An exploratory pilot study of Nab-paclitaxel based induction chemotherapy followed by response-stratified locoregional therapy for patients with stage III and IV HPV-related Oropharyngeal Cancer - the OPTIMA HPV Trial

OPTIMA = O*ro***P***haryngeal* **T***umor* **I***nduction chemotherapy and response-stratified locoregional therapy trial in order to* **M***inimize long term* **A***dverse events*

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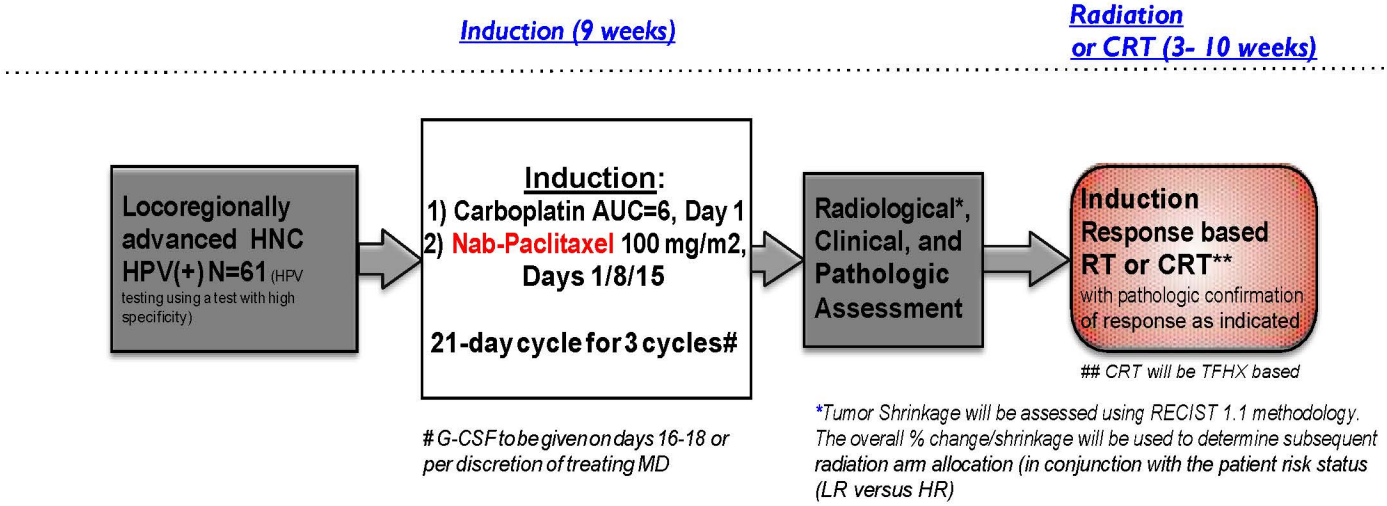
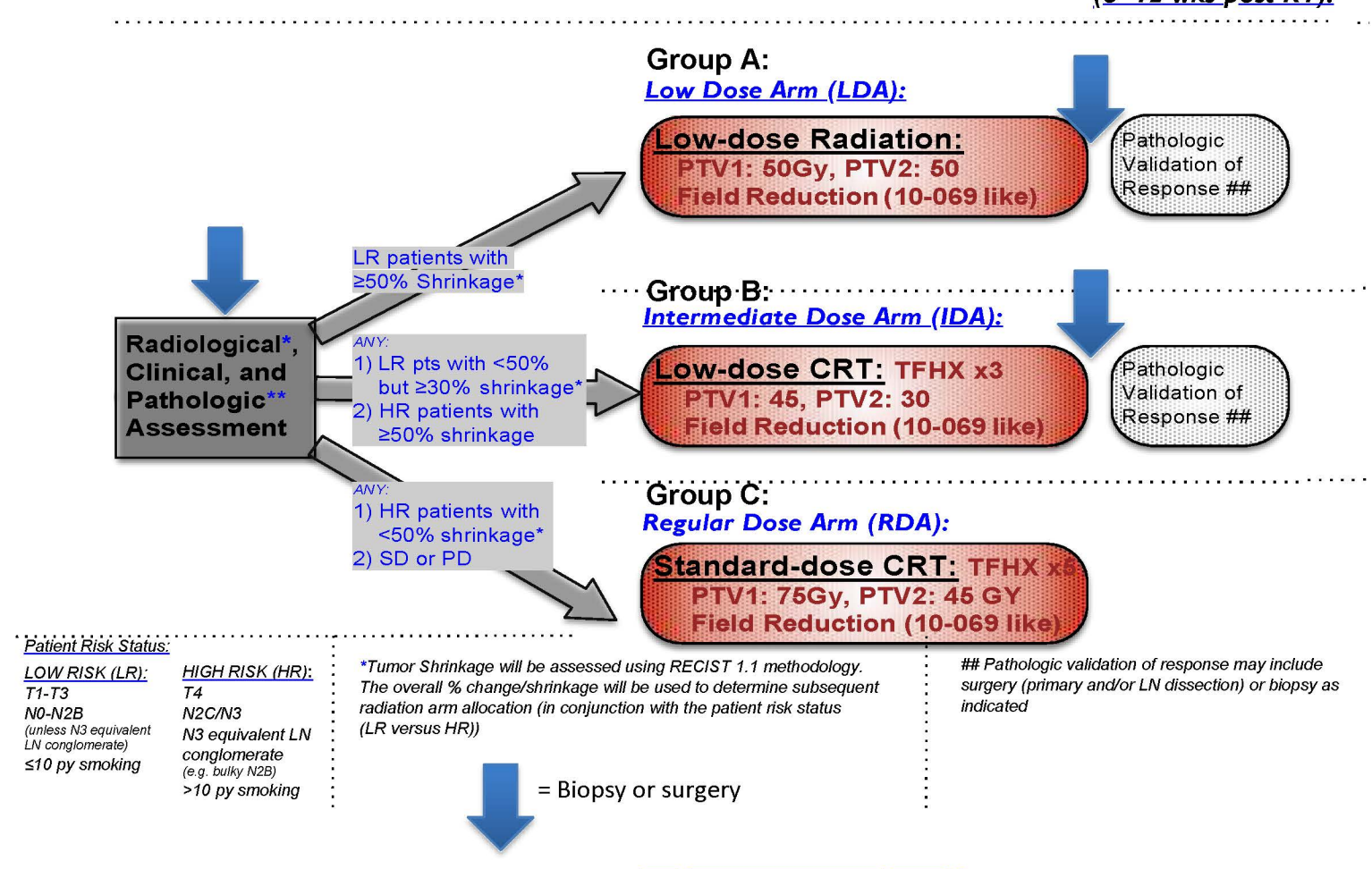
BRIEF SCHEMA



