-hour collection or estimated by Cockcroft-Gault formula: |

\[
CCr \text{ male} = \frac{[140 - \text{age}] \times \text{wt in kg}}{([\text{Serum Cr mg/dl}] \times 72)}
\]
CCr female = 0.85 x (CrCl male)

3.1.9 Negative pregnancy test within 2 weeks prior to registration for women of childbearing potential;

3.1.10 Women of childbearing potential and male participants must agree to use a medically effective means of birth control throughout their participation in the treatment phase of the study (until at least 60 days following the last study treatment);

3.1.11 Patients participating in 0619 also are eligible for and are strongly encouraged to participate in RTOG 0514, the Head and Neck tissue banking protocol.

3.1.12 Must sign a study-specific informed consent prior to study entry, which includes mandatory submission of tissue for pathology central review and for patients with oropharyngeal carcinoma, mandatory submission of tissue for HPV analysis.

3.2 Conditions for Patient Ineligibility

3.2.1 Evidence of distant metastases or simultaneous primaries;

3.2.2 Prior invasive malignancy (except non-melanomatous skin cancer) unless disease free for a minimum of 3 years with the exception of cervical carcinoma in situ and adequately treated basal cell or squamous cell carcinoma of the skin or untreated/treated low-risk prostate cancer (defined as clinical or pathologic T1c, N0 M0, PSA <10, Gleason < 7, < 50% of the total cores positive for cancer);

3.2.3 Prior systemic chemotherapy for the study cancer; note that prior chemotherapy for a different cancer is allowable.

3.2.4 Prior radiotherapy to the head and neck area that would result in overlap of radiation therapy fields;

3.2.5 Major surgery within 3 weeks prior to registration or incompletely healed surgical incision at registration;

3.2.6 Severe, active co-morbidity, defined as follows:

3.2.6.1 Clinically significant cardiovascular event (e.g., myocardial infarction, superior vena cava syndrome [SVC], or New York Heart Association (NYHA) classification ≥ 2 (see Appendix III) or presence of cardiac disease that, in the opinion of the investigator, increases the risk of ventricular arrhythmia within 3 months prior to registration;

3.2.6.2 Unstable angina and/or congestive heart failure requiring hospitalization within 3 months prior to registration;

3.2.6.3 Transmural myocardial infarction within 3 months prior to registration;

3.2.6.4 History of arrhythmia (multifocal premature ventricular contractions [PVCs], bigeminy, trigeminy, ventricular tachycardia, or uncontrolled atrial fibrillation), which is symptomatic or requires treatment (CTCAE grade 3) or asymptomatic sustained ventricular tachycardia; patients with atrial fibrillation, controlled on medication, are eligible.

3.2.6.5 Previous history of QTc prolongation as a result from other medication that required discontinuation of that medication;

3.2.6.6 Congenital long QT syndrome or first degree relative with unexplained sudden death under 40 years of age;

3.2.6.7 Presence of left bundle branch block (LBBB);

3.2.6.8 (6/8/09) QTc with Bazett’s correction that is unmeasurable, or ≥ 480 msec on screening EKG; if a patient has QTc ≥ 480 msec on screening EKG, the screening EKG may be repeated twice (at least 24 hours apart). The average QTc from the three screening EKGs must be < 480 msec in order for the patient to be eligible for the study. Patients who are receiving a drug that has a risk of QTc prolongation (see Appendix VII) are excluded if QTc is ≥ 460 msec.

3.2.6.9 (6/8/09) Any concomitant medication that may cause QTc prolongation, induce Torsades de Pointes (see Appendix VII) or induce CYP3A4 function (see Section 9.2) drugs listed in Appendix VII that in the investigator’s opinion cannot be discontinued, are allowed, but must be monitored closely;

3.2.6.10 Hypertension not controlled by medical therapy (systolic blood pressure greater than 160 mm Hg or diastolic blood pressure greater than 100 mm Hg);

3.2.6.11 CTCAE, v. 3.0 grade 3-4 electrolyte abnormalities:

- Serum calcium (ionized or adjusted for albumin) < 7 mg/dl or > 12.5 mg/dl despite supplementation;
- Glucose < 40 mg/dl or > 250 mg/dl;
- Magnesium < 0.9 mg/dl or > 3 mg/dl despite supplementation;
- Potassium < 4 mmol/L or > 6 mmol/L despite supplementation;
- Sodium < 130 mmol/L or > 155 mmol/L
3.2.6.12 Patients with ≥ grade 1 CTCAE, v. 3.0 diarrhea (Increase of < 4 stools per day over baseline; mild increase in ostomy output compared to baseline);

3.2.6.13 Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration

3.2.6.14 Chronic Obstructive Pulmonary Disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy within 30 days prior to registration;

3.2.6.15 Hepatic insufficiency resulting in clinical jaundice and/or coagulation defects; note, however, that laboratory tests coagulation parameters are not required for entry into this protocol.

3.2.6.16 Acquired Immune Deficiency Syndrome (AIDS) based upon current CDC definition; note, however, that HIV testing is not required for entry into this protocol. The need to exclude patients with AIDS from this protocol is necessary because the treatments involved in this protocol may be significantly immunosuppressive. Protocol-specific requirements may also exclude immuno-compromised patients.

3.2.7 Pregnancy, breast feeding, or women of child-bearing potential and men who are sexually active and not willing/able to use medically acceptable forms of contraception; this exclusion is necessary because the treatment involved in this study may be significantly teratogenic.

3.2.8 Prior allergic reaction to cisplatin or vandetanib or derivatives similar to these drugs;

3.2.9 Patients who receive any investigational agents other than the study agents within 30 days prior to registration;

3.2.10 (6/8/09) Concomitant use of the known potent inducers of CYP3A4: rifampicin, phenytoin, carbamazepine, barbiturates, and St. John's Wort within 2 weeks prior to registration (see Section 9.2 for restrictions of these medications during the study).

4.0 PRETREATMENT EVALUATIONS/MANAGEMENT

Note: This section lists baseline evaluations/procedures required or recommended before the initiation of protocol treatment that do not affect eligibility (in addition to the required evaluations in Section 3.0).

4.1 Required Evaluations/Management (2/25/10)

4.1.1 Surgical evaluation and clearance within 4 weeks prior to the start of treatment so that the surgeon can certify that the patient may initiate postoperative radiation therapy (PORT) [i.e., healed wound, no fistulae, etc.];

4.1.2 Sites must submit tissue specimens for central review (see Section 10.2) within 2 weeks prior to start of treatment;

4.1.3 Dental evaluation with management according to the guidelines in Appendix V within 4 weeks prior to the start of treatment;

4.1.4 Medical oncology examination to evaluate medical contraindications within 4 weeks prior to the start of treatment;

4.1.5 (6/8/09) For patients randomized to Arm 2: A baseline EKG to be done post-study entry but pre-vandetanib administration. This baseline EKG is different from and in addition to the screening EKG done for eligibility.

Note: For the baseline EKG, investigators must do 3 consecutive EKGs (within 5-10 minutes of one another) prior to day 1 of vandetanib (5-10 minutes apart), and take the average. Exception: If the screening QTc (see Section 3.1.3.4) is obtained with 3 consecutive EKGs within 3 days before Day 1, then the screening QTc will be considered to be the baseline EKG, and repeat EKGs will not be necessary on Day 1.

4.2 Highly Recommended Evaluations/Management (6/8/09)

4.2.1 Baseline audiogram within 12 weeks prior to start of treatment;

4.2.2 Nutritional evaluation within 4 weeks prior to the start of treatment;

4.2.3 Prophylactic gastrostomy tube placement (if the patient is ≥ 10% below ideal body weight) is highly recommended but not required.

5.0 REGISTRATION PROCEDURES

Note: It is mandatory the treating physician determine the radiation therapy technique (3D-CRT vs. IMRT) to be used prior to the site registering the patient.

5.1 Pre-Registration Requirements for 3D-CRT Treatment Approach (6/8/09)

5.1.1 Only institutions that have met the technology requirements and that have provided the baseline physics information that are described in 3D-CRT Quality Assurance Guidelines may enter patients onto this study.
5.1.2 The new facility questionnaire (one per institution, available on the ATC web site at http://atc.wustl.edu) is to be sent to RTOG for review prior to entering any cases. Upon review and successful completion of a "Dry-Run" QA test, the ITC will notify both the registering institution and RTOG Headquarters that the institution has successfully completed this requirement. RTOG Headquarters will notify the institution when all requirements have been met and the institution is eligible to enter patients onto this study. Institutions that have previously enrolled patients on 3DCRT trials of this same disease site may enroll patients on this study without further credentialing.

5.2 Pre-Registration Requirements for IMRT Treatment Approach (6/8/09)

In order to utilize IMRT on this study, the institution must have met specific technology requirements and have provided baseline physics information. Instructions for completing these requirements or determining if they already have been met are available on the Radiological Physics Center (RPC) web site. Visit http://rpc.mdanderson.org/rpc and select “Credentialing” and “Credentialing Status Inquiry”.

5.2.1 An IMRT phantom study with the RPC must be successfully completed (if the institution has not previously met this IMRT credentialing requirement). Instructions for requesting and irradiating the phantom are available on the RPC web site at http://rpc.mdanderson.org/rpc; select “Credentialing” and “RTOG”. Upon review and successful completion of the phantom irradiation, the RPC will notify both the registering institution and RTOG Headquarters that the institution has completed this requirement. Subsequently, RTOG Headquarters will notify the institution that the site can enroll patients on the study.

5.2.2 The institution or investigator must complete a new IMRT Facility Questionnaire, send it to RTOG for review prior to entering any cases, and/or set up an SFTP account for digital data submission, both of which are available on the Image-Guided Center (ITC) web site at http://atc.wustl.edu. Upon review and successful completion of the “Dry-Run” QA test, the ITC will notify both the registering institution and RTOG Headquarters that the institution is eligible to enter patients onto this study. RTOG Headquarters will notify the institution when all requirements have been met and the institution is eligible to enter patients onto this study.

5.3 Regulatory Pre-Registration Requirements (6/8/09)

5.3.1 U.S. and Canadian institutions must fax copies of the documentation below to the CTSU Regulatory Office (215-569-0206), along with the completed CTSU-IRB/REB Certification Form, http://www.rtog.org/pdf_file2.html?pdf_document=CTSU-IRBCertifForm.pdf, prior to registration of the institution’s first case:
- IRB/REB approval letter;
- IRB/REB approved consent (English and native language versions*)
  *Note: Institutions must provide certification of consent translation to RTOG Headquarters.
- IRB/REB assurance number

5.3.2 Pre-Registration Requirements FOR CANADIAN INSTITUTIONS

5.3.2.1 Prior to clinical trial commencement, Canadian institutions must complete and fax to the CTSU Regulatory Office (215-569-0206) Health Canada’s Therapeutic Products Directorates’ Clinical Trial Site Information Form, Qualified Investigator Undertaking Form, and Research Ethics Board Attestation Form.

5.3.3 Pre-Registration Requirements FOR NON-CANADIAN INTERNATIONAL INSTITUTIONS

5.3.3.1 For institutions that do not have an approved LOI for this protocol:
International sites must receive written approval of submitted LOI forms from RTOG Headquarters prior to submitting documents to their local ethics committee for approval. See http://www.rtog.org/pdf_forms.html?members/forms=Intl_LOI_Form.doc

5.3.3.2 For institutions that have an approved LOI for this protocol:
All requirements indicated in your LOI Approval Notification must be fulfilled prior to enrolling patients to this study.

5.3.4 For the initial shipment of vandetanib (10/13/09)

5.3.4.1 U.S. and Canadian institutions:
All pre-registration requirements must be met before registering the first case. Institutions must electronically complete (versus hand write) a Study Agent Shipment Form (SASF) available on the RTOG web site, www.rtog.org (next to the protocol). U.S. and Canadian institutions must fax the SASF to the CTSU Regulatory Office (Fax 215-569-0206) as soon as the individual responsible for the study agent has been identified.
5.3.4.2 **Non-Canadian International Institutions:**
Please refer to your LOI Approval Notification. Your institution will be responsible for acquiring any drug noted in the protocol as commercially available and not provided for the study. Before drug can be provided your institution must comply with all pre-registration requirements and certifications and provide all necessary documentation listed in your LOI Approval Notification document. After receipt of written approval of submitted LOI forms from RTOG Headquarters, International institutions must electronically complete (versus hand write) a Study Agent Shipper Form (SASF) available on the RTOG web site, www.rtog.org, (next to the protocol) and submit the SASF and documentation of IRB approval to RTOG Headquarters (Fax 215-574-0300). This must be done prior to registration of the institution’s first case.

5.4 **Registration**

5.4.1 **Summary of Procedures (11/18/08)**

This study incorporates a two-step registration process.

5.4.1.1 **All patients** must consent to submission of tissue for central review; see Section 10.2 for details of submission. The institution must submit a tissue block to the RTOG Biospecimen Resource at UCSF (see Section 10.5 for shipping information). **All institutions will receive a 0.5 case credit for submission of tissue.**

5.4.1.2 Patients with oral cavity/hypopharyngeal or laryngeal cancer can then be registered and randomized. Steps 1 and 2 of registration/randomization entail online registration as detailed in Section 5.4.2.

5.4.1.3 **For patients with oropharyngeal carcinoma:** These patients also must consent to use of submitted tissue for HPV analysis. The site can complete Step 1 of registration, but the site will not be able to randomize the patient (Step 2 of registration) until the RTOG Biospecimen Resource processes 2 unstained sections from the tissue block submitted and HPV status is determined (see Section 10.3). The results of HPV analysis are expected in approximately 7-10 business days, and **RTOG Headquarters will inform the institution by e-mail that Step 2 of registration can be completed and these patients can be randomized.**

5.4.2 **General Online Registration Instructions**

Patients can be registered only after eligibility criteria are met.

Each individual user must have an RTOG user name and password to register patients on the RTOG web site. To get a user name and password:

- The investigator and research staff must have completed Human Subjects Training and been issued a certificate (Training is available via http://cme.cancer.gov/clinicaltrials/learning/humanparticipant-protections.asp).
- A representative from the institution must complete the Password Authorization Form at www.rtog.org/members/webreg.html (bottom right corner of the screen), and fax it to 215-923-1737. RTOG Headquarters requires 3-4 days to process requests and issue user names/passwords to institutions.

An institution can register the patient by logging onto the RTOG web site (http://www.rtog.org), going to “Data Center Login” and selecting the link for new patient registrations. The system triggers a program to verify that all regulatory requirements (OHRP assurance, IRB approval) have been met by the institution. The registration screens begin by asking for the date on which the eligibility checklist was completed, the identification of the person who completed the checklist, whether the patient was found to be eligible on the basis of the checklist, and the date the study-specific informed consent form was signed.

Once the system has verified that the patient is eligible and that the institution has met regulatory requirements, it assigns a patient-specific case number. The system then moves to a screen that confirms that the patient has been successfully enrolled. This screen can be printed so that the registering site will have a copy of the registration for the patient’s record. Two e-mails are generated and sent to the registering site: the Confirmation of Eligibility and the patient-specific calendar. The system creates a case file in the study’s database at the DMC (Data Management Center) and generates a data submission calendar listing all data forms, images, and reports and the dates on which they are due.
If the patient is ineligible or the institution has not met regulatory requirements, the system switches to a screen that includes a brief explanation for the failure to register the patient. This screen can be printed.

(10/13/09) Institutions can contact RTOG web support for assistance with web registration: websupport@acr-arrs.org.

In the event that the RTOG web registration site is not accessible, participating sites can register a patient by calling RTOG Headquarters, at (215) 574-3191, Monday through Friday, 8:30 a.m. to 5:00 p.m. ET. The registrar will ask for the site’s user name and password. This information is required to assure that mechanisms usually triggered by web registration (e.g., drug shipment, confirmation of registration, and patient-specific calendar) will occur.

6.0 RADIATION THERAPY

IMRT is permitted for this study. See pre-registration requirements for the IMRT treatment approach in Section 5.2.

(6/8/09) Protocol treatment must begin within 1 week after registration-step 2 (randomization). Patients randomized to Arm 2, radiation plus weekly cisplatin and vandetanib, must start vandetanib at least 14 calendar days prior to radiation.

6.1 Dose Specifications

6.1.1 Patients will be randomized post-operatively, and radiation therapy (RT) will begin within 8 weeks after surgery. Note: If there are wound complications after surgery, e.g., a major active fistula or wound dehiscence, and RT will be delayed, sites should document this on the appropriate case report form (see Section 12.1).

Once daily (2 Gy/day) RT is given to a total minimum dose of 58 Gy and maximum prescribed boost dose of 66 Gy to involved areas, over 5.5-6.5 weeks. If the first scheduled radiation day falls on a Thursday, Friday, weekend, or holiday, then RT should be deferred to the next business day (unless the patient is treated over the weekend/holiday) so that the patient receives at least three consecutive early RT fractions before a two-day non-work day interruption.

(6/8/09) For 3D-CRT, the prescribed dose should cover at least 95% of this volume. For IMRT planning, plan normalization should guarantee that 95% of the PTV is covered by the 58 Gy prescribed dose. Additionally, in order to avoid severe undertreatment, 98% of the PTV must receive a dose that is > 53.5 Gy. This number is 92% of the prescribed dose of 58 Gy.

For all treatment techniques, the maximum dose should not exceed 110% of the prescribed dose. However, if a boost to involved areas is used, the maximum dose can be increased to a value that is 10% higher than the value of the boost dose. This maximum dose is allowed to spill outside of the involved region into the 58 Gy region. See the table in Section 6.7 for a complete statement of the review criteria used to determine protocol compliance.

6.1.2 Primary Tumor Bed (6/8/09)

Final dose (using shrinking field technique): Minimum 58 Gy to resected regions. Boost to 60-66 Gy for high-risk factors. A simultaneous boost technique should be used for IMRT.

6.1.3 Neck Lymph Nodal Bed (6/8/09)

Final dose (using shrinking field technique): Minimum 58 Gy to resected regions. Boost to 62-66 Gy for high-risk factors. A simultaneous boost technique should be used for IMRT.

6.1.4 Contralateral and other non-dissected lymph node regions (Levels 2-5 [plus level 1 for oral cavity cancers], and for pharyngeal cancers, the retropharyngeal lymph node region): 50 Gy minimum dose.

6.2 Technical Factors

6.2.1 Photon beams of ≥ 4 MV and/or electron beams from 6-25 MeV are required.

6.2.2 Treatment distance must be ≥ 80 cm SAD for isocentric techniques.

6.2.3 IMRT: Megavoltage equipment capable of delivering intensity modulated beams using a step-and-shoot technique with a multileaf collimator or using dynamically moving leaves. Additionally, a binary multileaf collimator or tomotherapy can be used to modulate the beam.
Other techniques, e.g. physical compensators, are acceptable as long as dose specifications and constraints are satisfied.

6.3 Localization, Simulation, and Immobilization for 3D-CRT or IMRT (6/8/09)

6.3.1 Immobilization

Head and neck immobilization device(s) must be utilized. A thermoplastic head mask is strongly recommended. If the treatment volume includes the lower neck, immobilization should include the shoulders as well (e.g., combination head and shoulder mask is recommended). If the target volume includes oral tongue, a form of tongue immobilization also is recommended.

6.3.2 Treatment Planning CT Scan

A treatment planning CT scan is mandatory. CT scan thickness should be 0.5 cm or smaller (preferably 0.3 cm) through the treatment volume. Intravenous contrast is recommended in patients who do not have a contraindication to it. MRI and/or pre-operative PET scans with image fusion also may be helpful in treatment planning, particularly if these scans can be performed with the same immobilization device as was used for the planning CT scan.

6.4 Treatment Planning/Target Volumes

The use of IMRT is permitted after completing the IMRT credential process (see Section 5.2).

6.4.1 Volume Definitions

For IMRT, the treatment plan used for each patient will be based on an analysis of the volumetric dose, including dose-volume histogram (DVH) analyses of the PTV (CTV with a 5 mm margin) and critical normal structures. An “inverse” planning technique that employs computerized optimization should be used.

Gross Tumor Volume (GTV): Strictly speaking, there should be no formal GTV as a region of interest as eligible patients for this post-operative trial have undergone complete surgical resection of all gross disease.

6.4.2 (2/25/10) Clinical Target Volume (CTV): This is the region of interest that the treating physician deems at risk for occult or microscopic residual disease involvement following complete surgical resection. A high-risk CTV1 and a lower risk CTV2 may be designated per physician discretion. In cases in which the contralateral neck has not been resected, the CTV1 and CTV2 should include a 5 mm margin around the areas of high and low risk regions.

6.4.3 PTV: This includes the CTV plus a margin to compensate for various uncertainties, such as systematic treatment setup variables, organ motion, and organ displacement (e.g., laryngeal motion). A minimum of 5 mm around the CTV is recommended in all directions, except where the CTV is immediately adjacent to the spinal cord or brainstem (in which case, the margin from CTV to PTV may be as small as 3 mm). The recommended margin from CTV to PTV where the spinal cord or brainstem is not a concern is 10 mm (1.0 cm).

6.5 Critical Structures

6.5.1 Spinal Cord

The dose to any point within the spinal cord should not exceed 48 Gy to any volume larger than 0.03 cc (approximately equivalent to a 3x3x3 mm cube). Spinal cord dose must be clearly documented. For non-IMRT plans, spinal cord blocks should be inserted into all fields at a dose of 40-44 Gy to achieve this goal.

6.5.2 Brachial plexus

The dose to the brachial plexus must be carefully reviewed in patients with level IV node(s). No more than 5% of the volume of the brachial plexus can receive > 60 Gy, and none can receive > 66 Gy.

6.5.3 Parotid glands

When using IMRT, the objective is to limit the mean dose to at least one gland to ≤ 26 Gy; alternatively at least 20 cc of the combined volume of both parotid glands to < 20 Gy or at least 50% of one gland to < 30 Gy.

6.5.4 Glottic larynx

In patients with resected oropharyngeal carcinoma without extension to the larynx, placing the isocenter just above the arytenoids and irradiating the lower neck with an anterior matching field with larynx block can minimize the dose to the glottic larynx. Alternatively, if the CTV1 and CTV2 are to be encompassed in a single port, it is recommended that the dose to the larynx should be kept < 45 Gy whenever feasible.

6.5.5 Unspecified Tissue Outside the Targets

No more than 5% of unspecified tissue can receive greater than 58 Gy and no more than 1% or 1cc of unspecified tissue can receive 64 Gy or more. When a boost is used to increase the dose to high risk regions to as much as 66 Gy, these numbers can be increased. In this case,
no more than 5% of the unspecified dose should exceed the level of the boost dose, and no more than 1% or 1 cc should exceed the boost dose value plus 10%.

### 6.6 Documentation Requirements

#### 6.6.1 Portal Image of Each Field of 3-D Radiotherapy or Orthogonal Images That Localize the Isocenter Placement of IMRT

Portal image of each field of 3-D radiotherapy or orthogonal images that localize the isocenter placement of IMRT must be obtained on the first day of therapy but should not be submitted. However, this information should be archived by the submitting institution so that it can be made available for possible future review.

#### 6.6.2 Weekly Verification or Orthogonal Images

Weekly verification or orthogonal images are required to be taken, but not submitted. This information should be archived by the submitting institution so that it can be made available for possible future review. This verification information also can be gathered with cone-beam CT or other CT devices that are present in the treatment room.

#### 6.6.3 Isodose Plans

Isodose plans for 3-D radiotherapy and IMRT and DVHs of GTV, CTVs, and critical normal structures must be submitted digitally to ITC.

### 6.7 Compliance Criteria

Treatment breaks must be clearly indicated in the treatment record along with the reason(s) for the treatment break(s). Treatment breaks, if necessary, should ideally not exceed five treatment days at a time and ten treatment days total. Treatment breaks should be allowed only for resolution of severe acute toxicity and/or for intercurrent illness and not for social or logistical reasons. Any treatment break(s) exceeding two treatment days for reasons other than toxicity/illness will be considered a protocol deviation.

### 6.8 R.T. Quality Assurance Reviews

The Principal Investigator/Radiation Oncologist, David Raben, M.D., will remotely perform RT Quality Assurance Reviews. These reviews will be ongoing and performed remotely. RT Quality Assurance reviews will be facilitated by RTOG RTQA.

### 6.9 Radiation Therapy Adverse Events

This study will utilize the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 for grading of all adverse events. A copy of the CTCAE v3.0 can be downloaded from the CTEP home page (http://ctep.info.nih.gov). The CTEP home page also can be accessed from the RTOG web page at http://www.rtog.org/regulatory/regs.html. All appropriate treatment areas should have access to a copy of the CTCAE v3.0.

Grade 3-4 therapy-induced mucositis and/or dysphagia, which are enhanced by cisplatin, are expected to develop in about two thirds of patients. Nutritional evaluation prior to the initiation of therapy for a prophylactic gastrostomy (PEG) tube placement is highly recommended. Placement of a feeding tube should be recorded on the appropriate case report form (see Section 12.1), as should use of a feeding tube during and after treatment (e.g., greater than or less than 50% of nutrition by tube). Other common radiation adverse events include: fatigue, weight loss, regional alopecia, xerostomia, hoarseness, transient ear discomfort, dysgeusia, and skin erythema and desquamation within the treatment fields.
Less common long-term treatment adverse events include: hypothyroidism, loss of hearing, chronic swallowing dysfunction requiring permanent feeding tube, and cervical fibrosis. Much less common radiation adverse events include: mandibular osteoradionecrosis (< 5% incidence with attention to the dental recommendations provided in Appendix V), and cervical myelopathy (< 1% with restriction of spinal cord dose to ≤ 45 Gy).

6.10 Radiation Adverse Event Reporting
See AdEERS Expedited Reporting Requirements in Section 7.7.

7.0 DRUG THERAPY
Institutional participation in chemotherapy studies must be in accordance with the Medical Oncology Quality Control guidelines stated in the RTOG Procedures Manual.

(6/8/09) Protocol treatment must begin within 1 week after registration-step 2 (randomization). Patients randomized to Arm 2, radiation plus weekly cisplatin and vandetanib, must start vandetanib at least 14 calendar days prior to radiation.

7.1 Treatment

7.1.1 Arm 1: Radiation Plus Cisplatin, Every 3 Weeks for 3 Cycles (2/25/10)
Patients will receive cisplatin at 100 mg/m² intravenously on days 1, 22, and 43 of the treatment course. Use actual body weight for dose calculation if BSA is ≤ 2.0. If the BSA is > 2.0, then recalculate using the ideal weight, and use the recalculated BSA to determine the dose with no cap or use a cap with a BSA of 2.0, whichever is higher. Use the formulas below:

Males (kg): 51.65 + (1.85x (height [inches] - 60))
Females (kg: 48.67 + (1.85x (height [inches] - 60))

7.1.1.1 Institutional guidelines for highly emetogenic regimens should be followed for cisplatin administration. Suggested regimens include:

- Premedication for acute nausea with a 5-HT3 antagonist (such as granisetron, 1mg i.v.; ondansetron, up to 32 mg i.v.; or palonosetron). Aprepitant (125 mg p.o. before cisplatin and 80 mg p.o. daily for two additional days), with a corticosteroid such as dexamethasone (up to 12 mg before cisplatin and up to 8 mg [4 mg bid] for three days following cisplatin).

- Breakthrough and delayed nausea and vomiting may be managed at the discretion of the treating physician. Suggested regimens include:
  - Unless palonosetron was given, a 5HT3 antagonist (e.g., granisetron, or ondansetron) may be given for 3 days.
  - Alternatively, delayed emesis also may be managed by the addition of dexamethasone 8 mg bid x 2 days, followed by dexamethasone 4 mg bid x 2 days, beginning day after chemotherapy; oral metoclopramide 0.5 mg/kg (usually 20-40 mg) in addition qid x 2-4 days; 5HT3 antagonist (e.g., granisetron, ondansetron) may be given for 3 days, only if palonosetron was not given prior to chemotherapy. Adjust dexamethasone downward if aprepitant was given in the preceding four days.

7.1.1.2 Patients must receive vigorous hydration and diuresis. A suggested regimen is prehydration with a 1 liter of D5N S over 2-4 hours and mannitol 12.5 g i.v. bolus immediately prior to cisplatin. Then cisplatin 100 mg/m² in 500 ml NS is administered over 1-2 hours with an additional 1 to 1.5 liters of fluid given post-hydration. Any pre-existing dehydration must be corrected prior to cisplatin administration.

Overnight hospitalization for hydration after cisplatin is strongly encouraged if it is allowed by the patient's insurance company. Additional i.v. hydration and BUN/creatinine check should be strongly considered later in the week after cisplatin administration, in order to prevent dehydration and severe fluid/electrolyte imbalance.

7.1.2 Dose Modifications for Arm 1, Cisplatin Days 22 and/or 43

7.1.2.1 Neutropenia: If on the day of scheduled treatment with cisplatin the absolute neutrophil count (ANC) is < 1200, hold treatment until ANC ≥ 1200, then treat at 100% dose. Neutropenic fever will require permanent 25% dose reduction.

7.1.2.2 Thrombocytopenia: If on the day of scheduled treatment with cisplatin the platelet count is < 75,000, hold treatment until platelets are ≥ 75,000, then treat at 100% dose. Thrombocytopenia that results in bleeding will require a permanent 25% dose reduction.
7.1.2.3 Neurotoxicity: If any signs of grade 3 or greater neurotoxicity occur, discontinue cisplatin. Continue radiation therapy.

7.1.2.4 Nephrotoxicity: Cisplatin should be administered on the scheduled day of treatment using the following guidelines:

Note: If creatinine is > 1.2 mg/dl, clearance must be done in order to make dose adjustment. If the calculated nomogram is 50 mL/min or above, a 24-hour urine collection is not needed, but if the nomogram calculation is less than 50 mL/min, a 24-hour urine collection is mandated.

The Cockcroft-Gault formula should be used for estimated CrCl. The table below is to be followed for those patients who have actual creatinine clearance measured by 24-hour urine collection.

<table>
<thead>
<tr>
<th>Creatinine Clearance</th>
<th>Cisplatin Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 50 ml/min.</td>
<td>100 mg/m²</td>
</tr>
<tr>
<td>40-50 ml/min.</td>
<td>50 mg/m²</td>
</tr>
<tr>
<td>&lt; 40 ml/min.</td>
<td>Discontinue and notify Dr. Wong</td>
</tr>
</tbody>
</table>

7.1.2.5 Other Adverse Events:
- **Mucositis**: Grade 4 will require a 25% dose reduction (see Section 6.9).
- **Ototoxicity**: For new clinical hearing loss not requiring a hearing aid or for tinnitus that interferes with activities of daily living, treat at 50% dose reduction. For hearing loss requiring a hearing aid, discontinue cisplatin. Continue radiation therapy.
- If the physician is unsure about the severity of the hearing loss, an audiogram is encouraged.

7.1.2.6 If the second or third doses of cisplatin are delayed more than 14 days because of hematologic toxicity, that dose will be omitted. If radiation is completed before cycle 3 is due for any reason, cycle 3 should still be given up to 2 weeks after completion of radiation therapy.

7.1.3 Arm 2: Radiation Plus Weekly Cisplatin and Vandetanib
7.1.3.1 Daily Vandetanib

Vandetanib will begin 14 days prior to the start of radiation therapy (and cisplatin) and no earlier than 3 weeks after surgery. Arm 2 patients will receive vandetanib alone during weeks 1 and 2. During weeks 3-8, patients will receive vandetanib concurrently with RT and cisplatin.

(10/13/09) Institutions should dispense the entire 8 week supply of vandetanib to the patient in the original bottle shipped by Biologics, Inc. (see Section 7.3.9.1). In addition, institutions should document on the Treatment Summary Form (TF) the amount of vandetanib dispensed and the amount of vandetanib returned unused by the patient. Patients will document daily vandetanib on the pill diary (DP), which will be collected by the institution and submitted to RTOG (see Section 12.1).

(6/8/09) **Baseline EKG**: To be done post-study entry but pre-vandetanib administration. Note: This baseline EKG is different from and in addition to the screening EKG done for eligibility. Investigators must do 3 consecutive EKGs prior to day 1 of vandetanib (5-10 minutes apart), and take the average. If the screening QTc (see Section 3.1.3.4) is obtained with 3 consecutive EKGs within 3 days before Day 1, then the screening QTc will be considered to be the baseline EKG, and repeat EKGs will not be necessary on Day 1.

(6/8/09) **Note**: If the patient is receiving one of the medications that has a risk of QTc prolongation prior to study entry (see Appendix VII) [but where the risk of Torsades is not clear] and the medication(s) cannot be discontinued before study entry, then the screening QTc must be < 460 msec, and an additional EKG must be obtained 4-8 hours after the first dose of vandetanib.

Patients will take one 100 mg vandetanib pill each day on an empty stomach (e.g., one hour prior to or two hours after a meal) for a total of 8 weeks, including weekends, holidays,
and on days on which radiation therapy is being held. Vandetanib will be taken on days on which make-up radiation therapy is administered.

7.1.3.2 Weekly Cisplatin
Patients will receive cisplatin at 30 mg/m² intravenously weekly for 6 weeks beginning on day 1 of RT. Cisplatin will start within 24 hours from the start of radiotherapy and be administered on Monday, Tuesday, or Wednesday (and on the same day each week). For patients starting radiotherapy on a Thursday or Friday, cisplatin should start on the following week.

Patients must be adequately hydrated prior to receiving cisplatin. The cisplatin should be infused over 1 hour. It is highly recommended that all patients receive 1 liter of sodium chloride 0.9% over 2 hours prior to treatment. Attention should be given to K+ and Mg++ levels with replacement as needed.

Institutional guidelines for emetogenic regimens should be followed for cisplatin administration. See Section 7.1.1.1 for suggested regimens.

7.1.4 Dose Modifications for Arm 2, Weekly Cisplatin

7.1.4.1 Neutropenia: If on the day of scheduled weekly cisplatin the absolute neutrophil count (ANC) is < 1000/mm³, then hold dose for the week. Resume weekly cisplatin when ANC ≥ 1000/mm³ at 100% of dose. If ANC < 1000/mm³ continues > 7 days, then decrease cisplatin to 20 mg/m² and resume when ANC recovers to ≥ 1000/mm³. If neutropenic fever occurs, decrease cisplatin to 20mg/m² and resume when ANC recovers to ≥ 1000/mm³. For recurrent grade 3 neutropenia or neutropenic fever, discontinue cisplatin.

7.1.4.2 Thrombocytopenia: If on the day of scheduled weekly cisplatin the platelet count is < 75,000, then hold dose for the week and resume therapy when platelet count is ≥ 75,000. If platelet < 75,000 persists for more than one week, then decrease cisplatin to 20mg/m² and resume when platelet count is ≥ 75,000. For recurrent ≥ grade 3 thrombocytopenia, discontinue cisplatin.

7.1.4.3 Neurotoxicity: For grade 2 neurotoxicity, decrease cisplatin to 20 mg/m². For grade 3-4 neurotoxicity, discontinue cisplatin. For recurrent ≥ grade 2 neurotoxicity, discontinue cisplatin.

7.1.4.4 Renal: For ≤ grade 1 adverse events (AEs), maintain therapy. For grade 2 AEs, decrease cisplatin to 20mg/m². For ≥ grade 3 AEs, hold cisplatin; resume cisplatin at 20mg/m² when ≤ grade 1. For recurrent ≥ grade 3 asthenia, discontinue cisplatin.

7.1.4.5 Asthenia: For ≥ grade 3 fatigue, decrease cisplatin to 20mg/m².

7.1.4.6 Nausea/Vomiting: For ≤ grade 2 nausea/vomiting with maximal medical management, maintain therapy. For ≥ grade 3 nausea/vomiting with maximal medical management, hold cisplatin until ≤ grade 2.

7.1.4.7 Mucositis in radiation field: For ≤ grade 3 mucositis, maintain therapy. For grade 4 mucositis, hold cisplatin until ≤ grade 3.

7.1.4.8 Rash in radiation field: For ≤ grade 3 rash, maintain therapy. For grade 4 rash, hold cisplatin until ≤ grade 3.

7.1.4.9 Other non-hematologic Grade 4 Adverse Events: Hold cisplatin until ≤ grade 1.

7.1.4.10 If cisplatin is delayed more than 21 days because of hematologic or renal adverse events, discontinue cisplatin.

7.2 Cisplatin
Refer to package insert for additional information.

7.2.1 Formulation: Each vial contains 10 mg of DDP, 19 mg of sodium chloride, 100 mg of mannitol, and hydrochloric acid for pH adjustment. One vial is reconstituted with 10 ml of sterile water. The pH range will be 3.5 to 4.5. Cisplatin injection also is available from the manufacturer in aqueous solution, each ml containing 1 mg cisplatin and 9 mg NaCl and HCL or NaOH to adjust pH. The lyophilized formulation of cisplatin is not commercially available in the U.S.

7.2.2 Mechanism of Action: The mechanism of action of DDP has not been clearly elucidated. However, preliminary 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.

7.2.3 Preparation: Reconstituted solution of cisplatin is stable for 20 hours when stored at 27°C and should be protected from light if not used within 6 hours.
7.2.4 **Administration:** Intravenous.

7.2.5 **Adverse Events**

The following adverse events are anticipated:

- **Hematologic:** Myelosuppression, often with delayed erythrosuppression; rarely, acute leukemia;
- **Gastrointestinal:** Nausea, vomiting, anorexia, loss of taste;
- **Dermatologic:** Alopecia;
- **Renal:** Elevation of BUN, creatinine and impairment of endogenous creatinine clearance, as well as renal tubular damage which appears to be transient; hyperuricemia; much more severe and prolonged adverse events have been observed in patients with abnormal or obstructed urinary excretory tracts;
- **Hepatic:** Hypomagnesemia, hypokalemia, hypocalcemia,
- **Neurologic:** Restlessness; involuntary movements; loss of coordination; seizures; peripheral neuropathy;
- **Allergic:** Flushing, bronchoconstriction, tachycardia, hypotension;
- **Other:** Ototoxicity (with hearing loss which initially is in the high-frequency range, as well as tinnitus); muscle cramps; weakness.

7.2.6 **Storage:** Intact vials of the dry powder and the aqueous injection should be stored at room temperature (15-25°C) and protected from light; the vials and injection should not be refrigerated. Following initial entry, cisplatin aqueous solution, provided in a multi-use vial, is stable for 28 days protected from light or for 7 days under fluorescent room light.

7.2.7 **Supply:** Commercially available

7.3 **Vandetanib** (ZD6474) [Zactima™]

7.3.1 **Formulation**

Vandetanib is an orally bioavailable receptor tyrosine kinase (RTK) inhibitor that, in isolated enzyme assays, potently inhibits vascular endothelial growth factor receptor-2 (VEGFR-2) tyrosine kinase activity (IC50 = 40 nM), and shows additional inhibitory activity at sub-micromolar concentrations against REarranged during Transfection (RET) receptor tyrosine kinase (inhibitory concentration [IC50] = 100 nM), Flt-4 (VEGF receptor-3: IC50 = 110 nM) and EGF receptor (IC50 = 500 nM) tyrosine kinases. A copy of the vandetanib Investigator Brochure is available on the RTOG web site at [http://www.rtog.org/investbrochure.html](http://www.rtog.org/investbrochure.html). Vandetanib consists of white film-coated tablets supplied in 100 mg.