RADIATION - DE-ESCALATION SCHEMA



Trial Design

A Phase II trial in Human Papillomavirus Associated (HPV) – positive head and neck cancer as determined by HPV ISH or HPV PCR in any anatomic site, or p16 immunohistochemistry with confirmatory ISH or PCR in oropharyngeal primary tumors (see Section 4.4 HPV testing) to determine response to induction chemotherapy based on clinical, radiologic and surgical criteria. Patients will undergo evaluation by a multidisciplinary team prior to risk assessment. The patients will be assigned to high and low risk groups based on tumor size, lymph node involvement, and smoking history. Patients will be assigned treatment with radiation with or without chemotherapy following induction chemotherapy with carboplatin and nab-paclitaxel based on RECIST measurement of tumor shrinkage. Patients with low risk disease (T1-3,non-bulky N0-N2B, < 10 pack years tobacco- see Study Rationale section 3.3) (1) who have ≥ 50% reduction by RECIST following induction chemotherapy will be given A) de-intensified treatment with **radiation alone** to 50 Gy. Patients with low risk features and with < 50% but ≥ 30% reduction OR high risk features with ≥ 50% reduction will receive B) de-intensified chemoradiation with TFHX to 45 Gy (3 cycles). Patients who have high risk disease with < 50% reduction or any patients with progression or stable disease during induction chemotherapy will undergo C) chemoradiotherapy with TFHX to 75 Gy (or Cisplatin based CRT as a fallback option in case TFHX is not feasible (see section 5.5).

Background and Rationale

HPV-positive oropharyngeal cancer is associated with improved prognosis compared to HPV-negative squamous cell carcinomas of the head and neck (HNSCCs). Notably, patients with HPV-positive oropharyngeal cancers with a 10 pack year or less smoking history have a greater than 80% 5 year overall survival. (2)These improved outcomes have suggested that toxic multimodality treatment regimens may be de-intensified in order to prolong survival while minimizing toxicity. Previous studies have suggested that response to induction chemotherapy is a highly reliable prognostic factor for outcome following definitive treatment. This was also recently demonstrated in ECOG1308, which showed promising results. The problem is however, that not all HPV positive patients have good outcomes. While there are some reliable factors, which are associated with outcome, there are some factors, which remain unclear, and patients should warrant more intensified treatment to reduce likelihood of recurrence. Therefore, this trial will prospectively analyze response to induction chemotherapy in individual pts (grouped at study enrollment into high and low risk groups based on tumor characteristics) to determine who should have deintensified treatment (allocation to three arms – see schema above).

Patient Population

Patients with locally advanced squamous cell cancer of the head and neck area that are positive for HPV using an E6/E7 based assay is preferred (by HPV ISH or HPV PCR, see section 4.4) will be enrolled. For oropharyngeal HNSCC p16 IHC positivitivity is acceptable (with recommended validation by HPV DNA *in situ* hybridization or PCR post enrollment, see section 4.4). The goals of this study are to diminish long-term

toxicities by testing less intense treatment regimens without compromising chance of cure.

Key Inclusion Criteria

- Patients with locally advanced HPV(+) squamous cell carcinoma. HPV positivity should be determined by HPV ISH or HPV PCR for any anatomic site, or by p16 IHC for oropharyngeal tumors (with confirmatory by ISH or PCR testing after enrollment/start of induction
- Normal Organ function
- Meaurable disease by RECIST 1.1.
- No previous radiation or chemotherapy for a head and neck cancer.
-
- ECOG performance status 0-1 (Karnofsky ≥ 70%; Appendix A).
- Age ≥ 18 yrs
- Obtained informed consent.

(please see full elgibility criteria under 4.1 and 4.2)

Treatment Plan:

Induction therapy: All enrolled patients will receive three (3) 21-day cycles of chemotherapy consisting of nab-paclitaxel (100 mg/m^2 on day 1, 8, 15), and carboplatin (AUC 6 on day 1). Growth factor support will be provided using G-CSF administered on days 16-18). Following induction patients will undergo biopsy if technically feasible. Surgery should not be done at this point, unless diagnostic in intent and residual tumor is left behind.

Surgery/ pan-endoscopy and biopsies: Following chemoradiotherapy, patients will undergo surgical evaluation, and pathologic response evaluation will be considered. This may include either surgery or (e.g. TORS is acceptable). Particular focus will be on the first 50% of patients in groups A and B.

Radiation/CRT/TFHX:

The patients will be assigned to three treatment arms based on response to induction chemotherapy, and high or low risk status. High or low risk status is based on tumor size, lymph node involvement, and smoking history at enrollment on study.