7.3.2 **Labeling**

Labeling of the investigational product will be performed in accordance with Good Manufacturing Practices (GMP). AstraZeneca or a company acting on their behalf will pack tablets into high-density polyethylene (HDPE) bottles with child-resistant tamper-evident closures. Each bottle will be labeled with the statement: "Caution: New Drug - Limited by Federal (or USA) Law to Investigational Use". Instructions stating that the tablets are to be taken orally “as directed by your doctor” will be included. Information on the label will indicate the identity and quantity of tablets and storage conditions. Additional subject information will be identified as dictated by the protocol; it may be necessary for information to be recorded on the label by the investigator at the time the bottle is dispensed.

7.3.3 **Storage**

All investigational products must be kept in a secure place under appropriate storage conditions. A description of the appropriate storage and shipment conditions is specified on the investigational product label and investigator brochure. The stored study drug supplies must be accessible to authorized staff only. The storage area must also have adequate control of temperature in order to maintain stability and potency of study drug supplies. The tablets should be stored in the original pack until use. For further information, investigators should refer to the investigational product label.

7.3.4 **Route of Administration**

Tablets may be taken orally by mouth or by gastric tube.

7.3.5 **Preparation**

Vandetanib tablets (100 mg) contain ZD6474, calcium hydrogen phosphate, microcrystalline cellulose, sodium starch glycollate, povidone, sodium lauryl sulphate and magnesium stearate with a film coating containing methylhydroxypropylcellulose, polyethylene glycol 300 and titanium dioxide.
7.3.6 **Pharmacokinetics: Dose and Time-Dependencies**
On once daily dosing, the time to attain steady state exposure to Vandetanib is long and is achieved from about 6 weeks onwards. In order to optimize serum drug levels during radiation, vandetanib is started before the start of radiation.

7.3.7 **Adverse Events** (6/8/09)
- Pulmonary: Cough, dyspnea, pharyngolaryngeal pain, epistaxis, dysphonia, hiccups, respiratory alkalosis, rhinorrhea, pulmonary embolism, and pulmonary artery thrombosis;
- Gastrointestinal: Diarrhea, nausea, vomiting, constipation, abdominal pain, upper abdominal pain, abdominal discomfort, abdominal distention, flatulence, dry mouth, dry lip, mouth ulceration, dyspepsia, dysphagia, gastroesophageal, stomatitis, aphthous stomatitis, acquired esophageal stenosis, and gingival bleeding;
- Dermatologic: Rash, acne, macular papular rash, dry skin, night sweats, acneiform dermatitis, exfoliative dermatitis, contusion, rash photosensitivity, photosensitivity reaction, desquamation, erythema, erythematous rash, macular rash, pruritic rash, pustular rash, follicular rash, skin eruption, hyperhidrosis, nail discoloration, skin ulcer, urticaria, and alopecia;
- Cardiac: QTc prolongation, chest pain, chest tightness, heart failure;
- Vascular: Hypertension, peripheral edema, pulmonary thrombosis and deep venous thrombosis and 1 instance of pulmonary hemorrhage after cavitation have been observed, but it is unclear whether these may be related to vandetanib or instead reflect the underlying cancer or comorbid conditions.
- Renal: Proteinuria and hematuria;
- Neurological: Headache, dizziness, dysesthesia, reversible posterior leukoencephalopathy;
- Psychiatric: Mood disorders (anxiety, depression, insomnia); it is possible that these events are not direct effects of vandetanib but rather are secondary to symptoms of cancer or to other effects of vandetanib (e.g., rash, etc.).
- Other: Neutropenia, thrombocytopenia, hypokalemia, joint/muscle pain, abnormal gait, mucosal inflammation, fever, rigors, fatigue/lethargy/asthenia.

7.3.8 **Supply**
AstraZeneca will supply Zactima™ free of charge to patients on study.

7.3.9 **Drug Ordering and Accountability** (6/8/09)
**U.S. and Canadian institutions** must submit the Study Agent Shipment Form (SASF) [available on the RTOG web site, www.rtog.org, to the CTSU Regulatory Office (Fax 215-569-0206) as soon as the individual responsible for the study agent has been identified.

7.3.9.1 **Non-Canadian International Institutions** (6/8/09)
Please refer to your LOI Approval Notification. Your institution will be responsible for acquiring any drug noted in the protocol as commercially available and not provided for the study. Before drug can be provided your institution must comply with all pre-registration requirements and certifications and provide all necessary documentation listed in your LOI Approval Notification document.

(10/13/09) The drug supply will not be shipped by Biologics, Inc. until the patient has been registered to the vandetanib arm (Arm 2) of the study. Biologics, Inc. will ship the patient-specific, complete 8-week supply of vandetanib (1 bottle) the same day for orders received prior to 4:00 p.m. EST, Monday through Friday. Orders received after 4:00 p.m. EST, Monday through Friday will be processed the next business morning. All U.S. shipments are sent via Federal Express, **Second Day Delivery**. All international shipments are sent via Federal Express, **International Priority**. Upon notification of a new patient registration, Biologics places an outbound call to the site contact, confirming that their shipment is being processed and providing the courier, date and time of anticipated delivery. The Biologics distribution team monitors packages throughout the duration of transit via the FedEx web site and FedEx One Call Solution (live support). Real-time monitoring enables the Biologics distribution team to mitigate potential delivery delays (e.g., misrouted packages). Each institution should contact Biologics, Inc. for shipment tracking information and anticipated delivery dates or if a shipment has not been received by the expected date.

(10/13/09) Additional questions about supply, shipment tracking, and delivery should be directed to:
Drug accountability records must be maintained at all sites according to good clinical practices and NCI guidelines. The investigator or designated study personnel are responsible for maintaining accurate dispensing records of the study drug. All study drug must be accounted for, including study drug accidentally or deliberately destroyed. All discrepancies between amounts of study drug dispensed and amounts returned must be documented. Under no circumstances will the investigator allow the investigational drug to be used other than as directed by the protocol without prior AstraZeneca approval. If appropriate, drug storage, drug dispensing, and drug accountability may be delegated to the pharmacy section of the investigative site.

Opened vials must be disposed of at the site as chemotherapy or biohazardous waste according to the institution's policy for drug destruction. At the completion of the study, all unused drugs will be destroyed at the site according to the institution's policy for drug destruction. It is the responsibility of the Investigator to ensure that a current record of investigational product disposition is maintained at each study site where investigational product is inventoried and disposed, including dates and quantities.

### 7.4 Vandetanib Dose

#### 7.4.1

There will be no dose reduction for vandetanib. In all cases in which the dose of study treatment has been reduced/modified or the patient withdrawn due to unusual or unusually severe toxicity considered related to study treatment, the investigator must contact and inform either the Principal Investigator, Dr. Raben, or the Medical Oncology Co-Chair, Dr. Wong.

For guidance on the management of QTc prolongation, see Section 7.4.3. For all other toxicities, see Section 7.4.4.

#### 7.4.3 Management of QTc prolongation

Patients will have EKGs performed while receiving vandetanib to monitor QTc interval (using Bazett's correction) as outlined in Appendix II. See the flowchart below detailing management of QTc prolongation:

```
| QTc ≥ 550 msec OR Δ in baseline of ≥ 100 msec | Yes | Withhold study drug. Follow for resolution of QTc prolongation. |
| QTc ≥ 500 msec and < 550 msec OR Δ QTc from baseline ≥ 60 msec but < 100 msec (to ≥ 480 msec) | No | Continue study drug |
| Continue study drug. Repeat ECG in triplicate within 48 hours | Yes | Repeat EKG |
| QTc ≥ 500 msec and < 550 msec OR Δ QTc from baseline ≥ 60 msec but < 100 msec (to ≥ 480 msec) | No | Continue study drug |
| | Yes | Withhold study drug. Follow for resolution of QTc prolongation. |
```
7.4.3.1 For this study, QTc prolongation is defined as:
- A single QTc value of ≥ 550 msec or an increase of ≥ 100 msec from baseline;
- Two consecutive EKG measurements, within 48 hours of one another, in which either of the following criteria are met for both QTc values (the second being the mean of 3 consecutive EKGs):
  - A QTc interval ≥ 500 msec but < 550 msec
  - An increase of ≥ 60 msec, but < 100 msec, from baseline QTc to a QTc value ≥ 480 msec.

The baseline will be the average of the screening and Day 1 pre-dose QTc values. Electrolyte supplementation with regular laboratory monitoring should be used, when appropriate, to maintain electrolytes within normal limits and prevent an increased risk of QTc prolongation.

7.4.3.2 Treatment Modification for QTc Prolongation During Vandetanib

See flowchart in Section 7.4.3 and table in Section 7.4.4, under “QTc Value”.

7.4.4 Treatment Modification for Vandetanib-Related Adverse Events

<table>
<thead>
<tr>
<th>CTCAE, v. 3.0 Term</th>
<th>CTCAE Grade/Definition</th>
<th>Action to Be Taken</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pruritus/itching</td>
<td>Grade 1: Mild or localized</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Grade 2: Intense or widespread</td>
<td>Immediate symptomatic treatment</td>
</tr>
<tr>
<td></td>
<td>Grade 3: Intense or widespread and interfering with ADL</td>
<td>Withhold vandetanib until recovery to ≤ grade 1; vandetanib should be withheld with each occurrence.</td>
</tr>
<tr>
<td>Rash/desquamation</td>
<td>Grade 1: Macular or papular eruption or erythema without associated symptoms</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Grade 2: Macular or papular eruption or erythema with pruritus or other associated symptoms; localized desquamation or other lesions covering &lt; 50% of body surface area (BSA)</td>
<td>Immediate symptomatic treatment</td>
</tr>
<tr>
<td></td>
<td>Grade 3: Severe, generalized erythroderma or macular, papular or vesicular eruption; desquamation covering ≥ 50% BSA</td>
<td>Withhold vandetanib until recovery to ≤ grade 1; if vandetanib must be withheld for &gt; 3 wks, discontinue vandetanib</td>
</tr>
<tr>
<td></td>
<td>Grade 4: Generalized, exfoliative, ulcerative, or bullous dermatitis</td>
<td>Vandetanib should be withheld with each occurrence.</td>
</tr>
<tr>
<td>Rash/acne/acneiform</td>
<td>Grade 1: Intervention not indicated</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Grade 2: Intervention indicated</td>
<td>Immediate symptomatic treatment</td>
</tr>
<tr>
<td></td>
<td>Grade 3: Associated with pain, disfigurement, ulceration, or desquamation</td>
<td>Hold vandetanib until recovery to ≤ grade 1; if vandetanib must be withheld for &gt; 3 wks, discontinue vandetanib. If recurs, discontinue vandetanib.</td>
</tr>
<tr>
<td>CTCAE, v. 3.0 Term</td>
<td>CTCAE Grade/Definition</td>
<td>Action to be Taken</td>
</tr>
<tr>
<td>-------------------</td>
<td>------------------------</td>
<td>--------------------</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Grade 1: Asymptomatic, transient (&lt; 24 hrs.) increase by &gt;20 mmHg (diastolic) or to &gt;150/100 if previously WNL; intervention not indicated Pediatric: Asymptomatic, transient (&lt; 24 hrs.) BP increase &gt;ULN; intervention not indicated</td>
<td>Maintain vandetanib; no antihypertensive therapy; standard BP monitoring; consider diuretics</td>
</tr>
<tr>
<td></td>
<td>Grade 2: Recurrent or persistent (≥ 24 hrs.) or symptomatic increase by &gt;20 mmHg (diastolic) or to &gt;150/100 if previously WNL; monotherapy may be indicated Pediatric: Recurrent or persistent (≥ 24 hrs.) BP &gt;ULN; monotherapy may be indicated</td>
<td>Maintain vandetanib; initiate beta blocker or calcium channel blocker and/or angiotensin converting enzyme inhibitor or vasodilator and/or increase doses or number of medications until BP controlled or at maximum dose. Increase frequency of BP monitoring until stabilized, e.g., every 48 hrs. If partial or no control and BP still grade 3 for 24-48 hrs., <em>hold vandetanib and add additional drugs</em> increasing until hypertension controlled; monitor for hypotension; <strong>Restart vandetanib if hypertension is controlled.</strong></td>
</tr>
<tr>
<td></td>
<td>Grade 3: Requiring more than one drug or more intensive therapy than previously</td>
<td>Start immediate therapy with 2 drug combination including at least a calcium channel blocker; escalate doses to achieve optimal control of BP, up to the maximum dose. If partial or no BP control, add additional drugs up to 4; increase to optimal or maximum doses of all drugs; Increased frequency of BP monitoring until stabilized, e.g., every 48 hours; supervised by healthcare professional. <strong>Hold vandetanib;</strong> if control of BP in the mild range, restart vandetanib. If blood pressure cannot be stabilized with increased antihypertensive medication, <strong>discontinue vandetanib and do not resume until blood pressure is controlled to baseline level.</strong> <strong>Stop vandetanib if hypertension is symptomatic; hospitalize patient for management of BP.</strong></td>
</tr>
<tr>
<td>Grade 4: Life-threatening consequences (e.g., hypertensive crisis) Pediatric: Same as adult</td>
<td>Optimal management with intensive support IV in ICU; hospitalize patient for management; <strong>discontinue vandetanib;</strong> monitor closely for hypotension</td>
<td></td>
</tr>
</tbody>
</table>

**Hypertension:**
- If patients require a delay of > 2 weeks for management of hypertension, discontinue protocol treatment.
- If patients require > 2 dose reductions discontinue protocol treatment.
- Patients may have up to 2 drugs for management of hypertension prior to resuming vandetanib.
- 24-48 hours should elapse between modifications of hypertensive therapy.
<table>
<thead>
<tr>
<th>CTCAE, v. 3.0 Term</th>
<th>CTCAE Grade/Definition</th>
<th>Action to be Taken</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mucositis/stomatitis</strong> (clinical exam)</td>
<td>Grade 1: Erythema of the mucosa</td>
<td>Maintain vandetanib</td>
</tr>
<tr>
<td></td>
<td>Grade 2: Patchy ulcerations or pseudomembranes</td>
<td>Maintain vandetanib</td>
</tr>
<tr>
<td></td>
<td>Grade 3: Confluent ulcerations or pseudomembranes; bleeding with minor trauma</td>
<td>Maintain vandetanib</td>
</tr>
<tr>
<td></td>
<td>Grade 4: Tissue necrosis; significant spontaneous bleeding; life-threatening consequences</td>
<td>Discontinue vandetanib.</td>
</tr>
<tr>
<td><strong>Nausea</strong> <strong>Nausea (Continued)</strong></td>
<td>Grade 1: Loss of appetite without alteration in eating habits</td>
<td>Maintain vandetanib; treat with standard medications to avoid interruption, if possible</td>
</tr>
<tr>
<td></td>
<td>Grade 2: Oral intake decreased without significant weight loss, dehydration or malnutrition; IV fluids indicated ≤ 24 hrs.</td>
<td>Maintain vandetanib; treat with standard medications to avoid interruption, if possible</td>
</tr>
<tr>
<td></td>
<td>Grade 3: Inadequate oral caloric or fluid intake; IV fluids, tube feedings, or TPN indicated ≥ 24 hrs.</td>
<td>Hold vandetanib until ≤ grade 1; if vandetanib must be withheld for &gt; 3 wks, discontinue vandetanib. If recurs, discontinue vandetanib.</td>
</tr>
<tr>
<td></td>
<td>Grade 4: Life-threatening consequences</td>
<td>Hold vandetanib until ≤ grade 1; if vandetanib must be withheld for &gt; 3 wks, discontinue vandetanib. If recurs, discontinue vandetanib. Patients who are clinically unstable must be admitted and evaluated using telemetry until clinically stable.</td>
</tr>
<tr>
<td><strong>Vomiting</strong></td>
<td>Grade 1: One episode in 24 hrs.</td>
<td>Maintain vandetanib; treat with standard medications to avoid interruption, if possible</td>
</tr>
<tr>
<td></td>
<td>Grade 2: Two to five episodes in 24 hrs.; IV fluids indicated ≤ 24 hrs.</td>
<td>Maintain vandetanib; treat with standard medications to avoid interruption, if possible</td>
</tr>
<tr>
<td></td>
<td>Grade 3: ≥ Six episodes in 24 hrs.; IV fluids or TPN indicated ≥ 24 hrs.</td>
<td>Hold vandetanib until ≤ grade 1; if vandetanib must be withheld for &gt; 3 wks, discontinue vandetanib. If recurs, discontinue vandetanib.</td>
</tr>
<tr>
<td></td>
<td>Grade 4: Life-threatening consequences</td>
<td>Hold vandetanib until ≤ grade 1; if vandetanib must be withheld for &gt; 3 wks, discontinue vandetanib. If recurs, discontinue vandetanib. Patients who are clinically unstable must be admitted and evaluated using telemetry until clinically stable.</td>
</tr>
<tr>
<td>CTCAE, v. 3.0 Term</td>
<td>CTCAE Grade/Definition</td>
<td>Action to be Taken</td>
</tr>
<tr>
<td>-------------------</td>
<td>------------------------</td>
<td>--------------------</td>
</tr>
<tr>
<td><strong>Diarrhea</strong></td>
<td>Grade 1: Increase of &lt; 4 stools per day over baseline; mild increase in ostomy output compared to baseline</td>
<td>Maintain vandetanib; treat with standard medications to avoid interruption, if possible</td>
</tr>
<tr>
<td></td>
<td>Grade 2: Increase of 4-6 stools per day over baseline; IV fluids indicated &lt; 24 hrs.; moderate increase in ostomy output compared to baseline; not interfering with ADL</td>
<td>Maintain vandetanib; treat with standard medications to avoid interruption, if possible</td>
</tr>
<tr>
<td></td>
<td>Grade 3: Increase of ≥ 7 stools per day over baseline; incontinence; IV fluids ≥ 24 hrs; hospitalization; severe increase in ostomy output compared to baseline; interfering with ADL</td>
<td>Hold vandetanib until ≤ grade 1; if vandetanib must be withheld for &gt; 3 wks, discontinue vandetanib. If recurs, discontinue vandetanib.</td>
</tr>
<tr>
<td></td>
<td>Grade 4: Life-threatening consequences (e.g., hemodynamic collapse)</td>
<td>Hold vandetanib until ≤ grade 1; if vandetanib must be withheld for &gt; 3 wks, discontinue vandetanib. If recurs, discontinue vandetanib. Patients who are clinically unstable must be admitted and evaluated using telemetry until clinically stable.</td>
</tr>
<tr>
<td><strong>QTc Value</strong></td>
<td>Grade 1: QTc &gt;0.45 - 0.47 second [450-470 msec]</td>
<td>Maintain vandetanib.</td>
</tr>
<tr>
<td></td>
<td>Grade 2: QTc &gt;0.47 - 0.50 second [&gt; 470-500 msec]; ≥ 0.06 second above baseline</td>
<td>If this is a &gt; 60 msec change from baseline and QTc is ≥ 500 msec, maintain vandetanib but repeat EKG in triplicate within 48 hours. If QTc remains ≥ 500 msec, hold vandetanib and monitor 3x/week until QTc resolves to &lt; 480 msec.</td>
</tr>
<tr>
<td></td>
<td>Grade 3: QTc &gt;0.50 second [&gt; 500 msec]</td>
<td>For QTc between 500 and 549 msec, maintain vandetanib and repeat EKG in triplicate within 48 hours. If QTc remains ≥ 500 msec, hold vandetanib and monitor 3x/week until QTc resolves to &lt; 480 msec. For QTc &gt; 550 msec, hold vandetanib and monitor 3x/week until QTc resolves to &lt; 480 msec.</td>
</tr>
<tr>
<td></td>
<td>Grade 4: QTc &gt;0.50 second; [&gt; 500 msec] life-threatening signs or symptoms (e.g., arrhythmia, CHF, hypotension, shock syncope); Torsade de pointes</td>
<td>Hold vandetanib and monitor 3x/week until QTc resolves to &lt; 480 msec. if vandetanib must be withheld for &gt; 3 wks, discontinue vandetanib. If recurs, discontinue vandetanib.</td>
</tr>
</tbody>
</table>

**7.4.5 Management of Other Adverse Events**

For adverse events (AEs) that resolve promptly with supportive care, maintain dose level. Grade 3 or higher (non-hematologic) or grade 4 (hematologic) AEs related to vandetanib and lasting > 5 days that do not resolve to grade 2 or below despite maximum supportive care for < 48 hours, hold vandetanib. If vandetanib must be withheld for > 3 weeks for resolution of toxicity, the patient will not restart vandetanib.

**7.5 Modality Review**

The Medical Oncology Co-Chair, Stuart Wong, M.D., will perform a Chemotherapy Assurance Review of all patients who receive or are to receive chemotherapy in this trial. The goal of the review is to evaluate protocol compliance. The review process is contingent on timely
substitution of chemotherapy treatment data as specified in Section 12.1. The scoring mechanism is: Per Protocol, Not Per Protocol, and Not Evaluable. A report is sent to each institution once per year to notify the institution about compliance for each case reviewed in that year.

The Medical Oncology Co-Chair, Stuart Wong, M.D., will perform a Quality Assurance Review after complete data for the first 20 cases enrolled has been received at RTOG Headquarters. Dr. Wong will perform the next review after complete data for the next 20 cases enrolled has been received at RTOG Headquarters. The final cases will be reviewed within 3 months after this study has reached the target accrual or as soon as complete data for all cases enrolled has been received at RTOG Headquarters, whichever occurs first.

### 7.6 Adverse Events

This study will utilize the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0, MedDRA, version 9.0 for grading of all adverse events. A copy of the CTCAE v 3.0 can be downloaded from the CTEP home page (http://ctep.cancer.gov). The CTEP home page also can be accessed from the RTOG web page at http://www.rtog.org/regulatory/regs.html. All appropriate treatment areas should have access to a copy of the CTCAE v3.0.

All adverse events (AEs) as defined in the tables below will be reported via the AdEERS (Adverse Event Expedited Reporting System) application accessed via the CTEP web site (https://webapps.ctep.nci.nih.gov/openapps/psql/gadeers_main$.startup).

In the rare occurrence when Internet connectivity is lost, an AE report may be submitted using CTEP's Adverse Event Expedited Report-Single Agent or Multiple Agent paper template (available at http://ctep.cancer.gov) and faxed to 301-230-0159. A 24-hour notification is to be made to CTEP by telephone at 301-897-7497, only when Internet connectivity is disrupted. Once Internet connectivity is restored, an AE report submitted on a paper template or a 24-hour notification phoned in must be entered electronically into AdEERS by the original submitter at the site.

Serious adverse events (SAEs) as defined in the tables below will be reported via AdEERS. Sites also can access the RTOG web site (http://www.rtog.org/members/toxicity/main.html) for this information.

In order to ensure consistent data capture, serious adverse events reported on AdEERS reports also must be reported on an RTOG case report form (CRF). In addition, sites must submit CRFs in a timely manner after AdEERS submissions.

#### 7.6.1 Adverse Events (AEs)

**Definition of an AE:** Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite). [CTEP, NCI Guidelines: Expedited Adverse Event Reporting Requirements. December 2004.]

The following guidelines for reporting adverse events (AEs) apply to all NCI/RTOG research protocols. AEs, as defined above, experienced by patients accrued to this protocol should be reported via AdEERS. Use the patient's case number as the patient ID when reporting via AdEERS. **NOTE:** If the event is a Serious Adverse Event (SAE) [see next section], further reporting may be required. Reporting AEs only fulfills Data Management reporting requirements.

**NOTE:** If the event is a Serious Adverse Event (SAE) [see next section], further reporting will be required. Reporting AEs only fulfills Data Management reporting requirements.

#### 7.6.2 Serious Adverse Events (SAEs) — All SAEs that fit any one of the criteria in the SAE definition below must be reported via AdEERS within 24 hours of discovery of the event. Contact the CTEP Help Desk if assistance is required.

Certain SAEs as outlined below will require the use of the 24 Hour AdEERS Notification:
- **Phase II & III Studies:** All unexpected potentially related SAEs
- **Phase I Studies:** All unexpected hospitalizations and all grade 4 and 5 SAEs regardless of relationship
Definition of an SAE: Any adverse drug experience occurring at any dose that results in any of the following outcomes:
- Death;
- A life-threatening adverse drug experience;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant disability/incapacity;
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE drug experience, when, based upon medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition. Any pregnancy occurring on study must be reported via AdEERS as a medically significant event.

Pharmaceutically supported studies will require additional reporting over and above that which is required by CTEP.

SAEs (more than 30 days after last treatment) attributed to the protocol treatment (possible, probable, or definite) should be reported via AdEERS.

All supporting source documentation indicated as being provided in the Additional Information Section of the AdEERS Report, must be properly labeled with the study/case numbers and the date of the event and must be faxed to both the NCI at 301-230-0159 and the RTOG dedicated SAE FAX, 215-717-0990, before the five or ten-calendar-day deadline to allow RTOG to comply with the reporting requirements of the pharmaceutical company/companies supporting the RTOG trial. The RTOG Case Number without any leading zeros should be used as the Patient ID when reporting via AdEERS. Non-RTOG intergroup study and case numbers must also be included, when applicable. Submitted AdEERS Reports are forwarded to RTOG electronically via the AdEERS system. Use the patient’s case number as the patient ID when reporting via AdEERS.

SAE reporting is safety related and separate and in addition to the Data Management reporting requirements as outlined in the previous AE reporting section. Any event that meets the above outlined criteria for an SAE but is assessed by the AdEERS System as “expedited reporting NOT required” must still be reported for safety reasons and to fulfill the obligations of RTOG to the pharmaceutical company/companies supporting the RTOG trial. Sites must bypass the “NOT Required” assessment and complete and submit the report. The AdEERS System allows submission of all reports regardless of the results of the assessment. Note: Sites must print the AdEERS report and fax it to the FDA, FAX 1-800-332-0178.

7.6.3 Acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS)
AML or MDS that is diagnosed during or subsequent to treatment in patients on NCI/CTEP-sponsored clinical trials must be reported using the NCI/CTEP Secondary AML/MDS Report Form available at http://ctep.cancer.gov/forms/index.html. The report must include the time from original diagnosis to development of AML/MDS, characterization such as FAB subtype, cytogenetics, etc., and protocol identification (RTOG study/case numbers). This form will take the place of a report via the AdEERS system and must be faxed to the Investigational Drug Branch, FAX 301-230-0159, and mailed to RTOG Headquarters (address below) within 30 days of AML/MDS diagnosis.

<table>
<thead>
<tr>
<th>RTOG Headquarters AML/MDS Report</th>
</tr>
</thead>
<tbody>
<tr>
<td>1818 Market Street, Suite 1600</td>
</tr>
<tr>
<td>Philadelphia, PA 19103</td>
</tr>
</tbody>
</table>

7.7 AdEERS Expedited Reporting Requirements
7.7.1 Phase 2 and 3 Trials Utilizing an Agent under a Non-CTEP IND: AdEERS Expedited Reporting Requirements for Adverse Events that Occur within 30 Days of the Last Dose of the Investigational Agent (vandetanib) in this Study (Arm 2)
Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause must be provided. “On study” is defined as during or within 30 days of completing protocol treatment.

- Expedited AE reporting timelines defined:
  - “24 hours; 5 calendar days” – The investigator must initially report the AE via AdEERS within 24 hours of learning of the event followed by a complete AdEERS report within 5 calendar days of the initial 24-hour report.
  - “10 calendar days” - A complete AdEERS report on the AE must be submitted within 10 calendar days of the investigator learning of the event.
- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.
- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via AdEERS if the event occurs following treatment with an agent under a CTEP IND.
- Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

**Additional Instructions or Exceptions to AdEERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing an Agent under a Non-CTEP-IND:**

Pregnancy should be excluded before randomization. Should a pregnancy occur during study participation, it must be reported if there is a suspicion that vandetanib may have interfered with the effectiveness of a contraceptive medication. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the subject was discontinued from the study. Should pregnancy occur during a subject’s trial participation, the subject will immediately be discontinued from the trial and followed as per protocol. All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. All outcomes of pregnancy must be followed-up, documented and reported via AdEERS.

**8.0 SURGERY**

**8.1 (2/25/10)** Patients must have been found to have high-risk pathologic features, including pT4a-b disease, (see Section 3.1.2) after having undergone gross total surgical resection with curative intent of squamous cell carcinoma of the oral cavity, oropharynx, larynx, or hypopharynx...
(excluding lip, nasopharynx, or sinuses) within 6 weeks of randomization. Patients with cancers of the lip, nasopharynx, or sinuses are not eligible. Surgical re-resection of the microscopic involved margin is NOT permitted.

8.2 Surgical Quality Assurance Reviews
The Surgical Oncology Co-Chair, John A. Ridge MD, PhD will perform a modified Quality Assurance Review after complete data for the first 50 cases enrolled has been received at RTOG Headquarters. This quality assurance review will specifically examine the issues related to eligibility and the presence of high-risk features (see Section 3.1.2). No S1 case report form is required for this study.

Dr. Ridge will perform the next review after complete data for the next 50 cases enrolled has been received at RTOG Headquarters. The final cases will be reviewed within 3 months after this study has reached the target accrual or as soon as complete data for all cases enrolled has been received at RTOG Headquarters, whichever occurs first.

9.0 OTHER THERAPY
9.1 Permitted Supportive Therapy
All supportive therapy for optimal medical care will be given during the study period at the discretion of the attending physician(s) within the parameters of the protocol and documented on each site’s source documents as concomitant medication. Institutions must report the supportive therapy given on the appropriate case report forms (see Section 12.1).

9.1.1 (2/25/10) Nausea, vomiting, or both may be controlled with antiemetic therapy. 5HT-3 antagonists may prolong QTc interval risk. Increased monitoring is suggested and discussed below.

9.1.2 (2/25/10) Co-administration of drugs that in some reports might be associated with Torsades de Pointes, but at this time lack substantial evidence, should be avoided if possible (see Appendix VII). However, these drugs will be allowed, at the discretion of the Investigator, if considered absolutely necessary. In such cases, the patient must be closely monitored including regular checks of QTc and electrolytes. For patients who start on one of the drugs in this group while on study, the EKG must be checked within 24 hours of commencing the concomitant medication and then at least once per week while the patient remains on the medication. The frequency of EKG monitoring could revert to the standard schedule if no EKG prolongation has been noted during 4 weeks of co-administration of a drug from Appendix VII, Group 2. Electrolytes should be maintained within the normal range using supplements if necessary.

9.2 Non-permitted Supportive Therapy
9.2.1 Concomitant use of the known potent inducers of CYP3A4: rifampicin, phenytoin, carbamazepine, barbiturates, and St. John's Wort is not allowed during the study.

9.2.2 Concomitant use of medications generally accepted as having a risk of causing Torsades de Pointes (see Appendix VII) are not allowed within 2 weeks of study or during study.

9.3 Restrictions (6/8/09)
9.3.1 Patients who are blood donors should not donate blood during the trial and for 3 months following their last dose of vandetanib.

9.3.2 Exposure to vandetanib is increased with renal impairment; thus, caution must be adopted if being given to such patients, especially those with severe renal impairment where the exposure could potentially double.

10.0 TISSUE/SPECIMEN SUBMISSION (6/8/09)
For patients on the study who have consented to submit optional specimens for banking and translational research (see Appendix I)

If the patient consents to participate in the tissue/specimen component of the study, the site is required to submit the patient’s specimens as specified in Section 10.0 of the protocol. Note: Sites are not permitted to delete the tissue/specimen component from the protocol or from the sample consent.

10.1 Tissue/Specimen Submission (6/8/09)
The RTOG Biospecimen Resource at the University of California San Francisco receives, assesses, and maintains specimens obtained from patients enrolled in RTOG trials. Archival
blocks and, when available, fresh frozen tissue and from tumor and non-tumor mucosa will be stored and annotated by the bank.

In this study, it is required that tissue will be submitted to the RTOG Biospecimen Resource for the purpose of central review of pathology and HPV assay for oropharyngeal carcinomas. In addition, it is highly recommended (but optional) that fresh and archival tissues and blood be submitted for banking for future translational research through enrollment on RTOG 0514 (see Section 10.4 below). The RTOG Biospecimen Resource provides tissue specimens to investigators for approved studies. Translational research studies integrate the newest research findings into current protocols to investigate important biologic questions.

10.2 Tissue Collection For Central Review: Required (2/25/10)

Patients must consent to participate in submission of tissue for central review.

Hematoxylin and eosin stained slides of tumor tissue will be reviewed centrally. The purpose of central review is to: 1) ensure consistency in tumor diagnosis and grading; 2) assess quality of tumor tissue and representation; and 3) provide consistent evaluation of margin status and the presence or absence of perineural and vascular invasion. This process will ensure that morphologic features as well as surgical margin status of each case will be assessed and reported uniformly. Microscopic absence of tumor on the inked margins will be accepted as a negative margin resection. The final margin status (R status) of each case will also be assessed.

A tissue block submitted for central review will be taken from surgical specimens. Institutions that are unable to submit a tissue block for the required central review (and for patients with oropharyngeal carcinoma, the required HPV analysis) may instead take 3 unstained sections from the block then obtain three 3mm core punches of the block and re-imbed the core punches into a recipient paraffin for submission. Institutions can request an FFPE specimen plug kit from the RTOG Biospecimen Resource free of charge for this purpose: 415-476-RTOG (7864)/FAX 415-476-5271; RTOG@ucsf.edu.

If an institution is uncomfortable with obtaining the unstained sections and punches and wants to retain the tissue block, the site can send the entire block to the RTOG Biospecimen Resource, and the Resource will obtain the unstained sections and the core punches from the block and return the remaining block to the site. Please indicate this request (to obtain the sections, perform the core punch procedure, and return the block) on the submission form. Note: For oropharyngeal carcinoma patients, there is a 10-day turnaround needed for HPV assays, so institutions should send the block by overnight courier to the Biospecimen Resource as soon as possible with their request.

All institutions will receive a 0.5 case credit for submission of tissue for analysis. The following material must be provided to the RTOG Biospecimen Resource for central review:

10.2.1 Representative H & E stained slides
10.2.2 Corresponding tissue block
10.2.3 A Pathology Report documenting that the submitted block contains tumor; the report must include the RTOG protocol number and patient’s case number. The patient’s name and/or other identifying information should be removed from the report. The surgical pathology numbers and information must NOT be removed from the report.
10.2.4 A copy of the gross description of the tumor must accompany the specimen in order to evaluate the closest margin and distance.
10.2.5 A Specimen Transmittal Form stating that the tissue is being submitted for central review. Sites can access the form (no password required) at http://www.rtog.org/members/forms/list.html (under “Pathology”). The form must include the RTOG protocol number and the patient’s case number. If the patient is also enrolled on other RTOG trials, this should be indicated on the form.
10.2.6 Central review will be performed for every case by the Pathology Co-Chair, Adel El-Naggar, MD or Richard Jordan, DDS, PhD, of the Biospecimen Resource.
10.3 Tissue Collection for HPV Analysis: Required (6/8/09)

Patients with oropharyngeal carcinoma must consent to participate in use of submitted tissue for HPV analysis.

Institutions must ship tissue blocks from patients with oropharyngeal carcinoma to the RTOG Biospecimen Resource by overnight courier. Note: Prepaid Federal Express labels can be requested from the Biospecimen Resource.

For patients with oropharyngeal carcinoma, the RTOG Biospecimen Resource will process 2 unstained sections from the tissue block submitted for central review and will send the sections to Dr. Maura Gillison who will determine HPV status by in situ hybridization within 7-10 business days. Physicians or institutions can request the patient’s HPV status from RTOG Headquarters after the patient has completed study treatment.

10.4 Specimen Collection for Tissue Banking and Translational Research: Highly Recommended (But Optional) [2/25/10]

NOTE: Consult RTOG 0514 for details of specimen collection, submission instruction, and reimbursement. Sites can access RTOG 0514 at http://www.rtog.org/members/protocols/0514/0514.pdf

Note: If the institution is unable to open RTOG 0514 at the time of patient enrollment, the following instructions should be followed for the optional but highly recommended specimens:

10.4.1 Peripheral Blood: Plasma, Serum, and Whole Blood

The following materials need to be provided to the RTOG Biospecimen Resource: A Specimen Transmittal Form documenting the date of collection of the biospecimen; the RTOG protocol number, the patient’s case number, and method and time of storage (for example, stored at -80° C for 3 days) must be included.

A blood collection kit can be obtained free of charge from the Biospecimen Resource. See Appendices VIII-X for detailed collection instructions, including information pertaining to collection kits. Note: Kits include a shipping label.

Storage Conditions
Store at –80° C (-70°C to -90°C) until ready to ship. If a -80°C Freezer is not available:
- Samples can be stored short term in a -20° C freezer (non-frost free preferred) for up to one week (please ship out Monday-Wednesday only).

OR:
- Samples can be stored in plenty of dry ice for up to one week, replenishing daily (ship out Monday-Wednesday only).

OR:
- Samples can be stored in liquid nitrogen vapor phase (ship out Monday-Wednesday only).

Please indicate on Specimen Transmittal Form the storage conditions used and time stored.

10.4.2 Recurrent Tumors: Frozen or Fixed

We also encourage submission of recurrent tumors. A cohort of patients treated on RTOG 0619 will manifest tumor recurrence at some point following protocol treatment. Recurrent tumor specimens represent valuable materials for studying biologic features of resistance to radiation and drug therapy and metastatic spread. Such tumor recurrences may derive from the locoregional head and neck area or from a distant metastatic site if the clinical impression and pathology review are most consistent with recurrence of the squamous cell carcinoma of the head and neck that originally caused the patient to be enrolled on RTOG 0619.

10.4.3 Since the clinical data will not be available for correlative analysis for many years, it is premature to propose a firm plan for biomarker studies. Assay technology, particularly for high throughput tests, is rapidly evolving. Based on currently available data, the lead candidates include:
- EGFR wild type (previously shown to correlate strongly with tumor response to radiation alone or chemoradiotherapy by RTOG and ECOG investigators, respectively);
- EGFRvIII (found in ~40% of HNSCC);
- EGFR ligands, e.g., epiregulin-amphiregulin, found to predict response of colorectal carcinoma to cetuximab);
• VEGF (preliminary data suggest it predictive value for response to vandetanib);
• Lysyl oxidase, a marker for tumor hypoxia, which we recently found to be a marker for distant metastasis in HNSCC;
• E-Cadherin (a marker for epithelial-to-mesenchymal transition, which is a feature associated with a higher risk for recurrence);
• ERCC1 (a marker, when elevated, has been recently associated with resistance to cisplatin);
• Serum proteomics to predict Vandetanib response;
• HPV DNA detection in plasma samples for blood-based diagnosis and recurrence surveillance;
• Assessment of single nucleotide polymorphisms in the genes associated with EGFR and VEGFR signaling pathways to predict response to vandetanib.

Investigators of the Head and Neck Translational Research Program (HN-TRP) will carefully monitor new data, particularly those coming from the ongoing HN-TRP sponsored projects, and update this list when appropriate.

10.4.4 Specimen Collection Summary

Note: See Appendices VIII through X for collection kits and instructions.