Low Risk Status:

- T1-3

- N 0 - N2B (unless N3 equivalent lymph nodal conglomerate)
- ≤ 10 pack year history tobacco use

High Risk Status:

- T4
- N2C-N3
- N2B disease with N3 equivalent amount of tumor (conglomerate bulky disease ≥ 6cm)
- > 10 pack year history tobacco use

Response Stratified Grouping

Patients will be assigned to Radiation alone or CRT/TFHX based on response to induction chemotherapy. TFHX will consist of 14-day cycles of paclitaxel (100 mg/m^2 Day 1 over 1 hour), 5FU (continuous infusion at 600 mg/m^2/day × 5 days), and hydroxyurea (500 mg PO BID day 0-5, 11 doses/cycle) with twice daily radiation (150 cGy per fraction).

No therapy on days 6-14. Supportive care should be administered as specified in Section 5. For patients in the

Group A/Low Dose Arm (LDA) – Radiation only:

Patients who have **low risk** disease and > 50% reduction of tumor by RECIST with induction chemotherapy will receive 50Gy radiation alone.

Group B/Intermediate Dose Arm (IDA) – Low dose CRT (3 cycles TFHX):

Patients who have **low risk** disease and < 50% but ≥ 30% reduction of tumor by RECIST with induction chemotherapy will receive 45 Gy in 3 cycles TFHX.

OR

Patients who have **high risk** disease and ≥ 50% reduction of tumor by RECIST with induction chemotherapy will receive 45 Gy in 3 cycles TFHX.

Group C/Regular Dose Arm (RDA) – Standard dose CRT (5 cycles TFHX):

Patients who have **low risk** disease and < 30% reduction of tumor by RECIST with induction chemotherapy will receive 75 Gy in 5 cycles TFHX.

OR

Patients who have **high risk** disease and < 50% reduction of tumor by RECIST with induction chemotherapy will receive 75 Gy in 5 cycles TFHX.

OR

Any patient who has progressive disease will receive 75 Gy in 5 cycles TFHX. Cisplatin based CRT may be considered as a fallback option (see details under 4.6)

Duration of treatment:

9 weeks of induction chemotherapy.

Assessment with clinical and radiologic evaluation. Surgical biopsies as clinically indicated.

3-5 cycles (6-10 weeks) of active chemoradiation (2 week cycles) or 5 weeks radiation depending on group/arm allocation following induction chemotherapy.

Number of patients expected to be enrolled:

61 patients.

Statistical analysis

Patients will receive induction chemotherapy for three cycles followed by clinical and radiologic evaluation, and response-based allocation to RT/CRT treatment arms.

Response will be assessed after completion of induction chemotherapy by clinical (per the ENT surgeon), and radiological examination.

We expect to enroll 3-5 patients per month for a total of 61 patients over a period of 18-24 months. Study is designed to accrue 61 evaluable patients for the primary endpoint to allow sufficient statistical power. We expect to activate ~2 additional sites to allow rapid enrollment.

Overall Primary Objective: Non-inferiority compared to HPV(+) patients treated with carboplatin, paclitaxel, cetuximab on the #14401 protocol (EPIC-HN trial)

- We will employ a non-inferiority test in which the objective is to establish that the 2-year PFS rate for an overall treatment regimen that uses induction chemotherapy with nab-paclitaxel/carboplatin, is within an acceptable margin of that for carboplatin, paclitaxel, and cetuximab as part of the EPIC HN trial (2-year PFS=85%) as well as the efficacy goal for 2-year PFS in the ECOG 1308 study (85%). Therefore we assume the true 2-year PFS rate is 85%, and set the non-inferiority margin at 11%, corresponding to 2-year PFS rate for carboplatin, nab-paclitaxel of at least 74%. We will test H_0: Δ<-11% vs. H_A: Δ>=-11%.

- Using Power Analysis and Sample Size (PASS v11) software, a sample of 61 patients will provide 80% power to test this hypothesis using a (one-sided) type I error rate of 0.10. Essentially, H_0 will be rejected and nab-Paclitaxel/Carboplatin based therapy declared not materially inferior to EPIC/E1308 comparators if the lower, one-sided 90% confidence limit for the 2-year PFS rate exceeds 74% (which will occur if 50 or more of the 61 patients are alive and progression-free at two years, i.e., if the *observed 2-year PFS rate* is at least 82%). (This calculation assumes that the true PFS rate for nab-paclitaxel is 85% and that all patients will be followed for a minimum of 2 years.) If dropouts occur, the PFS rate will be estimated using the Kaplan-Meier procedure and its standard error via Greenwood's formula, with corresponding (large-sample) confidence limit. No interim analysis will be conducted.

Response rates will be determined together with 95% confidence intervals. Toxicity will be summarized by type and grade for both late and early toxicity..

2.0 OBJECTIVES

2.1 Primary Objective

To determine the 2-year progression-free survival (PFS).

2.2 Secondary Objectives

- Clinical Complete Response Rate *(Nab-paclitaxel based induction, compared to EPIC induction (Paclitaxel based)*
- Response Rate *(Nab-paclitaxel based induction, compared to EPIC induction (Paclitaxel based)*
- Proportion of Patients with ≥50% shrinkage by RECIST *(Nab-paclitaxel based induction) compared to EPIC induction, Paclitaxel based)*
- Toxicity *(Nab-paclitaxel based induction, compared to EPIC induction (Paclitaxel based)*
- To assess swallowing function and speech at 6 mos and 12 mos post therapy.
- To determine the rates of late toxicity with chemoradiation following surgery as determined by xerostomia, dental decay, osteroradionecrosis, G-tube dependency, tracheostomy placement and dysphagia.
- 2-year OS in patients treated on the Low-Risk, Intermediate-Risk Arm, and High-Risk Arms
- 2-year PFS in patients treated on the Low-Risk, Intermediate-Risk Arm, and High-Risk Arms - Early and Late toxicities
- Evaluate need for post RT/CRT surgery on low- and intermediate-risk arms based on response from induction chemotherapy
- Evaluate in a descriptive manner the role of TORS resection / LND when integrated into a de-escalation trial

2.31 Laboratory Objectives

- To evaluate pathologic/histologic appearance of tumor after induction chemotherapy and after CRT. See section 8.
- Translational research on blood and tissue samples as detailed in section 8.
- To profile tumors genetically and immunolotically in order to assess in a descriptive manner genetic or immunological features characteristic of clinical behavior. See section 8.4.

3.0 BACKGROUND

3.1 Locally Advanced Head and Neck Cancer

Approximately 50,000 new cases of head and neck cancer are diagnosed annually in the United States (3). The majority (90-95%) of these cases are squamous cell carcinomas of the head and neck (HNSCC) and approximately two-thirds are locoregionally advanced cancers (AJCC Stage III-IV) (4). Despite advances in the multimodality treatment of locoregionally advanced HNSCC (LA-HNSCC) over the past two decades, these patients still experience significant morbidity and mortality.

Historically, locoregionally advanced tumors were treated with surgery, radiation therapy, or both. Locoregional failure rates were approximately 30% at 2 years and locoregional failures accounted for nearly 60% of failures. Survival at 5 years was reported to be only 40% (10–30% for patients with stage IVa and IVb tumors). Approximately 20% of patients developed metastatic disease and nearly one-fifth of these patients died of distant metastases without evidence of locoregional recurrence (5-8).

3.1.1Chemoradiotherapy

Given discouraging outcomes with surgery and radiation, investigators became increasingly interested in the incorporation of chemotherapy for the treatment of LA-HNSCC. The feasibility of a non-surgical, organ preservation approach with concomitant chemoradiation was first established by the landmark Veterans Affairs Laryngeal Cancer Study (9, 10). Since then, several randomized trials and meta-analyses have demonstrated improved disease-free and/or overall survival with concomitant chemoradiotherapy and confirmed its role as standard therapy for patients with locoregionally advanced unresectable disease (11-16). The positive effects on disease-free and overall survival seem to be predominantly mediated through improved locoregional control, thus affecting the traditionally predominant pattern of failure for this disease.

Concurrent chemoradiotherapy attempts to capitalize on both the radiosensitizing properties of chemotherapy at sites of known disease targeted by radiation in addition to delivering agents that function systemically to treat occult metastatic disease. However, sensitizing effects are not tumor specific and exert both locoregional effects on adjacent normal tissues within the radiation field as well as systemic effects, particularly on the bone marrow and peripheral nervous system. Concurrent chemoradiotherapy trials have consistently reported an increased incidence of acute grade 3 and 4 toxic effects, with mucositis, dermatitis, and cytopenias being the most prominent (4).This rise creates concern about chronic toxic effects, including consequential late effects, which evolve from persistent severe acute toxic effects.

Optimizing the therapeutic ratio of treatment benefit to toxicity has thus become a focus of recent investigation. Advances in the delivery of conformal radiation, including the development of intensity modulated radiation therapy (IMRT), have allowed significant improvements in sparing normal tissue structures. This is best exemplified by the reduction in rates of xerostomia with sparing of the parotid glands (17). However, other treatment-related morbidities such as dysphagia are still problematic; indeed, 2-year rates of feeding tube dependence have been reported as high as 50% (18-20). This is particularly significant given recent data that quality of life among patients with HNSCC treated with radiotherapy is substantially affected by swallowing dysfunction and the need for enteral nutrition support (21). Efforts are now focused on decreasing the dose of radiation to dysphagia-related structures, particularly the pharyngeal constrictors, which are prone to stricture formation with doses ≥50 Gy (22).

3.1.2 TFHX regimen

At the University of Chicago, we have investigated multiple intensive concomitant chemoradiotherapy regimens. We initially studied the interaction of 5-FU, hydroxyurea and radiotherapy (FHX) (23, 24). Both chemotherapy agents have known systemic activity and have been shown to act as radiation enhancers in vitro and in vivo (6, 25, 26). Cytotoxic activity is synergistic as hydroxyurea modulates the activity of 5-FU by depleting cellular pools of deoxyuridine monophosphate (dUMP) and facilitating binding of the 5-FU metabolite 5-FdUMP to its target enzyme thymidylate synthase (27). Paclitaxel was subsequently added to the FHX regimen (TFHX) and the radiation scheme changed to twice daily to further intensify the treatment (28-32).

The TFHX regimen was demonstrated to be a highly active and tolerable concomitant chemotherapy and hyperfractionated radiation regimen: overall survival and locoregional control rates at 3 years were 60% and 86%, respectively (30, 32). Since surgery was used primarily as a salvage procedure, excellent organ preservation was also achieved. Acute toxicities were severe in a majority of patients but were considered tolerable overall. Mucositis (84% grade 3/4), “in-field” dermatitis (38% grade 3/4), leukopenia (34% grade 3/4), and anemia (22% required transfusion) were the most common serious side effects. At 1 year post-treatment, 61% of patients had severe xerostomia and 47% had compromised swallowing; the rate of feeding tube dependence was 20% (30, 32).