<table>
<thead>
<tr>
<th>Specimens taken from patient:</th>
<th>Collected when:</th>
<th>Submitted as:</th>
<th>Shipped:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Representative H&amp;E stained slides of the primary tumor</td>
<td>Within 2 weeks prior to treatment</td>
<td>H&amp;E stained slide Pre-treatment</td>
<td>Slide shipped ambient</td>
</tr>
<tr>
<td>A paraffin-embedded tissue block of the primary tumor taken before initiation of treatment or a 2 mm diameter core of tissue, punched from the tissue block with a punch tool</td>
<td>Within 2 weeks prior to treatment</td>
<td>Paraffin-embedded tissue block or punch biopsy</td>
<td>Block or punch shipped ambient</td>
</tr>
<tr>
<td>5-10 mL of whole blood in each of 1 red-top tubes and centrifuge for serum</td>
<td>Within 2 weeks prior to treatment</td>
<td>Frozen serum samples containing a minimum of 0.5 mL per aliquot in 1 mL cryovials</td>
<td>Serum sent frozen on dry ice via overnight carrier</td>
</tr>
<tr>
<td>5-10 mL of anticoagulated whole blood in EDTA tube #1 (purple/lavender top) and centrifuge for plasma</td>
<td>Within 2 weeks prior to treatment</td>
<td>Frozen plasma samples containing a minimum of 0.5 mL per aliquot in 1 mL cryovials</td>
<td>Plasma sent frozen on dry ice via overnight carrier</td>
</tr>
<tr>
<td>5-10 mL of anticoagulated whole blood in EDTA tube #2 (purple/lavender top) aliquotted for DNA</td>
<td>Within 2 weeks prior to treatment</td>
<td>Frozen whole blood aliquots in 1 mL cryovials</td>
<td>Whole blood sent frozen on dry ice via overnight carrier</td>
</tr>
</tbody>
</table>

10.5 (6/8/09) Submit materials for Central Review, Tissue Banking, and Translational Research as follows:

U.S. Postal Service Mailing Address: For Non-frozen Specimens Only
RTOG Biospecimen Resource
University of California San Francisco
Campus Box 1800
1657 Scott Street, Room 223
San Francisco, CA 94143-1800

Courier Address (FedEx, UPS, etc.): For Frozen Specimens
RTOG Biospecimen Resource
University of California San Francisco
1657 Scott Street, Room 223
San Francisco, CA 94115

Questions: 415-476-RTOG (7864)/FAX 415-476-5271; RTOG@ucsf.edu
10.6 Reimbursement (2/25/10)

For specimens submitted via RTOG 0514: Sites should consult the RTOG 0514 protocol for details of reimbursement. Sites can access RTOG 0514 at http://www.rtog.org/members/protocols/0514/0514.pdf

For institutions unable to open RTOG 0514 at the time of patient registration: RTOG will reimburse institutions per case for the protocol specified materials submitted to the Biospecimen Resource at the University of California San Francisco. After confirmation from the RTOG Biospecimen Resource that appropriate materials have been received, RTOG Administration will prepare the proper paperwork and send a check to the institution. Pathology payment cycles are run twice a year in January and July and will appear on the institution’s summary report with the institution’s regular case reimbursement.

10.7 Confidentiality/Storage

(See the RTOG Patient Tissue Consent Frequently Asked Questions, http://www.rtog.org/biospecimen/tissuefaq.html for further details.)

10.7.1 Upon receipt, the specimen is labeled with the RTOG protocol number and the patient's case number only. The RTOG Biospecimen Resource database only includes the following information: the number of specimens received, the date the specimens were received, documentation of material sent to a qualified investigator, type of material sent, and the date the specimens were sent to the investigator. No clinical information is kept in the database.

10.7.2 Specimens for tissue banking will be stored for an indefinite period of time. Specimens for central review will be retained until the study is terminated. Specimens for the translational research component of this protocol will be retained until the specimen is consumed/exhausted or study is terminated, unless the patient has consented to storage for future studies. If at any time the patient withdraws consent to store and use specimens, the material will be returned to the institution that submitted it.

11.0 PATIENT ASSESSMENTS

11.1 Study Parameters: See Appendix II for a summary of assessments and time frames.

11.2 Evaluation During Treatment (6/8/09)

11.2.1 For Arm 2 only:
After the baseline EKGs have been performed and vandetanib started, EKGs will then be performed on weeks 2 (coinciding with day 8 of the start of vandetanib), 3 (coinciding with the start of radiation and cisplatin), and 8, as specified in Appendix II, Study Parameter Table.

Note: Patients who are receiving drug(s) that may induce Torsades de Pointes (for which no alternative medication is appropriate) must have an additional EKG 4-8 hours after the 1st dose of vandetanib.

11.2.2 For Arm 2 only: Institutions will collect the patient's pill diary for vandetanib during patient visits. Institutions will keep the pill diary as source documentation.

11.2.3 CBC, Mg++, electrolytes, AST/ALT, and creatinine will be performed weekly during RT.

11.3 Evaluation After Treatment (6/8/09)

11.3.1 For Arm 2 only: An EKG 4 weeks after radiation ends.

11.3.2 (2/25/10) The following assessments should be done at three months from start of treatment (for Arm 2 patients: 3 months from the first day of RT): history/physical; performance status; CT, CT-PET, or MRI of tumor & neck; CBC with diff and platelets; Mg++, Na+, K+, glucose, BUN; evaluation of adverse events. In addition, an evaluation by a Medical Oncologist can be done at the discretion of the treating Radiation Oncologist.

11.3.3 The following assessments should be done at six months from start of treatment: history/physical; performance status; a CT, CT-PET, or MRI of tumor & neck; CBC with diff and platelets; Mg++, Na+, K+, glucose, BUN; bilirubin, AST or ALT, Alk phos, serum creatinine; and evaluation of adverse events. In addition an evaluation by a Medical Oncologist can be done at the discretion of the treating Radiation Oncologist.

11.3.4 Long-term follow up will take place every 3 months for years 1-2, then every 6 months for years 3-6, then annually. The following assessments should be done in long-term follow up: history/physical; performance status; CBC with diff and platelets; Mg++, Na+, K+, glucose, BUN; evaluation of adverse events. The following should be done at the discretion of the treating Radiation Oncologist: Evaluation by a Medical Oncologist and a CT, CT-PET, or MRI of tumor & neck. In addition, a chest x-ray or CT scan should be done annually for 5 years.
11.4 **Response Criteria/Outcome Definitions**

11.4.1 **No evidence of disease (NED):** All patients must have no measurable tumor following surgery.

11.4.2 **Local-Regional Relapse:** Recurrent cancer in the tumor bed and/or neck not clearly attributable to a second primary neoplasm; biopsy confirmation is strongly encouraged.

11.4.3 **Distant Relapse:** Clear evidence of distant metastases (lung, bone, brain, etc.); biopsy is recommended where possible. A solitary lung mass/nodule is considered a second primary neoplasm unless proven otherwise.

11.4.4 **Second Primary Neoplasm:** All second primary neoplasms will be biopsy proven with documentation of specific histology. Modified rigorous criteria for a second primary (below) have been adapted from the definition by Warren and Gates. Localized non-melanoma skin cancers are not considered new primary tumors.

11.4.4.1 A distinct lesion separated from the primary tumor site by > 2 cm of normal epithelium;

11.4.4.2 A new cancer with different histology;

11.4.4.3 Any cancer, regardless of head and neck mucosal subsite, occurring 5 or more years after initial treatment;

11.4.4.4 In the lung, new primary tumors, if squamous cell cancer, must have histologic findings of dysplasia or CIS.

11.5 **Criteria for Discontinuation of Protocol Treatment**

Protocol treatment may be discontinued for any of the following reasons:

- Progression of disease;
- Sustained, severe debilitation resulting in chronic dehydration and/or progressive unintentional weight loss (> 25% of baseline weight) unresponsive to tube feeding;
- Unacceptable adverse events [at the discretion of the treating physician(s)];
- A delay in protocol treatment > 2 weeks.

If protocol treatment is discontinued, follow up and data collection will continue as specified in the protocol.

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12.0 **DATA COLLECTION**

Data should be submitted to:

RTOG Headquarters*
1818 Market Street, Suite 1600
Philadelphia, PA 19103

*If a data form is available for web entry, it must be submitted electronically.

Patients will be identified by initials only (first middle last); if there is no middle initial, a hyphen will be used (first-last). Last names with apostrophes will be identified by the first letter of the last name.

12.1 **Summary of Data Submission (11/18/08)**

<table>
<thead>
<tr>
<th>Item</th>
<th>Due</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic Form (A5)</td>
<td>Within 2 weeks of study entry</td>
</tr>
<tr>
<td>Initial Evaluation Form (I1)</td>
<td></td>
</tr>
<tr>
<td>Pathology Report (P1)</td>
<td></td>
</tr>
<tr>
<td>Slides/Blocks (P2)</td>
<td></td>
</tr>
<tr>
<td>Operative Note (S2)</td>
<td></td>
</tr>
<tr>
<td>Surgical Pathology Report (S5)</td>
<td></td>
</tr>
<tr>
<td>Staging Diagram (Nodes) [I7]</td>
<td></td>
</tr>
<tr>
<td>Staging Diagrams (I6)</td>
<td></td>
</tr>
<tr>
<td>Treatment Form (TF)</td>
<td>At end of treatment</td>
</tr>
<tr>
<td>Pill Diary (DP)</td>
<td>For Arm 2 patients only: At end of treatment</td>
</tr>
<tr>
<td>Initial Follow-up Form (F0)</td>
<td>2 weeks after completion of RT</td>
</tr>
<tr>
<td>Follow-up Form (F1)</td>
<td>From the start of treatment every 3 months for</td>
</tr>
</tbody>
</table>
12.2 Summary of Dosimetry Digital Data Submission for 3D-CRT or IMRT (Submit to ITC; see Section 12.2.1) [10/13/09]

<table>
<thead>
<tr>
<th>Item</th>
<th>Due</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preliminary Dosimetry Information (DD)</td>
<td>Within 1 week of start of RT</td>
</tr>
<tr>
<td>†Digital Data Submission – Treatment Plan submitted to ITC via SFTP account exported from treatment planning machine by Physicist. Digital data submission includes the following:</td>
<td></td>
</tr>
<tr>
<td>• CT data, critical normal structures, all GTV, CTV, and PTV contours</td>
<td></td>
</tr>
<tr>
<td>• Digital beam geometry for initial and boost beam sets</td>
<td></td>
</tr>
<tr>
<td>• Doses for initial and boost sets of concurrent treated beams</td>
<td></td>
</tr>
<tr>
<td>• Digital DVH data for all required critical normal structures, GTV, CTV, and PTVs for total dose plan (DV)</td>
<td></td>
</tr>
<tr>
<td>Digital Data Submission Information Form (DDSI) – Submitted online (Form located on ATC web site, <a href="http://atc.wustl.edu/forms/DDSI/ddsi.html">http://atc.wustl.edu/forms/DDSI/ddsi.html</a>)</td>
<td></td>
</tr>
<tr>
<td>Hard copy isodose distributions for total dose plan as described in QA guidelines† (T6)</td>
<td></td>
</tr>
</tbody>
</table>

**NOTE:** Sites must notify ITC via e-mail ([itc@wustl.edu](mailto:itc@wustl.edu)) after digital data is submitted. The e-mail must include study and case numbers or, if the data is phantom, “dry run” or “benchmark”.

**Final Dosimetry Information**

Within 1 week of RT end

- Radiotherapy Form (T1) [copy to HQ and ITC]
- Daily Treatment Record (T5) [copy to HQ and ITC]

Modified digital patient data as required through consultation with Image Guided Therapy QA Center

†Available on the ATC web site, [http://atc.wustl.edu/](http://atc.wustl.edu/)

12.2.1 Digital Data Submission to ITC (10/13/09)

Digital data submission may be accomplished using media or the Internet.

For network submission: The SFTP account assigned to the submitting institution by the ITC shall be used, and e-mail identifying the data set(s) being submitted shall be sent to: [itc@wustl.edu](mailto:itc@wustl.edu)

For media submission: Please contact the ITC about acceptable media types and formats. Hardcopies accompanying digital data should be sent by mail or Federal Express and should be addressed to:

**Image-Guided Therapy Center (ITC)**
ATTN: Roxana Haynes
4511 Forest Park, Suite 200
St. Louis, MO 63108
314-747-5415
FAX 314-747-5423
13.0 STATISTICAL CONSIDERATIONS

13.1 Primary Endpoint (6/8/09)

13.1.1 Disease-free survival

13.1.2 Secondary Endpoints

13.1.2.1 CTCAE, v. 3.0 grade 3-5 adverse events: cardiac arrhythmia, cardiac general, pulmonary/upper respiratory, gastrointestinal, and hemorrhage/bleeding (see Section 13.5.3 for more details);

13.1.2.2 Other grade 3-5 adverse events;

13.1.2.3 Death during or within 30 days of discontinuation of protocol treatment;

13.1.2.4 Local-regional control;

13.1.2.5 Time to distant metastases;

13.1.2.6 Overall survival.

13.2 Background and Sample Size Determination (6/8/09)

The study will be a randomized phase II screening trial as proposed by Rubinstein, et al (2005). It is designed as a one-sided test to detect a $\geq 35\%$ reduction of the hazard rate associated with disease-free survival (DFS) favoring the experimental arm. The type I error (alpha) is set at 0.20 while the statistical power is at 0.85. The DFS rate for the control arm will be based upon the chemoradiation arm from the completed postoperative trial, RTOG 95-01 and will be assumed to follow an exponential distribution for planning purposes. The 2-year DFS rate observed in RTOG 95-01 for 127 chemoradiation patients with positive margins and/or extracapsular extension was 54.8\% (95\% confidence interval [45.6, 63.1]). East® software for group sequential design was used in calculating the sample size with one planned interim analysis for early significance testing (2005). The Haybittle-Peto boundary for efficacy was utilized and was set at 0.001 for interim analysis and then the significance level 0.20 for the final analysis was derived in order to preserve a 0.20 significance level for the entire study. Futility will be tested using the lower boundary based on testing the alternative hypothesis at 0.005 level and because it was shown to have very little effect on the type I error, there will be no adjustment made to the sample size (Freidlin 2002). A total of 170 DFS failures and a total of 160 analyzable patients are required. Assuming that up to 6\% of patients may be ineligible or lost to follow up, the sample size required is 170 patients. The analysis will be restricted to eligible patients with follow-up data and may possibly exceed 160 patients.

In addition, the arms will be compared to detect a similar treatment effect excluding patients with HPV+ oropharyngeal primary. It is estimated from the RTOG 95-01 and EORTC trials that 40\% of patients entered on RTOG 0619 will have an oropharyngeal primary. In the completed ECOG trial 2399 prospectively evaluating HPV status, 61\% of the patients with an oropharyngeal primary were HPV+. In light of these data, it is projected that 25\% of the RTOG 0619 study population will be HPV+. Restricted to the 120 (= 0.80 * 160) HPV− patients, there will be 80\% statistical power to detect a 35\% reduction in the DFS failure rate using a 1-sided test at the 0.20 significance level. This subset analysis will be done when there are 62 DFS failures among the HPV− patients. If the hazard rate for the control arm is approximately the same for HPV− patients as it is for all patients, then the subset analysis would be projected to occur 3 months after 88 DFS have occurred in the entire population. However, because of differences in outcome reported in the ECOG trial 2399 with HPV− oropharyngeal patients failing at least twice faster than HPV+ oropharyngeal patients, there probably will be no lengthy delay until 62 DFS failures are observed in HPV− patients. To avoid possible bias in randomization of patients to the study, the patient’s HPV status will not be provided to the patient’s physician or institution until the patient has completed study treatment.

13.3 Patient Accrual

The patient accrual is projected to be 10 per month after the first 6 months while institutions are obtaining IRB approval. At this rate, it will take approximately 21 months to complete accrual.

If the total accrual during months 13 through 18 of the study is $\leq 20\%$ of the targeted accrual (< 12 cases), then the protocol will be discontinued. If the total accrual is between 21-49\%, then the protocol only will continue to accrue subject to approval of the RTOG Data Safety Monitoring Board (DSMB). If continued, the study must accrue at least 50\% of the targeted accrual (> 15 cases) during months 22 through 24 in order to remain open beyond 2 years.
13.4 Randomization
Patients will be stratified by 2 variables: Zubrod performance status (0 vs. 1) and primary site (oral cavity/hypopharynx vs. larynx vs. oropharynx, HPV+ vs. oropharynx, HPV- vs. oropharynx HPV not evaluable). The treatment allocation scheme described by Zelen (1974) will be used because it balances patient factors other than institution.

13.5 Analysis Plan
13.5.1 Statistical Methods (6/8/09)
Rates of local-regional control (LRC) and distant metastases (DM) will be estimated using the cumulative incidence method (Kalbfleisch 1980), while disease-free and overall survival rates will be estimated using the Kaplan-Meier method (1958). The distributions of the DFS and overall survival times will be compared between treatment arms with a log rank test (Mantel 1966). If the resulting p-value for DFS is < 0.20 with all patients, the result will be interpreted as an indication to test vandetanib in a phase III trial. With respect to LRC and DM, their failure rates for the experimental treatment will be compared against the control using failure-specific log-rank test (Prentice 1978).

All failure times will be measured from the date of study registration to the date of failure, competing risk, or last follow up. The following table shows how each first event will be counted for time to local-regional control, time to distant metastases, and disease-free survival (DFS). Anything not explicitly in the table (e.g., second primary tumor) is not considered an event, and the patient will continue to be followed for failure. For overall survival, death from any cause will be considered a failure.

<table>
<thead>
<tr>
<th>First Event</th>
<th>Local-Regional Control</th>
<th>Distant Metastases</th>
<th>Disease-Free Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>Censored</td>
<td>Censored</td>
<td>Censored</td>
</tr>
<tr>
<td>LR progression or recurrence</td>
<td>Failure</td>
<td>Competing risk</td>
<td>Failure</td>
</tr>
<tr>
<td>Distant metastasis</td>
<td>Competing risk</td>
<td>Failure</td>
<td>Failure</td>
</tr>
<tr>
<td>Death due to study cancer or from unknown causes</td>
<td>Failure</td>
<td>Competing risk</td>
<td>Failure</td>
</tr>
<tr>
<td>Death due to any other reason</td>
<td>Competing risk</td>
<td>Competing risk</td>
<td>Failure</td>
</tr>
</tbody>
</table>

For the endpoints in Sections 13.1.2.1 and 13.1.2.2, only adverse events (AEs) assessed to be definitely, probably, or possibly related (if relationship is missing, it will be assumed to be definitely, probably, or possibly) to protocol treatment will be considered. The rates of CTCAE, v.3.0 grade 3-5 cardiac arrhythmia, cardiac general, pulmonary/upper respiratory, gastrointestinal, and hemorrhage/bleeding (as described in Section 13.5.3) AEs, all grade 3-5 AEs, and death during or within 30 days of discontinuation of protocol treatment will be estimated using a binomial distribution along with their associated 95% confidence intervals and will be compared using Fisher’s exact test.

13.5.2 Interim Analysis to Monitor Study Progress
Interim reports will be prepared twice each year until the final analysis has been accepted for presentation or publication. In general, these reports will contain information about the accrual rate with projected completion date for the accrual phase, exclusion rates and reasons, pretreatment characteristics of patients accrued, compliance rate of treatment delivered with respect to the protocol prescription, and the frequency and severity of AEs. This study will be monitored by the Clinical Data Update System (CDUS), version 3.0. Cumulative CDUS data will be submitted quarterly by electronic means. Reports are due January 31, April 30, July 31, and October 31. The RTOG Data Safety Monitoring Board (DSMB) for phase I and II trials will review this study twice a year in conjunction with the RTOG semi-annual meetings with respect to patient accrual and morbidity. After the this study has been opened one year, the study design assumptions made about percentage of HPV+ oropharyngeal patients entered on RTOG 0619 will be checked semi-annually. If there is greater than 10% absolute difference between the projected study design frequency and the observed study frequency, its implication will be assessed in terms of when the projected final (definitive) treatment analysis will be performed. If timing of that analysis is lengthened by more than a year, a
recommendation of increasing the sample size will be explored. The DSMB also will review this study on an “as needed” basis between meetings.

13.5.3 Special Interim Analysis to Monitor Adverse Events and Early Death

Since there is limited experience with the experimental regimen, an interim analysis of AEs will be performed to assure that there are no unexpected problems. This analysis will occur after the first 40 patients are entered into the protocol (The data for this analysis will be available 6 months after the 40th patient is entered. The 6-month interval allows sufficient time for the treatment to be completed, the first AE assessment post-treatment, and the data processed). There will be about 20 patients on each arm available for analysis. Of particular concern is that the addition of vandetanib may increase the incidence of patients with the one or more of the following grade 3-5 AEs: Cardiac arrhythmia (prolonged QTc interval; ventricular arrhythmia); Cardiac general (hypertension); [all grade 3-5 cardiac events will be monitored because significant adverse cardiac events included a variety of terms without any apparent pattern]; Pulmonary/upper respiratory (cough, dyspnea, hemoptysis, pneumonitis/pulmonary infiltrates); Gastrointestinal (constipation, diarrhea, heartburn/dyspepsia, nausea, vomiting, perforation); Hemorrhage/bleeding (pulmonary/upper respiratory). The incidence rate of these combined AEs will be compared between the arms. If the rate is 15% higher (absolute difference) with the vandetanib arm as compared to the control arm, then modifications to the treatment will be considered. In addition, the rate of patients dying while on or within 30 days of discontinuation of protocol treatment (early death) will be used to monitor for unexpected fatalities that may be related to protocol treatment. In the completed postoperative study RTOG 95-01, the early death rate for the RT and chemoradiation arm was about 2%. If the early death rate is 10% higher (absolute difference) with the vandetanib arm as compared to control, then all early deaths will be reviewed and modifications to the treatment will be considered.

After reviewing the results from this analysis, the study chairs and study statistician will make a recommendation to the RTOG Head and Neck Steering Committee, the RTOG DSMB, and the corporate sponsor for their consideration. These committees and individuals jointly will decide the future course of action for the study.

13.5.4 Significance Testing for Early Termination and Reporting (6/8/09)

One interim treatment comparison will be performed when 50% (39 DFS failures) of the 78 required number of failures are observed. Only the primary endpoint will be tested in the interim analysis. The efficacy will be tested using Haybittle-Peto boundaries of 0.001 for the interim tests and 0.20 for the final analysis to preserve an overall alpha level of 0.20 for the study. The futility will be tested using the lower boundary based on testing the alternative hypothesis at 0.005 level. The results will be reported to the RTOG DSMB with the treatment blinded.

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Number of Events</th>
<th>p-value for Efficacy</th>
<th>p-value for Futility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interim</td>
<td>39</td>
<td>≤ 0.001</td>
<td>&lt; 0.005</td>
</tr>
<tr>
<td>Final</td>
<td>78</td>
<td>≤ 0.20</td>
<td>N/A</td>
</tr>
</tbody>
</table>

At the planned interim analysis, the results from the test for assessing treatment efficacy and futility will be reported to the RTOG DSMB. The responsible statistician may recommend early reporting of the results and/or stopping accrual (if applicable) of the trial if the treatment effect, with respect to DFS, is highly significant or if it is not likely to be; that is, if the p-value is less than the nominal value specified in a sequential design for either efficacy or futility. If the resulting p-value for efficacy is <0.20, this result will be interpreted as an indication to test vandetanib in a phase III trial for definitive confirmation. Before making such a recommendation, the accrual rate, treatment compliance, safety of the treatments, and the importance of the study also are taken into consideration with the p-value. The DSMB will then make a recommendation about the trial to the RTOG Group Chair.

13.5.5 Analysis for Reporting the Initial Treatment Results (6/8/09)

The analysis to report the initial results of treatment will be undertaken when 78 events (total from both arms) have been reported for the primary endpoint DFS, unless the criteria for early stopping are met. The time from opening this trial to patient entry to this analysis is projected to be approximately 5 years if the projected accrual rate is realized. Only eligible patients with both on-study and follow-up information will be included. Eligible patients that do not start protocol treatment will be included in this intent-to-treat analysis. The usual components of this analysis are:
- Tabulation of all cases entered, and any excluded from analysis with reasons for exclusion;
- Patient accrual rate;
- Institutional accrual;
- Distribution of important baseline prognostic variables;
- Frequency and severity of adverse events.

Observed results with respect to the endpoints described in Sections 13.1.1 and 13.1.2. The difference in DFS between the control arm and the experimental arm will be tested using the log-rank statistic at the significance level of 0.20 given that the one interim analysis is carried out and shows no statistical significance. If the resulting p-value for efficacy is <0.20, this result will be interpreted as an indication to test Vandetanib in a phase III trial for definitive confirmation.

### 13.5.6 Analysis of Tumor Markers

In addition to the clinical endpoints, this study also may conduct preliminary analysis of several tumor markers in patients with banked specimens. Each marker will be considered dichotomous (i.e., present/absent or overexpressed/not overexpressed) and correlated with outcome measures using Cox proportional hazards models (Cox 1972).

Because of the moderate number of failures expected, only very large differences in outcome can be detected with adequate statistical power. For this reason, all results will be considered hypothesis-generating to be confirmed in a future study.

### 13.6 Gender and Minorities

In conformance with the National Institutes of Health Revitalization Act of 1993 with regard to inclusion of women and minorities in clinical research, we have considered the possible interactions (treatment by race and treatment by gender). The study was designed under the assumption of the same results between the gender and among the races. Based on accrual to RTOG’s previous protocol, RTOG 0234, we project that 78% of patients enrolled on this study will be male, 90% white, and 4% Hispanic. The following table provides the projected number of patients in each race, ethnicity, and gender group.

<table>
<thead>
<tr>
<th>Projected Distribution of Gender and Minorities</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
</tr>
<tr>
<td><strong>Ethnic Category</strong></td>
</tr>
<tr>
<td>Hispanic or Latino</td>
</tr>
<tr>
<td>Not Hispanic or Latino</td>
</tr>
<tr>
<td><strong>Ethnic Category: Total of all subjects</strong></td>
</tr>
<tr>
<td><strong>Racial Category</strong></td>
</tr>
<tr>
<td>American Indian or Alaskan Native</td>
</tr>
<tr>
<td>Asian</td>
</tr>
<tr>
<td>Black or African American</td>
</tr>
<tr>
<td>Native Hawaiian or other Pacific Islander</td>
</tr>
<tr>
<td>White</td>
</tr>
<tr>
<td><strong>Racial Category: Total of all subjects</strong></td>
</tr>
</tbody>
</table>
References (6/8/09)


Brizel D. Concurrent VEGF and EGFR blockade in conjunction with curative intent chemo-radiation for locally advanced head and neck cancer. J Thor Onc. 1 (8), October 2006, Abstract #1.06.02.


References (Continued)


Eskens FA. Angiogenesis inhibitors in clinical development (Where are we now and where are we going?). Br J Cancer. 90(1): 1-7, 2004, Review.


Ho KF, Swindell R, Brammer. CV Dose intensity comparison between weekly and 3-weekly cisplatin delivered concurrently with radical radiotherapy for head and neck cancer: A retrospective comparison from New Cross Hospital, Wolverhampton, UK. Acta Oncol. 47(8):1513-8, 2008.


References (Continued)


References (Continued)


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

You are being asked to take part in this study because you have advanced head and neck cancer and have had surgery to remove your cancer.

Why is this study being done?

The purpose of this study is to determine whether adding vandetanib to the standard treatment of chemotherapy and radiation therapy (chemoradiotherapy) is safe and tolerable. The study will compare the effects, good and/or bad, of chemoradiotherapy with chemoradiotherapy and vandetanib on you and your cancer. In this study, you will get either chemoradiotherapy or chemoradiotherapy and vandetanib.

Vandetanib is an investigational agent that interferes with cell communication and growth and reduces the growth of new blood vessels. Vandetanib may delay the growth of tumor cells.

This study is being done because we do not know if a combination of chemoradiotherapy with vandetanib will better control your cancer or have more or fewer side effects than chemoradiotherapy alone.

How many people will take part in the study?

About 170 people will take part in this study.

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

Required Submission of Tumor Tissue

For all patients: Your study doctor will need to send some of your tumor tissue (obtained when you had surgery) to a central office. There, a pathologist will confirm your type of tumor. This tissue submission for review is required for this study.

For patients with oropharynx cancer: Your tumor tissue also will be tested for the Human Papillomavirus (HPV). This tissue test is required for this study. Some studies have suggested that HPV-related cancer is biologically and clinically different as compared to non-HPV-related cancer. Some studies have found that patients with HPV-related oropharynx cancer have a better response to treatment. This test will help researchers learn more about HPV-related cancer.

After you have completed treatment on this study, your study doctor can request your HPV status from The Radiation Therapy Oncology Group (RTOG) and discuss it with you.
Before you begin the study: (6/8/09)

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

- Physical examination by several doctors
- Evaluation of your ability to carry out daily activities
- CT scan (Computed Tomography) scan or CT-PET scan of your head and neck (CT scan: A study using x-rays to look at one part of your body; PET scan: a computerized image that looks at the activity of tumor cells in your entire body and that requires injection of a special marker into your vein, such as sugar (glucose) combined with a low-dose radioactive substance (a tracer). A camera records the tracer’s signal as it travels through your body.)
- Or an MRI (Magnetic Resonance Imaging) of your head and neck (MRI: Imaging using a strong magnetic field to look at one part of your body)
- An EKG (a test of your heart function)
- Chest x-ray or Chest CT scan
- Blood tests (about 2 teaspoons of blood will be taken from your vein)
- For women able to have children, a pregnancy test
- A dental evaluation before receiving radiation
- If your study doctor recommends:
  - An evaluation of your diet and ability to chew and swallow to see if a feeding tube is needed
  - A hearing test

You will be “randomized” into one of the study groups described below. Randomization means that you are put into a group by chance. A computer program will place you in one of the study groups. Neither you nor your study doctor can choose the group you will be in. You will have an equal chance of being placed in any group.

If you are in group 1 (often called “Arm A”), you will receive chemotherapy (cisplatin) and radiation therapy.

- (2/25/10) You will receive chemotherapy (cisplatin, 100 mg), through the vein, while you are receiving radiation therapy every 3 weeks x 3 (a total of 3 treatments). Each treatment will take about 6 hours. Some patients may stay overnight in the hospital after each chemotherapy treatment to receive medicines to replace body fluids. Your study doctor will discuss this with you.
- (6/8/09) You will receive radiation therapy once a day, Monday through Friday, for about 6 weeks. Each treatment may take up to 30 minutes, depending on the radiation technique being used.

If you are in group 2 (often called “Arm B”), you will receive chemotherapy (cisplatin), radiation therapy, and vandetanib.

- You will begin taking vandetanib 2 weeks before starting radiation therapy and will continue taking it while you are receiving radiation therapy and chemotherapy. You will take 1 pill each day, including weekends and holidays, for a total of 8 weeks or until you finish radiation therapy, which ever comes first. You will take the pill on an empty stomach (one hour before or two hours after a meal). You will be asked to keep a record of each dose of vandetanib you are take.
- (2/25/10) You will receive chemotherapy (cisplatin, 30 mg), through the vein, once a week while you are receiving radiation therapy for 6 weeks. Each treatment will take about 3 hours. Some patients may stay overnight in the hospital after each chemotherapy treatment to receive medicines to replace body fluids. Your study doctor will discuss this with you.
- (6/8/09) You will receive radiation therapy once a day, Monday through Friday, for about 6 weeks. Each treatment may take up to 30 minutes, depending on the radiation technique being used.

During the study: (6/8/09)

If the exams, tests and procedures show that you can be in the study, and you choose to take part, then you will need the following tests and procedures. They are part of regular cancer care.

For all patients weekly during radiation therapy:
• A physical examination
• Evaluation of any side effects from treatment you may be having
• Evaluation of your ability to carry out daily activities
• Blood tests (about 2 teaspoons of blood will be taken from your vein)

For Group 2 patients: You will need these tests and procedures that are either being tested in this study or being done to see how the study is affecting your body.

• EKGs (a test of your heart function) at the following times:
  ➢ Before you begin receiving vandetanib: 3 EKGs will be done 5-10 minutes apart, and your doctor will average the results
  ➢ 1 EKG at week 2 (the second week of vandetanib)
  ➢ 1 EKG at week 3 (when you begin receiving radiation, chemotherapy as well as vandetanib)
  ➢ 1 EKG at week 8 during radiation therapy, chemotherapy, and vandetanib
  ➢ 1 EKG 4 weeks after radiation therapy.

You will need these tests and procedures in follow-up visits. They are being done to see how you and your cancer was affected by the treatment you received.

At 3 months from the start of radiation therapy: (6/8/09)
• Physical examination
• A CT scan, CT-PET, or MRI of your head and neck
• Evaluation of your ability to carry out daily activities
• Blood tests (about 2 teaspoons of blood will be taken from your vein)
• Evaluation of any side effects you may be having
• If your study doctor recommends: A physical examination by a Medical Oncologist

At 6 months from the start of radiation therapy: (6/8/09)
• Physical examination
• A CT scan, CT-PET or MRI of your head and neck
• Evaluation of your ability to carry out daily activities
• Blood tests (about 2 teaspoons of blood will be taken from your vein)
• Evaluation of any side effects you may be having
• If your study doctor recommends: A physical examination by a Medical Oncologist

Every 3 months for years 1-2, then every 6 months for years 3-6 (6/8/09)
• A physical examination
• Evaluation of your ability to carry out daily activities
• Blood tests (about 2 teaspoons of blood will be taken from your vein)
• Evaluation of any side effects you may be having
• If your study doctor recommends:
  ➢ A physical examination by a Medical Oncologist
  ➢ A CT scan, CT-PET, or MRI of your head and neck

Annually for 5 years:
• Chest x-ray or CT scan of the chest
Study Plan

Another way to find out what will happen to you during the study is to read the chart below. Start reading at the top and read down the list, following the lines and arrows.

How long will I be in the study? (2/25/10)

Patients in Group 1 will receive treatment for about 9 weeks. Patients in Group 2 will receive treatment for about 8 weeks. After you are finished with treatment, the study doctor will ask you to visit the office for follow-up exams at every 3 months from the time you start radiation therapy for years 1 and 2, then every 6 months for years 3 through 6, then once a year for your lifetime.

Can I stop being in the study?

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

It is important to tell the study doctor if you are thinking about stopping so that any risks from the chemotherapy, radiation therapy, or vandetanib (if you receive vandetanib) can be evaluated by the study doctor.

Another reason to tell the study doctor that you are thinking about stopping is to discuss what follow up care and testing could be most helpful for you.

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

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

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

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

Risks Associated with Radiation to the Head and Neck

Combining cisplatin with radiation to the head and neck can increase the effectiveness of radiation therapy on your cancer, but also can increase the side effects of radiation on normal tissue in treatment area. In addition, receiving a combination of cisplatin with radiation can result in the side effects described below being more likely or more severe.

Very Likely
- Sores in the mouth and/or throat which can be painful and make it very difficult to chew and or swallow foods
- Mouth dryness or changes in taste and/or smell that may be permanent
- Thick saliva
- Hoarseness
- Tanning or redness and/or irritation of the skin in the head and neck area being treated with radiation
- Ear pain and/or pressure
- Fatigue
- Weight loss
- Permanent hair loss in the area treated with radiation
- Loss of teeth, or cavities in the teeth, if strict dental care is not followed and/or hypersensitivity of teeth

Less Likely, But Serious
- Decrease in function of the thyroid gland that may require you to take thyroid replacement medicine to prevent you from feeling tired or sleepy
- Serious damage to the spinal cord, nerves in the neck, jawbone, voice box, skin, or other parts of the head and neck that may require a major operation to correct and, rarely, can even be life threatening
- Temporary pain or scarring around nerves in the shoulder that could cause numbness and/or weakness
- Breathing problems
- Difficulty with swallowing and eating for which you might need a long term or permanent feeding tube; possibility of inhaling food and/or liquids into the lungs – which could also result in pneumonia.
- Serious ear infections and/or hearing loss
- Damage to the spinal cord leading to permanent weakness and/or symptoms like a “stroke”
- Permanent hair loss (of the face/chin/neck)

Risks Associated with Cisplatin

Very Likely
- Decrease in blood counts, which can lead to a risk of infection, decreased healing after surgery, and/or bleeding
- Anemia
- Loss of appetite and/or taste; metallic taste in your mouth
- Nausea and/or vomiting
- Fatigue
- Generalized loss of strength
- Hearing loss, ringing in the ears
- Loss of muscle or nerve function that may cause weakness or numbness in your hands and feet
- Loss of appetite and weight loss
- Low magnesium in the blood, which could result in muscle cramps and/or weakness
- Low calcium in the blood
- Kidney damage

Less Likely
- Allergic reactions (sweating, difficulty breathing, rapid heartbeat)
- Muscle cramps or spasm
- Facial swelling
- Loss of taste
- Loss of coordination
- Involuntary movement
- Restlessness
- Loss of hair, which is temporary
- Blood clots
- Low blood pressure

**Less Likely, But Serious**
- Seizures
- A severe allergic reaction, which could be life threatening
- Decrease in the kidneys’ ability to handle the body’s waste, which may be permanent
- Calcium or potassium levels so low that it may affect heart function
- Decrease in liver function
- Another cancer called acute leukemia
- A condition called hemolytic uremic syndrome that involves decreased red blood cells and platelets, fever, and kidney failure

**Risks Associated with Vandetanib (2/25/10)**

**Likely**
- Dry, red, or spotted skin, and/or skin rash
- Scaly skin or skin with wet sores or hives
- Rash or eruptions on patches of sun-exposed skin
- Rash similar to acne
- Bruising of skin
- Discoloration of the nails
- Night sweats
- Increased sweating from the armpits
- Hair loss
- Nausea and/or vomiting
- Loss of appetite and weight loss
- Diarrhea
- Dry mouth and/or mouth sores
- Bleeding of gums
- Painful or difficult swallow
- Tiredness and/or weakness
- Changes in heart rhythm, which may result in rapid or irregular heart beating, dizziness, light-headedness, chest tightness, chest pain, shortness of breath, and/or loss of consciousness

**Less Likely**
- Headache
- Dizziness
- Nosebleeds
- Hiccups
- Throat pain
- Loss of voice
- Feeling anxious and/or depressed
- Difficulty sleeping
- Change in sensation, especially touch
- Constipation
- Stomach pain and/or discomfort
- Cough
- Upper respiratory infection
- Increased breathing that can cause an imbalance in the acidity of the blood
- High blood pressure
- Bloating and fluid retention in the hands, feet, and/or ankles
- Fever and/or chills
- Decreased coordination while walking
- A decrease in white blood cells, which could lead to infection
- A decrease in platelets, which could lead to bleeding
- Low levels of potassium, which could lead to change in heart rhythm or muscle weakness
Irritation of the mucous membranes lining body passages
High levels of protein in the urine
Blood in the urine

Rare
Runny and/or irritated, inflamed nose

Rare but serious
Severe inflammation of the bowel
Blood clots in the legs or lung
Heart failure
Bleeding in the lung
Reversible Posterior Leukoencephalopathy Syndrome (RPLS): Fluid in brain tissue, which could result in headache, dizziness, confusion, decreased or abnormal vision, and/or seizures and which is temporary
Life threatening infections

AstraZeneca, manufacturer of vandetanib has observed changes in EKGs in some patients being treated with vandetanib, and these changes may be related to vandetanib. These changes in the EKG usually occur without symptoms, so frequent follow-up visits have been built into the study. Changes in heart rhythm may cause rapid or irregular heart beating, dizziness, light-headedness, chest discomfort, shortness of breath, and loss of consciousness. **You should report any of these symptoms to your doctor immediately.** The risk of developing changes in your EKG and developing serious heart rhythm changes will be greater if you have diarrhea, vomiting, high fever, faintness, or dizzy spells or if you are unable to maintain a normal diet. You should review your medications and diet with your doctor at each visit while you are continuing to receive vandetanib.