Toxicity rates with TFHX were higher than expected, with a significant number of patients experiencing grade 3/4 mucositis (76%) and dermatitis (61%) (33). Therefore, we attempted to decrease the toxicity of concomitant chemoradiation by decreasing the radiation dose in sequential cohorts to areas at risk for microscopic disease in patients who had either complete or partial (≥50%) response to ICT (34, 35). The cohort receiving 75 Gy to gross disease (high risk), 54 Gy to intermediate-risk volumes, and 39 Gy to low-risk volumes experienced the best therapeutic ratio. Again, high locoregional and distant control rates were seen, though the rate of dermatitis (45%) was significantly lower (34).

With improved locoregional control, the systemic control of micrometastatic disease emerged as an important treatment goal that was not achieved optimally with the chemotherapy doses applied during concomitant chemoradiotherapy. Indeed, approximately 20% of patients were noted to recur distantly, despite the addition of cytotoxic chemotherapy to radiation therapy as part of the TFHX regimen [26-28].

3.1.3 Induction Chemotherapy

On the basis of the aforementioned studies, induction chemotherapy was investigated as a method of successfully eradicating micrometastatic disease. At the University of Chicago, carboplatin and paclitaxel were initially chosen as an induction chemotherapy (ICT) regimen because they are typically well-tolerated with low rates of mucositis. The first report of this regimen demonstrated both high locoregional control and improved distant control (33). Systemic disease progression was noted in 7% of patients; this translated into improved 3-year progression-free and overall survival rates of 80% and 77%, respectively.

Currently, the triplet combination of a taxane (docetaxel or paclitaxel), cisplatin, and 5-FU (TPF) is considered a standard induction regimen (if induction therapy is considered). This is largely based on the results of a meta-analysis demonstrating a 5% increase in survival for cohorts using a cisplatin/fluorouracil (5-FU) combination. There are three recently published phase III trials demonstrating the superiority of induction docetaxel, cisplatin, and 5-fluorouracil over cisplatin and 5-fluorouracil when followed by radiotherapy or chemoradiotherapy (12, 36-39). Controversy still exists regarding the overall survival benefit of adding induction TPF to chemoradiotherapy. Recent studies demonstrating no additional survival benefit are limited by methodological deficiencies (40-42). Additionally, unpublished data demonstrates that TPF and carboplatin/ paclitaxel seem to have equivalent activity with less toxicity with carboplatin and paclitaxel. Two studies evaluating carboplatin/paclitaxel induction demonstrated 82% and 87% response rates compared to our DeCIDE trial 64% response to TPF. (33, 34, 42) Paclitaxel and nab-paclitaxel have the same activity with slightly better delivery and toxicity with nab-paclitaxel. Compared with solvent-based paclitaxel, nab-paclitaxel, delivers 33% higher drug concentration to tumors in preclinical xenograft models, and demonstrates enhanced transport across endothelial cell monolayers (Desai 2006,; Gardner, 2008). The Cremophor El-free medium enables nab-paclitaxel to be given in a shorter duration without the need for premedication to prevent solvent-related hypersensitivity reactions. Standard IV bags and tubing may be used for the delivery of nab-paclitaxel. Hence, in our study we have opted for use of nab-paclitaxel.

3.2 Human Papillomavirus (HPV) and HNSCC

Both epidemiologic and molecular evidence have recently elucidated the causative role of HPV in HNSCC. Approximately 25%–35% of all HNSCC is associated with HPV genomic DNA, with the majority of these cancers occurring in the oropharynx (43). The incidence of oropharyngeal cancer has risen dramatically over the past two

decades and it is now the most common HNSCC (44-46). Both seropositivity and oral infection with high-risk type HPV (HPV-16) have been shown to increase the risk of developing oropharyngeal cancer (OPC) (47, 48). HPV-positive tumors have a unique molecular profile: wild-type p53, upregulated p16, and downregulated pRb (49). There is direct evidence that HPV-16 is oncogenic, mechanistically driving the development and viability of cancer cells (50-52).

There is concern for an impending HNSCC-epidemic due to HPV. Extrapolating recent trends, the annual number of HPV-positive oropharyngeal cancers (HPVOPC) is expected to surpass the annual number of cervical cancers by the year 2020 (53, 54). This is especially concerning in light of the fact that patients with HPV-related OPC are approximately ten years younger on average than their HPV-negative OPC counterparts (46, 54, 55).

Recently, studies have demonstrated that patients with HPV-related OPC have superior response to therapy and survival compared to HPV-negative OPC. In retrospective analyses of survival and HPV status from three phase III trials, unprecedented overall survival of approximately 80-90% at three years was obtained (2, 56, 57). Improved survival in these studies was largely due to markedly improved local-regional control as a biologic consequence of the HPV-origin of these tumors. With the improvement in locoregional control, distant metastasis is now gaining recognition as a leading cause of death in HPV-positive patients and the rate of distant relapse is the same for both HPVOPC and non-HPV related tumors (57-59).

Recursive partitioning analysis has helped to stratify HPVOPC patients for both risk of death and distant relapse. In a retrospective analysis of the association between tumor HPV status and survival among patients with stage III/IV OPC who were enrolled in a randomized trial comparing accelerated-fractionation radiotherapy with standard-fractionation radiotherapy as part of concomitant chemoradiation with cisplatin, HPV status of the tumor was the major determinant of overall survival, followed by the number of pack-years of tobacco smoking (≤10 vs. >10), and then nodal stage (N0 to N2a vs. N2b to N3) for HPV-positive tumors (57). In another retrospective analysis of the association between tumor HPV status and distant metastatic risk in a prospectively assembled cohort of OPC patients treated with radiotherapy alone or concurrent chemoradiotherapy, both tumor size (T1 to T3 vs. T4) and nodal stage (N0 to N2c vs. N3) were found to be major determinants of distant relapse (60). Of note, patients with N2c disease treated with radiation alone, however, had reduced rates of distant control.