A small number of patients receiving vandetanib have developed blood clots affecting the legs or lungs. This may have been due to the patient’s cancer or other illness at the time; however, it is considered possible that vandetanib might increase the risk for developing blood clots. A small number of patients have developed stroke, heart attack, or problems with arteries in legs or arms. These patients had other possible causes for these conditions, but it is possible that vandetanib may have been part of the cause.

A very small number of patients with lung cancer receiving vandetanib have developed shortness of breath and cough because of an inflammation or scar tissue formation in the lungs, although this symptom could also be due to the underlying lung cancer.

At higher doses of vandetanib, AstraZeneca noted an increase in the number of patients experiencing skin rashes. The rashes appear to occur in patients who were exposed to direct sunlight. The rashes, which may become severe, are manageable with proper treatment. It is recommended that you follow the following guidelines to prevent the rash from occurring:

- Avoid direct sunlight.
- Cover sun exposed skin with clothing (long pants, long sleeve shirts and hats).
- Use a sun block of at least SPF 45.
- Notify the Study Doctor when the first sign of a rash occurs so the doctor can take the appropriate steps in preventing the rash from becoming severe.

**Risks Associated with a Combination of Chemotherapy, Radiation Therapy, and vandetanib**
Combining vandetanib with cisplatin and radiation to the head and neck may increase the effectiveness of chemo-radiation on your cancer. However, the combination also can increase the side effects of cisplatin and radiation on normal tissue in the treatment area and may result in the side effects described above being more likely and/or more severe.

**Reproductive risks**
You should not become pregnant or father a baby while on this study because the drugs and scans in this study can affect an unborn baby. Women who are able to have children will have a pregnancy test before beginning treatment. Women should not breast feed a baby while on this study and for at least 60 days after the last study treatment. **It is important you understand that you need to use birth control while on this study and for at least 60 days after the last study treatment.** Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study. There is a risk of not being able to have children in the future due to the chemotherapy. If you think that you may want to have children in the future, discuss this with the study doctor.
For more information about risks and side effects, ask your study doctor.

Are there benefits to taking part in the study?

Taking part in this study may or may not make your health better. While doctors hope radiation therapy, chemotherapy, and vandetanib (if you receive vandetanib) may keep your head and neck cancer from growing, there is no proof of this yet. The effects of a combination of chemotherapy, radiation therapy and vandetanib may be no different or worse than chemotherapy and radiation therapy alone. We do know that the information from this study will help doctors learn more about these therapies as a treatment for cancer. This information could help future cancer patients.

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

Your other choices may include:

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

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

Will my medical information be kept private?

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

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

- The Radiation Therapy Oncology Group (RTOG)
- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people
- Qualified representatives of AstraZeneca, makers of vandetanib (Zactima™)

What are the costs of taking part in this study?

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

AstraZeneca is supplying vandetanib at no cost to you. However, you or your health plan may need to pay for costs of the supplies for drug administration and personnel who give you the vandetanib.

If, during the study, vandetanib becomes approved for use in your cancer, you and/or your health plan may have to pay for drug needed to complete this study. **You will not be paid for taking part in this study.**
For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute’s Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage. You can print a copy of the “Clinical Trials and Insurance Coverage” information from this Web site.

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

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

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

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

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

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

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

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

Who can answer my questions about the study?

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

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

*You may also call the Operations Office of the NCI Central Institutional Review Board (CIRB) at 888-657-3711 (from the continental US only). [*Only applies to sites using the CIRB.]*

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

You can say “yes” or “no” to the following study. Below, please mark your choice.
Consent Form for Use of Tissue for Research

About Using Tissue for Research

You have had surgery to remove your cancer. Your doctor has removed some body tissue to do some tests. The results of these tests will be given to you by your doctor and will be used to plan your care.

We would like to keep some of the tissue that is left over for future research. If you agree, this tissue will be kept and may be used in research to learn more about cancer and other diseases. Please read the information sheet called "How is Tissue Used for Research" to learn more about tissue research. This information sheet is available to all at the following web site: http://www.cancerdiagnosis.nci.nih.gov/specimens/patient.pdf

Your tissue may be helpful for research whether you do or do not have cancer. The research that may be done with your tissue is not designed specifically to help you. It might help people who have cancer and other diseases in the future.

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

Things to Think About

The choice to let us keep the left over tissue for future research is up to you. No matter what you decide to do, it will not affect your care or your participation in the main part of the study.

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

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

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

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

Benefits

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

Risks

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

Making Your Choice

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

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

1. My specimens may be kept for use in research to learn about, prevent, or treat cancer, as follows:
   - Tissue ☐Yes ☐No
• Blood ☐Yes ☐No

2. My specimens may be kept for use in research to learn about, prevent or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease), as follows:
   • Tissue ☐Yes ☐No
   • Blood ☐Yes ☐No

3. Someone may contact me in the future to ask me to take part in more research.
   ☐Yes ☐No

Where can I get more information?

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

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

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

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

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

Signature

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

Participant ________________________________

Date _____________________________________
## APPENDIX II: STUDY PARAMETER TABLE
(See Sections 11.2 & 11.3 for details) [2/25/10]

<table>
<thead>
<tr>
<th>Assessments</th>
<th>Pretreatment</th>
<th>During Treatment</th>
<th>Follow Up</th>
<th>Long-term Follow Up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Within 12 weeks prior to registration</td>
<td>Within 4 weeks prior to registration</td>
<td>Within 2 weeks prior to start of treatment</td>
<td>Weekly during RT</td>
</tr>
<tr>
<td>History/physical</td>
<td>X</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Pre-op CT, CT-PET, or MRI of tumor &amp; neck</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>EKG</td>
<td>Screening EKG</td>
<td>Baseline EKG for Arm 2 pts.</td>
<td>* Arm 2 pts: Week 2 (start of vandetanib; prior to RT) then weeks 3 and 8 during RT. See Section 11.2.1.</td>
<td></td>
</tr>
<tr>
<td>Pill Diary</td>
<td>X</td>
<td>For Arm 2 pts.</td>
<td></td>
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</tr>
<tr>
<td>Chest x-ray or CT</td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td>Performance status</td>
<td>X</td>
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<td>X</td>
<td></td>
</tr>
<tr>
<td>Surgical eval &amp; clearance</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tissue for central review</td>
<td>Within 2 wks prior to tx</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Optional specimens for research</td>
<td>Within 2 wks prior to tx</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Med Onc exam</td>
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<td></td>
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<tr>
<td>Dental eval</td>
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<td></td>
<td></td>
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<tr>
<td>Nutritional eval, Feeding tube placement, Audiogram</td>
<td>Highly recommended; not required</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBC w/ diff &amp; platelets</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Mg++, Na+, K+, glucose, BUN</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Bilirubin, AST or ALT, Alk phos, serum creatinine</td>
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<td></td>
<td>X</td>
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<tr>
<td>Creatinine clearance</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Serum pregnancy test (if applicable)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Tumor response evaluation</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse event evaluation</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

[580x54]RTOG 0619
ZUBROD PERFORMANCE SCALE

0  Fully active, able to carry on all predisease activities without restriction
1  Restricted in physically strenuous activity but ambulatory and able to carry work of a light or sedentary nature. For example, light housework, office work
2  Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3  Capable of only limited self-care, confined to bed or chair 50% or more of waking hours
4  Completely disabled. Cannot carry on self-care. Totally confined to bed or
5  Death

NEW YORK HEART ASSOCIATION (NYHA) CARDIAC CLASSIFICATION

<table>
<thead>
<tr>
<th>Class</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I (Mild)</td>
<td>No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpititation, or dyspnea</td>
</tr>
<tr>
<td>Class II (Mild)</td>
<td>Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpititation, or dyspnea.</td>
</tr>
<tr>
<td>Class III (Moderate)</td>
<td>Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpititation, or dyspnea.</td>
</tr>
<tr>
<td>Class IV (Severe)</td>
<td>Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.</td>
</tr>
</tbody>
</table>
APPENDIX IV

AJCC STAGING SYSTEM, 6th Edition
HEAD & NECK

STAGING-PRIMARY TUMOR (T)

TX  Primary tumor cannot be assessed
T0  No evidence of primary tumor
Tis Carcinoma in situ

LIP and ORAL CAVITY

TX  Primary tumor cannot be assessed
T0  No evidence of primary tumor
Tis Carcinoma in situ
T1  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
T4 (lip) Tumor invades through cortical bone, inferior alveolar nerve, floor of mouth, or skin of face (i.e., chin or nose)
T4a (oral cavity) Tumor invades adjacent structures (e.g., through cortical bone, into deep [extrinsic] muscle of tongue [genioglossus, hyoglossus, palatoglossus, and styloglossus], maxillary sinus, skin of face
T4b Tumor invades masticator space, pterygoid plates or skull base and/or encases internal carotid artery

NASAL CAVITY and PARANASAL SINUSES

Maxillary Sinus
T1  Tumor limited to maxillary sinus mucosa with no erosion or destruction of bone
T2  Tumor causing bone erosion or destruction including extension into the hard palate and/or middle nasal meatus, except extension to posterior wall of maxillary sinus and pterygoid plates
T3  Tumor invades any of the following: bone of the posterior wall of maxillary sinus, subcutaneous tissues, floor or medial wall of orbit, pterygoid fossa, ethmoid sinuses
T4a Tumor invades anterior orbital contents, skin of cheek, pterygoid plates, infratemporal fossa, cribiform plate, sphenoid or frontal sinuses
T4b Tumor invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than maxillary division of trigeminal nerve (V2), nasopharynx or clivus

Nasal Cavity and Ethmoid Sinus
T1  Tumor restricted to any one subsite, with or without bony invasion
T2  Tumor invading two subsites in a single region or extending to involve an adjacent region within the nasoethmoidal complex, with or without bony invasion
T3  Tumor extends to invade the medial wall or floor of the orbit, maxillary sinus, palate, or cribiform 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 fossa, cranial nerves other than V2, nasopharynx, or clivus
APPENDIX IV (Continued)

PHARYNX

Nasopharynx
T1  Tumor confined to the nasopharynx
T2  Tumor extends to soft tissues of oropharynx and or nasal fossa
T2a without parapharyngeal extension
T2b with parapharyngeal extension
T3  Tumor invades bony structures and/or paranasal sinuses
T4  Tumor with intracranial extension and/or involvement of cranial nerves, infratemporal fossa, hypopharynx, orbit, or masticator space.

Oropharynx
T1  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 Tumor invades the larynx, deep/extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible.
T4b Tumor invades lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, or skull base or encases carotid artery.

Hypopharynx
T1  Tumor limited to one subsite of hypopharynx and 2 cm or less in greatest dimension.
T2  Tumor invades more than one subsite of hypopharynx or an adjacent site, or measures more than 2 cm but not more than 4 cm in greatest diameter without fixation of hemilarynx.
T3  Tumor measures more than 4 cm in greatest dimension or with fixation of hemilarynx.
T4a Tumor invades thyroid/cricoid cartilage, hyoid bone, thyroid gland, esophagus or central compartment soft tissue.
T4b Tumor invades prevertebral fascia, encases carotid artery, or involves mediastinal structures.
LARYNX

Supraglottis
T1 Tumor limited to one subsite of supraglottis with normal vocal cord mobility
T2 Tumor 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 pyriform sinus) without fixation of the larynx.
T3 Tumor limited to larynx with vocal cord fixation and/or invades any of the following: postcricoid area, pre-epiglottic tissues, paraglottic space, and/or minor thyroid cartilage erosion (e.g., inner cortex).
T4a Tumor invades through the thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of the neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus).
T4b Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures.

Glottis
T1 Tumor limited to the vocal cord(s) (may involve anterior or posterior commissure) with normal mobility
T1a Tumor limited to one vocal cord
T1b Tumor involves both vocal cords
T2 Tumor extends to supraglottis and/or subglottis, or with impaired vocal cord mobility
T3 Tumor limited to the larynx with vocal cord fixation, and/or invades paraglottic space, and/or minor thyroid cartilage erosion (e.g., inner cortex).
T4a Tumor invades through the thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus).
T4b Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures.

LARYNX (Continued)

Subglottis
T1 Tumor limited to the subglottis
T2 Tumor extends to vocal cord(s) with normal or impaired mobility
T3 Tumor limited to larynx with vocal cord fixation
T4a Tumor invades cricoid or thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of neck including deep extrinsic muscles of the tongue, strap muscles, thyroid, or esophagus).
T4b Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures.

REGIONAL LYMPH NODES (N) Excluding Nasopharynx
NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Metastasis in a single ipsilateral node, 3 cm or less in greatest dimension
N2 Metastasis in a single ipsilateral node, more than 3 cm, but not more than 6 cm in greatest dimension, or in multiple ipsilateral lymph nodes, none greater than 6 cm in greatest dimension, or bilateral or contralateral nodes, none more than 6 cm in greatest dimension
N2a Metastasis in a single ipsilateral node more than 3 cm, but not more than 6 cm in greatest dimension
N2b Metastasis in multiple ipsilateral 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 Metastases in a lymph node, more than 6 cm in greatest dimension
APPENDIX IV (Continued)

REGIONAL LYMPH NODES (N) Nasopharynx
NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Unilateral metastasis in lymph node(s), 6 cm or less in greatest dimension, above supraclavicular fossa*
N2 Bilateral metastasis in lymph node(s), 6 cm or less in greatest dimension, above supraclavicular fossa*
N3 Metastasis in lymph node(s) > 6 cm and/or to supraclavicular fossa
N3a Greater than 6 cm in dimension
N3b Extension to the supraclavicular fossa**
*Note: Midline nodes are considered ipsilateral nodes.
**Supraclavicular zone or fossa is relevant to the staging of nasopharyngeal carcinoma and is the triangular region originally described by Ho. It is defined by three points: 1) the superior margin of the sternal end of the clavicle; 2) the superior margin of the lateral end of the clavicle; 3) the point where the neck meets the shoulder. Note that this would include caudal portions of Levels IV and V. All cases with lymph nodes (whole or part) in the fossa are considered N3b.

DISTANT METASTASIS (M)
MX Distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis

<table>
<thead>
<tr>
<th>STAGE GROUPING Excluding Nasopharynx</th>
<th>STAGE GROUPING Nasopharynx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td>Stage 0</td>
</tr>
<tr>
<td>Tis, N0, M0</td>
<td>Tis, N0, M0</td>
</tr>
<tr>
<td>Stage I</td>
<td>Stage I</td>
</tr>
<tr>
<td>T1, N0, M0</td>
<td>T1, N0, M0</td>
</tr>
<tr>
<td>Stage II</td>
<td>Stage IIA</td>
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<tr>
<td>T2, N0, M0</td>
<td>T2a, N0, M0</td>
</tr>
<tr>
<td>Stage III</td>
<td>Stage IIB</td>
</tr>
<tr>
<td>T3, N0, M0</td>
<td>T1-T2a, N1, M0</td>
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<td>T1-3, N1, M0</td>
<td>T2b, N0-1, M0</td>
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<td>Stage IVA</td>
<td>Stage III</td>
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<td>T4a, N0-2, M0</td>
<td>T1-T2b, N2, M0</td>
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<td>Any T, N2, M0</td>
<td>T3, N0-2, M0</td>
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<tr>
<td>Stage IVB</td>
<td>Stage IVA</td>
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<tr>
<td>T4b, Any N, MO</td>
<td>T4, N0-2, M0</td>
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<tr>
<td>Any T, N3, M0</td>
<td>Any T, N3, M0</td>
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<td>Stage IVC</td>
<td>Stage IVB</td>
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<td>Any T, Any N, M1</td>
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<tr>
<td>Stage IVC</td>
<td>Stage IVC</td>
</tr>
<tr>
<td>Any T, Any N, M1</td>
<td>Any T, Any N, M1</td>
</tr>
</tbody>
</table>
APPENDIX V

MANAGEMENT OF DENTAL PROBLEMS IN IRRADIATED PATIENTS

Dental Care for Irradiated Patients
Goals for a dental care program include:
1. To reduce incidence of bone necrosis.
2. To reduce incidence of irradiation caries.
3. To allow proper fitting of dentures following treatment.

Pre-irradiation Care and Procedures
The patients may be grouped into four groups in accordance with the problems they present prior to irradiation.

**Group 1**
Includes edentulous patients. They may require surgical removal of any symptomatic cysts, infected retained root tips, or alveolar hyperplasia. These patients require hygiene instruction and precautionary instruction about trauma with premature use of a prosthesis.

**Group 2**
Includes those with poor dental hygiene, including those patients whose teeth are beyond repair by ordinary dental procedure, those with generalized oral sepsis, those with generalized periodontal disease, and those with chronic periapical abscesses or granulomas.

Procedures performed on this group include removal of all remaining teeth prior to irradiation with primary closure and surgical preparation of the alveolar ridges to laterally support a prosthesis. There should be antibiotic coverage during the healing stage and adequate time prior to the start of radiation therapy. These patients need complete hygiene instruction and precautionary instruction about premature use of a prosthesis.

**Group 3**
Includes those in whom dental condition is fair, including those patients whose teeth are restored, ordinary dental procedures, periodontal pockets are less than 3 mm deep, carious lesions are not in proximity to the pulp, and no more than 20 restorable carious lesions are present. X-ray examinations show at least 1/2 of the bone still present around root surfaces. These patients require removal of any teeth that are non-salvageable in accordance with the above and restorations of the remaining teeth as required. The patients are instructed for dental prophylaxis and the patients utilize custom-made fluoride carriers.

**Group 4**
Includes those in whom dental hygiene is good. This includes patients who do not have severe malocclusion in whom few carious lesions are present. Carious lesions are not in close proximity to the pulp and are correctable by conventional methods. These patients require periodontal evaluation and dental prophylaxis training, restorations as needed, no extractions prior to radiation therapy, and fitting for custom carriers.

Extraction of Teeth
If extraction of teeth is necessary prior to radiation therapy, the bone must be contoured so that closure at the extraction site is possible. All loose spicules and sharp projections must be removed. The approximation of the gingival tissue must be such that the closure is neither too loose nor too tight. At least 10 days are required for adequate healing prior to initiation of therapy.

Causative Factors
The major causative factors appear to be the reduction of the amount of saliva and secondarily, reduced pH in the mouth. This occurs following high dose radiation to the major salivary glands using parallel opposed fields. The decay process usually occurs in the first year following radiation therapy. It tends to occur more quickly in teeth which have a large amount of root cementum exposed to those teeth with large amounts of plaque formation present. Doses of radiation in excess of 20 Gy to salivary tissue place the teeth at risk.