3.3 Study Rationale

HPV-related HNSCC is a distinct clinical entity based on differing demographics, biology, and prognosis. The overall survival benefit in patients with HPVOPC compared non-HPV related cases is due largely to a marked improvement in locoregional control. Given the younger demographic of HPVOPC and the significant long-term morbidity incurred with high dose local therapy, reduction of RT intensity is a prudent consideration. Indeed, recent data indicates that quality of life in survivors of head and

neck cancer is most affected by swallowing dysfunction, with stricture formation occurring at doses of ≥50 Gy to the pharyngeal constrictors (21, 22).

Studies of anal cancer treatment provide evidence that excellent locoregional control may be obtained in HPV-related squamous cell cancers with lower doses of radiation as part of a chemoradiotherapy regimen. In a prospective trial of anal cancer patients receiving concomitant 5-FU/mitomycin C and 45 Gy of external beam radiation plus a boost in good responders of either 25 Gy with iridium implant or 15 Gy by external beam radiation, five year locoregional recurrence rates were 32% (61). More contemporary prospective data in head and neck are also promising. ECOG 1308, A Phase II trial of induction chemotherapy followed by cetuximab with low dose or standard dose IMRT in patients with HPV-associated resectable squamous cell carcinoma of the oropharynx reported promising preliminary 1 year progression free survival of 91% in low risk HPV patients treated with low dose radiation. Patients in this trial were placed in low risk and standard risk groups at study entry based on tobacco history, T stage and bulky lymph node status. Eighty patients were enrolled, 62 were in low risk group. Patients were treated with induction cisplatin, paclitaxel, and cetuximab followed by radiation and cetuximab to 54 Gy for low risk disease and 69.3 Gy for standard risk disease. All patients were HPV + by p-16 and/or ISH analysis. Interim analysis of progression free analysis was reported for low and high risk patients with 91% and 89%, respectively. Additionally, subset analysis of 1-year progression free analysis demonstrated 97%, 84% for ≤ and > 10 pack year history of tobacco, 92% (T1-T3)and 86% (T4), and 92% (N0-N2B), and 88% (N2C), respectively. (1)

We have previously demonstrated excellent locoregional control rates with a concomitant chemoradiotherapy regimen of TFHX. With superior locoregional control, the importance of distant control became apparent and ICT was incorporated with reduction in rates of distant relapse. This is an especially important consideration for HPV-related HNSCC, as the rate of distant metastases is the same for both HPVOPC and non-HPV related tumors and distant failure is now gaining recognition as a leading cause of death in HPV-positive patients.

We hypothesize that in locally advanced cases of HPV-related HNSCC, Carboplatin and nab-paclitaxel ICT will produce high rate of complete or good partial responses hence, allowing for reduced intensity chemoradiotherapy and will have excellent outcomes after reduced treatment intensiity radiation or chemoradiation. We hypothesize in particular that this approach wll reduce acute and long-term therapy-related toxicities.

In this study, we will specifically evaluate patients who have stage III or IV, HPV(+), squamous cell cancer of the oropharynx. Patients will be given a course of 3 cycles of carboplatin and nab-paclitaxel ICT followed by clinical, radiologic, and biopsy for pathologic assessment. Radiation to 45 Gy will be given to low dose arm (LDA) patients and concurrent chemoradiation with TFHX and twice-daily irradiation will be given to a total dose of 50 Gy for intermediate dose arm (IDA), or 75 Gy in standard dose arm (SDA) as outlined below.

Low Risk:

- T1-3
- N 0 - N2B (excluding N2B disease with N3 equivalent amount of tumor)
- ≤ 10 pack year history tobacco use

High Risk:

- T4
- N2C-N3
- N2B disease with N3 equivalent amount of tumor (conglomerate bulky disease ≥ 6cm)
- > 10 pack year history tobacco use

Patients will be assigned to Radiation alone or CRT/TFHX based on response to induction chemotherapy. TFHX will consist of 14-day cycles of paclitaxel (100 mg/m^2 Day 1 over 1 hour), 5FU (continuous infusion at 600 mg/m^2/day × 5 days), and hydroxyurea (500 mg PO BID day 0-5, 11 doses/cycle) with twice daily radiation (150 cGy per fraction).

No therapy on days 6-14. Supportive care should be administered as specified in Section 5.

Group A – Low Dose Arm (LDA) - Radiation only:

Patients who have **low risk** disease and > 50% reduction of tumor by RECIST with induction chemotherapy will receive 50Gy radiation alone.

Group B – Intermediate Dose Arm (IDA) - Low dose CRT (3 cycles TFHX):

Patients who have **low risk** disease and < 50% butr ≥ 30% reduction of tumor by RECIST with induction chemotherapy will receive 45 Gy in 3 cycles TFHX.

OR

Patients who have **high risk** disease and ≥ 50% reduction of tumor by RECIST with induction chemotherapy will receive 45 Gy in 3 cycles TFHX.

Group C – Standard Dose Arm (SDA) – regular CRT (5 cycles TFHX):

Patients who have **low risk** disease and < 30% reduction of tumor by RECIST with induction chemotherapy will receive 75 Gy in 5 cycles TFHX.

OR

Patients who have **high risk** disease and < 50% reduction of tumor by RECIST with induction chemotherapy will receive 75 Gy in 5 cycles TFHX.

OR

Any patient who has progressive disease will receive 75 Gy in 5 cycles TFHX.