Preventive Program
The rationale behind the use of fluoride treatments is to make the tooth surfaces less susceptible to the decay process. This is accomplished by a combination of increasing fluoride concentration on the tooth surface and by the effect of fluoride on the plaque and flora that are present in the oral cavity. Adequate results are obtained by:
1) cleansing the teeth thoroughly, followed by a good home care dental prophylaxis program, 2) construction of
APPENDIX V (Continued)

fluoride carriers, custom-made mouth guards, which provide local application of fluoride solution to the gingiva and tooth surfaces. Fluoride carriers are made individually with the use of casts. Material used for making a mouth guard is "Sta-Guard" plastic used in conjunction with vacutrole unit produced by Jelrus Technical Products, Corp., both of which are available through local dental supply. This material is molded to the cast impression and allowed to harden. A fluoride solution prepared at the M.D. Anderson Hospital is now available from the Emerson Laboratories, Inc., Dallas, Texas 75221. It has been used to coat the plastic carrier for use in the mouth. The patients are instructed to cleanse their teeth prior to placement of the carrier. It is then worn in place for 5 minutes each day. The patients are instructed to rinse their mouths thoroughly following the use of the carrier. This will be continued for an indefinite period of time. Close follow-up is necessary.

Results
In the 5-1/2 year program at the M.D. Anderson Hospital beginning in 1966, a study of 304 patients shows that the incidence of necrosis of the jaw was reduced to approximately 21% compared to 37% prior to initiation of the study. Groups 3 and 4 patients randomized with and without fluoride treatment showed reduction in radiation carries from 67% to 34% among Group 3 patients, and from 65% to 22% among Group 4 patients.

Failure to Control Decay
Management of failure to control radiation decay includes silver fillings with continued use of fluoride treatments. If the decay process is sufficiently advanced that a filling will no longer stay in place, these teeth are merely smoothed so that there will be no sharp, irritating edges. The mere existence of such a decayed tooth is not necessarily reason for extraction, for it must be remembered that extraction could lead to complications such as bone necrosis.

Pulp exposure resulting from the decay process can usually be handled by use of antibiotics and/or root-canal therapy.

Hypersensitivity of Teeth
Occasionally, a patient will exhibit extreme sensitivity of the teeth secondary to diminished amounts of saliva. This has been shown to be reduced in incidence with the fluoride treatments. Should this problem become manifest, increasing the fluoride treatment to 10 to 15 minutes 3 times a day is recommended.

Infections
Infections occurring in patients under or after radiation therapy are best managed conservatively with good oral hygiene, irrigation and flushing procedures, and systemic antibiotics.

Bone Necrosis
The patients receiving radiation therapy to a high dose to the head and neck region have increased susceptibility to bone necrosis for several reasons including: impairment of normal metabolism, increased susceptibility to infection and severely limited repair process. Bone necrosis occurs most often after post-irradiation surgery or other traumas. Conservative management should be tried first, though in more aggressive lesions a more radical approach may ultimately be necessary.
Appendix VI

Instructions for Dispersing Vandetanib Tablets for Administration Via Feeding Tubes

Do not crush tablets. Drop the number of vandetanib tablets required for a single dose into an appropriate container (ideally glass to help confirm removal of all the dispersed material) containing approximately 2 ounces (or 50 mL) of water (drinking water, sterile water for injection, or purified water) at room temperature. Stir the liquid occasionally to ensure complete break-up of the tablets. When the tablets have broken up into a fine dispersion (in approximately 10-15 minutes), they can be administered to the patient. Administration to the patient should occur immediately after dispersion is complete whenever possible.

To ensure delivery of the whole dose, rinse the container with 2 ounces (or 50 mL) of water to ensure removal of any material adhering to the walls of the container and administer the additional water to the patient. In the event of a delay in administration, the dispersion is chemically stable up to 4 hours after preparation.

Stability Summary

The data confirms that aqueous dispersal of vandetanib (as described above) has no detrimental effects on the release of the active pharmaceutical ingredient (API) when compared to administration of the intact tablet and that a delay of up to 4 hours between preparation of the dispersion and administration will not have any detrimental effect on the assay and degradation products or the release of API in the dispersed tablet.

Effect of Variation in pH and Temperature of Water for Dispersion

The temperature and pH of the water used to prepare the dispersed tablet may vary in the clinic. The effect of pH of the water used for dispersion was evaluated over the range pH 5 – 8. Over this range, the pH of the water used for dispersing the tablets has no significant effect on the dispersion times. The temperature range defined in the USP for controlled room temperature excursions that are experienced in hospitals is 15 °C to 30 °C. Over this range, the temperature of the water does have an effect on tablet dispersion times with the tablets taking longer to disperse at lower temperatures. All tablets tested dispersed within 10 minutes.

Compatibility With Delivery Devices

The dispersed tablet may be administered by nasogastric tube or gastrostomy tube. To ensure that the dose is not affected by the method of delivery, the vandetanib content and degradation products were determined after the dispersion had been passed through the delivery tube. See Table 1 for details of the feeding tubes tested.

<table>
<thead>
<tr>
<th>Tube No</th>
<th>Feeding tube type</th>
<th>Product details</th>
<th>Product Code</th>
<th>Lot No</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Nasogastric</td>
<td>Flocare nasointestinal feeding tube from Nutricia (CH10). (PD Ref. P/4163/07)</td>
<td>35231</td>
<td>200509353</td>
</tr>
<tr>
<td>2</td>
<td>Gastrostomy</td>
<td>Flocare PEG set from Nutricia (CH14). (PD Ref. P/4163/08)</td>
<td>35428</td>
<td>200506132</td>
</tr>
<tr>
<td>3</td>
<td>Nasogastric</td>
<td>CORFLO Controller PILL-NG enteral feeding tube from Viasys (10FR). (PD Ref. P/4163/011)</td>
<td>20-2551</td>
<td>18864</td>
</tr>
</tbody>
</table>

No significant difference was observed between the delivered dose obtained for the feeding tubes and the content of vandetanib in the control sample, indicating that the patient should receive the full dose when the dispersed tablet is administered using a feeding tube. For the assay and degradation products results, no significant difference was observed between the results obtained for the feeding tubes and those obtained for intact tablets indicating that there are no compatibility issues with any of the tubes.

The administration method and any change in that method must be recorded on the appropriate case report form.
Appendix VII (6/8/09)

Medications Generally Accepted by Authorities to Have a Risk of Causing Torsades De Pointes (Tdp)

It has been recognized for a number of years that certain prescription medications can prolong the QT/QTc interval and cause a form of acquired Long QT syndrome, known as drug induced LQTS. Many drugs prolong the QT/QTc interval but do not have a known risk of inducing TdP, whereas others are generally accepted as having a known risk of inducing TdP. Those drugs that prolong the QT/QTc interval and have a known risk of inducing TdP require additional study monitoring. The drugs that prolong the QT interval and have a risk of inducing Torsade de Pointes (TdP) are listed below.

Concomitant use of these drugs (Table 1) are **allowed on study only if the investigator believes that they are medically necessary and no acceptable alternative medication can be given.**

<table>
<thead>
<tr>
<th>Drug (Generic Names)</th>
<th>Drug Class (Clinical Usage)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albuterol (by parenteral administration)</td>
<td>Bronchodilator (asthma)</td>
<td>Inhaled Albuterol at normal doses acceptable</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>Anti-arrhythmic (heart rhythm)</td>
<td>females &gt; males TdP Cases in Literature</td>
</tr>
<tr>
<td>Arsenic trioxide</td>
<td>Anti-cancer (leukaemia)</td>
<td>TdP Cases in Literature</td>
</tr>
<tr>
<td>Bepridil</td>
<td>Anti-anginal (heart pain)</td>
<td>females &gt; males</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>Anti-psychotic/antiemetic (schizophrenia/nausea)</td>
<td>TdP Cases in Literature</td>
</tr>
<tr>
<td>Chloroquine</td>
<td>Anti-malaria (malaria infection)</td>
<td></td>
</tr>
<tr>
<td>Cisapride</td>
<td>GI stimulant (stimulates GI motility)</td>
<td>Open Prescription Restricted females &gt; males</td>
</tr>
<tr>
<td>Disopyramide</td>
<td>Anti-arrhythmic (heart rhythm)</td>
<td>females &gt; males</td>
</tr>
<tr>
<td>Dofetilide</td>
<td>Anti-arrhythmic (heart rhythm)</td>
<td></td>
</tr>
<tr>
<td>Domperidone</td>
<td>Anti-nausea (nausea)</td>
<td></td>
</tr>
<tr>
<td>Droperidol</td>
<td>Sedative/hypnotic (anaesthesia adjunct)</td>
<td>TdP Cases in Literature</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Antibiotic/GI stimulant (infection/GI motility)</td>
<td>females &gt; males; topical use is permitted</td>
</tr>
<tr>
<td>Halofantrine</td>
<td>Anti-malarial (malaria infection)</td>
<td>females &gt; males</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>Anti-psychotic (schizophrenia, agitation)</td>
<td></td>
</tr>
<tr>
<td>Ibutilide</td>
<td>Anti-arrhythmic (heart rhythm)</td>
<td>females &gt; males</td>
</tr>
<tr>
<td>Levomethadyl</td>
<td>Opiate agonist (narcotic dependence)</td>
<td></td>
</tr>
<tr>
<td>Mesoridazine</td>
<td>Anti-psychotic (schizophrenia)</td>
<td></td>
</tr>
<tr>
<td>Methadone</td>
<td>Opiate agonist (pain control/ narcotic dependence)</td>
<td>females &gt; males</td>
</tr>
<tr>
<td>Pentamidine</td>
<td>Anti-infective (pneumocystis)</td>
<td>females &gt; males</td>
</tr>
<tr>
<td>Drug (Generic Names)</td>
<td>Drug Class (Clinical Usage)</td>
<td>Comments</td>
</tr>
<tr>
<td>----------------------</td>
<td>----------------------------</td>
<td>----------</td>
</tr>
<tr>
<td>Pimozide</td>
<td>Anti-psychotic (Tourette's tics)</td>
<td>females &gt; males, TdP Cases in Literature</td>
</tr>
<tr>
<td>Procainamide</td>
<td>Anti-arrhythmic (heart rhythm)</td>
<td></td>
</tr>
<tr>
<td>Quinidine</td>
<td>Anti-arrhythmic (abnormal heart rhythm)</td>
<td>females &gt; males</td>
</tr>
<tr>
<td>Salbutamol (by parenteral administration)</td>
<td>Bronchodilator (asthma)</td>
<td>Inhaled salbutamol at normal doses acceptable</td>
</tr>
<tr>
<td>Sotalol</td>
<td>Anti-arrhythmic (heart rhythm)</td>
<td>females &gt; males</td>
</tr>
<tr>
<td>Sparfloxacin</td>
<td>Antibiotic (bacterial infection)</td>
<td></td>
</tr>
<tr>
<td>Thioridazine</td>
<td>Anti-psychotic (schizophrenia)</td>
<td></td>
</tr>
</tbody>
</table>
APPENDIX VIII (2/25/10)

RTOG FFPE SPECIMEN PLUG KIT INSTRUCTIONS

The specimen plug kit contains a shipping tube and a punch tool.

Step 1
Place the punch tool on the paraffin block over the selected tumor area. (Ask a pathologist to select area with tumor.) Push the punch into the paraffin block. Twist the punch tool once around to separate the plug from the block. Then pull the punch tool out of the block. The punch should be filled with tissue sample.

Step 2
Label the punch tool with the proper specimen ID. DON’T try to remove the specimen from the punch.

Use a separate punch tool for every specimen. Please do not mix specimens. Call or email us if you have any questions or need additional specimen plug kits.

Step 3
Once the punch tool is labeled, place it in the shipping tube and mail to the address below.

We will remove the specimen from the punch, embed it in a cassette, and label it with the specimen ID.

*NOTE: If your facility is uncomfortable with obtaining the plug but wants to retain the tissue block, please send the entire block to the RTOG Biospecimen Resource and we will sample a plug from the block and return the remaining block to your facility. Please indicate this request (to perform the plug procedure and return of the block) on the submission form.

Ship specimen plug kit, specimen in punch tool, and all paperwork to the address below:

**U.S. Postal Service Mailing Address: For Non-frozen Specimens Only**
RTOG Biospecimen Resource
University of California San Francisco
Campus Box 1800
1657 Scott Street, Room 223
San Francisco, CA 94143-1800

**Courier Address (FedEx, UPS, etc.): For Frozen Specimens or Trackable shipments**
RTOG Biospecimen Resource
University of California San Francisco
1657 Scott Street, Room 223
San Francisco, CA 94115

Questions: 415-476-RTOG (7864)/FAX 415-476-5271; RTOG@ucsf.edu
Instructions for use of frozen tissue kit:

This kit includes:
- Biohazard pads/wipes 4” x 4” (orange)
- Five (5) 5-mL cryovials
- Disposable scalpel blades
- Disposable forceps
- Biohazard bags
- Absorbent shipping material
- Styrofoam container (inner)
- Cardboard shipping (outer) box
- Prepaid shipping label
- UN 3373 Label
- UN 1895 Dry Ice Sticker

Preparation of Fresh Frozen Tissue:
- On sterile cutting board, lay out the underpads.
- Keep biohazard wipes nearby to keep area clean throughout process.
- Label cryovials with RTOG study and case numbers

Process:
- Using provided disposable scalpel, evenly cut tissue into 5 separate pieces (Note: if a frozen core was obtained, do not cut but send it whole).
- Use forceps to place each piece of tissue into individual 5-mL cryovials.
- Snap freeze tissue samples in liquid nitrogen, a dry ice slurry (dry ice with 95% ethanol or isopentane), or directly on dry ice.
- Once frozen, place all of the cryovials into biohazard bag
- Use RTOG labels* to label bag.

Storage:
- Store at −80°C (-70°C to -90°C) until ready to ship.
  - If a -80°C Freezer is not available,
    - Samples can be stored short term in a -20°C Freezer (non-frost free preferred) for up to one week (please ship out Monday-Wednesday only).
      - OR: Samples can be stored in plenty of Dry Ice for up to one week, replenishing daily (please ship out on Monday-Wednesday only).
      - OR: Samples can be stored in liquid nitrogen vapor phase (ship out Monday-Wednesday only).
- Please indicate on Specimen Transmittal Form the storage conditions used and time stored.

*RTOG labels are obtained at the time of patient registration. PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED.

(continued on next page)
Shipping/Mailing:

- Include all RTOG paperwork in pocket of biohazard bag.
- Place specimens and the absorbent shipping material in Styrofoam cooler filled with dry ice (if appropriate; double-check temperature sample shipping temperature). Place Styrofoam cooler into outer cardboard box, and attach shipping label to outer cardboard box.
- Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag and clearly identified.
- Send frozen specimens via overnight courier to the address below. Specimens should only be shipped Monday through Wednesday (Monday-Tuesday for Canada) to prevent thawing due to delivery delays. Saturday or holiday deliveries cannot be accepted. Samples can be stored frozen until ready to ship.

For Questions regarding collection/shipping please contact the RTOG Biospecimen Resource:

Courier Address (FedEx, UPS, etc.): For Frozen Specimens
RTOG Biospecimen Resource
University of California San Francisco
1657 Scott Street, Room 223
San Francisco, CA 94115

Questions: 415-476-RTOG (7864)/FAX 415-476-5271 ; RTOG@ucsf.edu
APPENDIX X (2/25/10)

RTOG BLOOD COLLECTION KIT INSTRUCTIONS

This Kit is for collection, processing, storage, and shipping of serum, plasma, or blood (as specified by protocol):

Kit contents:
- One Red Top tube for serum
- One Purple Top EDTA tube for plasma
- One Purple Top EDTA tube for Whole Blood
- Twenty (20) 1 ml cryovials
- Biohazard bags (3)
- Absorbent shipping material (3)
- Styrofoam container (inner)
- Cardboard shipping (outer) box
- Pre-paid shipping label(s)
- UN1845 DRY Ice and UN3373 Biological Substance Category B Stickers
- Specimen Transmittal Form
- Kit Instructions

Serum (if requested): Red Top Tube
- Label as many 1ml cryovials (up to 10) as serum collected. Label them with the RTOG study and case number, collection date and time, and clearly mark cryovials “serum”.

Process:
1. Allow one red top tube to clot for 30 minutes at room temperature.
2. Spin in a standard clinical centrifuge at ~2500 RPM for 10 minutes at room temperature.
3. Aliquot 0.5 ml serum into as many cryovials as serum collected (up to 10) labeled with RTOG study and case numbers, collection date/time, timepoint collected, and clearly mark specimen as “serum”.
4. Place cryovials into biohazard bag and immediately freeze at -70 to -90°C, and store frozen until ready to ship. See below for storage conditions.
5. Store serum at -70 to -90°C until ready to ship on dry ice. See below for storage conditions.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED.

Plasma (if requested): Purple Top EDTA tube #1
- Using four (4) or more 1 ml cryovials, label them with the RTOG study and case number, collection date and time, and clearly mark cryovials “plasma”.

Process:
1. After collection, invert tube(s) multiple times to ensure adequate mixing of EDTA.
2. Centrifuge specimen(s) within one hour of collection in a standard clinical centrifuge at ~2500 RPM for 10 minutes at room temperature.
3. If the interval between specimen collection and processing is anticipated to be greater than one hour, keep specimen on ice until centrifuging is performed.
4. Carefully pipette and aliquot 0.5 ml plasma into each cryovial labeled with RTOG study and case numbers, collection date/time, timepoint collected and clearly mark specimen as “plasma”.
5. Place cryovials into biohazard bag and immediately freeze at -70 to -90°C
6. Store frozen plasma until ready to ship on dry ice.
7. See below for storage conditions.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED.
(3/25/10) Whole Blood For DNA (if requested): Purple Top EDTA tube #2

- Using four (4) or more 1 ml cryovials, label them with the RTOG study and case number, collection date and time, and clearly mark cryovial(s) “blood”.

Process:
1. After collection, invert tube(s) multiple times to ensure adequate mixing of EDTA. Blood can also be mixed for 5 minutes on a mixer at room temperature.
2. Carefully pipette and aliquot 1.0 ml blood into as many cryovials labeled “blood” as possible. Clearly mark the tubes with date/time of collection and timepoint collected.
3. Place cryovials into biohazard bag and freeze immediately at -70 to -80°C Celsius.
4. Store blood samples frozen until ready to ship on dry ice. See below for storage conditions.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED.

Freezing
- Freeze Blood samples in a -80°C Freezer or on Dry Ice or snap freeze in liquid nitrogen.

Storage
- Store at -80°C (-70°C to -90°C) until ready to ship.
  - If a -80°C Freezer is not available,
    - Samples can be stored short term in a -20°C Freezer (non-frost free preferred) for up to one week (please ship out Monday-Wednesday only).
    - OR:
      - Samples can be stored in plenty of Dry Ice for up to one week, replenishing daily (please ship out on Monday-Wednesday only).
    - OR:
      - Samples can be stored in liq. nitrogen vapor phase (ship out Monday-Wednesday only).
- Please indicate on Specimen Transmittal Form the storage conditions used and time stored.

Shipping/Mailing:
- Ship specimens on Dry Ice overnight Monday-Wednesday (Monday-Tuesday from Canada) to prevent thawing due to delivery delays. Saturday and holiday deliveries cannot be accepted.
- Include all RTOG paperwork in a sealed plastic and tape to the outside top of the Styrofoam box.
- Wrap frozen specimens of same type (i.e., all serum together, plasma together and whole bloods together) in absorbent shipping material and place each specimen type in a separate biohazard bag. Place specimen bags into the Styrofoam cooler and fill with plenty of dry ice (10 lbs/5kg minimum). Add padding to avoid the dry ice from breaking the tubes.
- Place Styrofoam coolers into outer cardboard box, and attach shipping label and UN3373 and UN1895 stickers to outer cardboard box.
- Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag and that there is enough room for plenty of dry ice. Add padding to avoid the dry ice from breaking the tubes.
- For questions regarding collection, shipping or to order a Blood Collection Kit, please Email RTOG@ucsf.edu or call (415)476-7864

Shipping Address:
FedEx/UPS/Courier address (all courier packages & frozen samples)
RTOG Biospecimen Resource
UCSF
1657 Scott Street, Room 223
San Francisco, CA 94115
Contact # 415.476.7864