For group C cisplatin based CRT is acceptable as a fallback option if approved by the PI (Dr. Vokes), and should be completed analogous to the RTOG 0522 or EPIC trials, albeit without cetuximab, and still implement field reductions as outlined in this protocol. (62)

4.0 PATIENT SELECTION

4.1 Eligibility Criteria

- Patients must have pathologically confirmed HPV-positive squamous cell carcinoma.
- HPV testing must follow the following criteria (also see section 4.4)
    - HPV testing using an E6/E7 based assay is preferred, and does not require any validation (e.g. HPV ISH or HPV E6/E7 PCR).
    - For oropharyngeal tumors p16 IHC positivity is sufficient to enroll and initiate treatment (p16 IHC interpretation to follow guidelines by Jordan/Lingen et al 2012). It is recommended that p16 IHC positivity is validated at a later point (during or after treatment) using an E6/E7 based test at the University of Chicago and provided slides will be used.
    - For non-OP tumors accurate HPV testing (i.e. ISH, or E6/E7 based testing) is required for enrollment and treatment initiation.
- Availibility of ≥10 unstained 5 micron slides (to be provided to Dr. Seiwert/Vokes at the University of Chicago)
- Patients must be at least 18 years of age.
- Patients with AJCC (7^{th} edition, 2010) T1-T4 nodal stage N2 or N3 or aT3 or T4 primary tumor with any nodal stage.
- The primary and nodal involvement must be assessable on clinical exam (mucosal and lymph node exam).
- The primary and nodal involvement must have been defined bi- or uni-dimensional measurements measurable by RECIST.
- No previous radiation or chemotherapy for a head and neck cancer.
- No surgical resection for a head and neck cancer within 8 weeks of enrollment (although lymph node biopsy including excision of an individual node with presence of residual nodal disease, or surgical biopsy of the tumor is acceptable).
- ECOG performance status 0-1 (Karnofsky $\geq$ 70%, see Appendix A).

- Leukocytes ≥ 3000/mm3, platelets ≥ 100,000/mm3, Absolute neutrophil count ≥ 1,500, Hemaglobin > 9.0 gm/dL, Albumin > 2.9 gm/dL, total bilirubin ≤ 1.5 mg/dl, creatinine clearance > 45 mL/min (or SCr $\leq$ 1.5 mg/dL), normal within 2 weeks prior to start of treatment.
    - The standard Cockcroft and Gault formula or the measured glomerular filtration rate must be used to calculate CrCl for enrollment or dosing.

    - Patients must have adequate liver function: AST and ALT $\leq$ 2.5 X ULN; alkaline phosphatase $\leq$ 2.5 X ULN

    - Patients must sign a study-specific informed consent form prior to study entry. Patients should have the ability to understand and the willingness to sign a written informed consent document.

4.2 Exclusion Criteria

- Unequivocal demonstration of distant metastases (M1 disease).

- Intercurrent medical illnesses which would impair patient tolerance to therapy or limit survival. Including but not limited to ongoing or active infection, immunodeficiency, symptomatic congestive heart failure, pulmonary dysfunction, cardiomyopathy, unstable angina pectoris, cardiac arrhythmia or psychiatric illness/social situations that would limit compliance.

- Pregnant and nursing women are excluded because of the potential teratogenic effects and potential unknown effects on nursing newborns. Men and women of child-bearing potential are eligible but must consent to using effective contraception during therapy and for at least 3 months after completing therapy. Women with child-bearning potential must have a negative serum or urine B-hCG pregnancy test at screening.

- Other coexisting malignancies or malignancies diagnosed within the previous 3 years no evidence of disease for at least 3 years. Exceptions to this include non-melanoma skin cancer, cervical cancer in situ, well differentiated thyroid cancer or prostate cancer. Other cancers that per assessment of the PI are not prognosis limiting can be allowed after review by the PI.

- Prior surgical therapy other than incisional or excisional biopsy and organ-sparing procedures such as debulking of airway-compromising tumors or neck dissection in a patient with an unknown primary tumor. Residual tumor is required for enrollment on study.

- Patients receiving other investigational agents.

- Peripheral Neuropaghy ≥grade 1

4.3 Criteria for discontinuation/withdrawal of informed consent

Patients may be discontinued from trial treatment at any time, at the discretion of the investigator(s). Specific reasons for discontinuing a patient from study treatment include:

- Objective progression of disease if deemed inappropriate for further study treatment e.g. continuation on the regular dose arm (RDA).

- Unacceptable adverse events.

- Protocol non-compliance.

- Study closure.

- Patient decision to withdraw from the study.

- In the judgment of the investigator, further treatment would not be in the best interest of the patient.

All deaths that occur within the trial period or within 30 days after administration of the last dose of trial drug must be reported primarily for the purposes of serious adverse event (SAE) reporting; however, deaths due unequivocally to progression are not SAEs.

All trial treatment-related toxicities and SAEs must be followed up until resolution. All patients who have new or worsening CTC grade 3 or 4 laboratory values at the time of withdrawal must have additional testing performed, and the results must be recorded in the patients' medical records. In these cases, the investigators must record their opinions in the patients' medical records. Laboratory abnormalities should not be reported as adverse events unless a criterion for an SAE is fulfilled, the laboratory abnormality causes the patient to discontinue from the study, or the investigator insists the abnormality should be reported as an AE.

4.4 HPV testing

As this trial makes treatment decision based on HPV status the specificity of the HPV test is important (63). Therefore certain HPV testing requirements have to be met that take into account varying HPV performance characteristics in oropharyngeal and non-oropharyngeal primary tumors (64):

-1- HPV testing using an E6/E7 based assay is preferred, and does not require any validation (e.g. HPV ISH or HPV E6/E7 PCR).

-2- For oropharyngeal tumors p16 IHC positivity is sufficient to enroll and initiate treatment (p16 IHC interpretation to follow guidelines by Jordan/Lingen et al 2012). It is recommended that p16 IHC positivity is validated at a later point (during or after treatment) using an E6/E7 based test at the University of Chicago and provided slides will be used.

-3- For non-OP tumors E6/E7 based HPV testing (i.e. ISH, or E6/E7 based testing) is required for enrollment and treatment initiation.

5.0 TREATMENT PLAN

5.1 General Considerations

Induction chemotherapy will be administered on an outpatient basis followed by chemoradiotherapy and surgery (as indicated) will be administered on an inpatient basis. All patients will be evaluated by surgical, medical and radiation oncologists prior to entry on the trial to determine optimal local treatment. Patients will start on induction chemotherapy within 6 weeks of enrollment. Three cylces of carboplatin and nab-paclitaxel induction chemotherapy will be followed by response-adjusted radiation/chemoradiation.

Patients in Group A will receive radiation to 50 Gy in standard daily fractionation. For patients in groups B and C, concurrent chemoradiation will consist of twice daily radiation with paclitaxel, 5-FU, hydroxyurea TFHX) given on an alternating week basis. Patients should have a pre-induction chemotherapy CT simulation performed and fused to the planning CT scan. TFHX will be given to a total dose of 50 Gy to patients in Group B and 70 Gy to patients in Group C as outlined below (See Section 5.3).

Surgical validation of patients in Group A and Group B will be planned after completion of radiation/chemoradiotherapy (especially the first 50% of patients in groups A/B). Surgical extent and surgical procedures will be determined by the surgeon (biopsy versus resection versus TORS) based on the protocol guidelines and disease status. Standard resection or Trans oral robotic surgical resection (TORs) and lymph node dissection (LND) will be done for any patients who have residual disease (gross disease or radiologic evidence of disease) following chemoradiotherapy as surgical salvage. (See section 5.7)

5.2 Pre-treatment evaluation

Patients must have completed the following within 4 weeks of registration unless noted:

- Inclusion and Exclusion criteria reviewed.
- Physical examination to define measurable disease.
- Pan-endoscopy with mapping biopsies and documentation (Please see section 7 with respect to biopsy).
- Biopsy proven squamous cell carcinoma of the head and neck with HPV testing (see section 4.4).

- Baseline CT or MRI scans of head and neck that includes entire disease extent within 3 months before study entry. (Scans of the head and upper abdomen should be used as clinically indicated.)

- PET/CT scan prior to start of induction chemotherapy.

- One week prior to chemotherapy, CBC with differential and platelet count, and complete metabolic profile.
- Liver ultrasound or CT scan if the liver chemistries (SGOT, SGPT, and bilirubin) are > 2 times normal values.

- Additional studies (bone scan, barium swallow, etc.) to exclude distant metastases or second primaries as clinically indicated.

- Complete dental evaluation.

- Speech and swallowing consultation.

- Informed consent.

5.3 Study evaluations

Patients will have the following exams and tests throughout the study at specified timepoints (please see study chart):

- Physical examination to define measurable disease.

- Performance status evaluation

- CBC with differential and platelet count.

- Complete metabolic panel.

- Toxicity evaluations

- PET/CT prior to induction chemotherapy and 10-12 weeks after chemoradiation, if no gross residual disease. Patients who have gross residual disease will undergo surgical resection without waiting for PET/CT per ENT recommendations, 4-8 weeks following completion of chemoradiation.

- CT of the head and neck after induction chemotherapy week 3 of 3rd cycle of induction chemotherapy in order to determine radiation fields.

5.4 Induction Chemotherapy

5.4.1 Induction chemotherapy will be administered on an outpatient basis and concurrent chemoradiation will be administered on an inpatient basis. Expected adverse events (AEs) and appropriate dose modifications for these agents are described in Section 5. No other investigational agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

5.4.2 Induction Therapy Details

Carboplatin, and nab-paclitaxel combination will be administered for three cycles of 3 weeks duration each. Chemoradiotherapy will begin after induction chemotherapy (i.e. day 64 of therapy). Dose delays and dose modifications should take place as in section 5.2 **In no case should the three cycles of induction chemotherapy be given over a period exceeding twelve (12) weeks.**

Pre-medications: Premedication with dexamethasone is recommended for all patients receiving weekly paclitaxel or nab-paclitaxel therapy to reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions.

Dexamethasone 20 mg x 1 dose taken intravenously or orally the morning of treatment will be administered.

Nab-Paclitaxel: 100 mg/m^2 in 250 ml of D5W over 60minutes (on Day 1, 8, and 15).

Carboplatin: Start after completion of paclitaxel on Day 1, AUC 6 in 250 ml of NS over 30 -60 minutes

A baseline creatinine level should be drawn within 1 week prior to starting chemotherapy.

Antiemetics: Pre-treatment with a 5 HT-3 antagonist [eg ondansetron hydrochloride (Zofran®), dolasetron mesylate (Anzemet®), or granisetron hydrochloride (Kytril®)] plus a corticosteroid prior to chemotherapy on Day 1 is recommended. The use of additional antiemetics and the prevention of delayed emesis are left to the discretion of the treating physician.

Hydration:
Hydration is left to the discretion of the treating physician.

For each cycle: Use of filgrastim (neupogen) is to be given on Days 16/17/18, but can be modified – increased or decreased as clinically indicated.

5.5 Radiation and Concomitant Chemoradiotherapy Details and Guidelines.

Radiation or concurrent chemoradiation will be administered depending on response-stratified grouping noted below.

Low Risk:

- T1-3
- N 0 - N2B (excluding N2B disease with N3 equivalent amount of tumor)
- $\leq$ 10 pack year history tobacco use

High Risk:

- T4
- N2C-N3
- N2B disease with N3 equivalent amount of tumor (conglomerate bulky disease $\geq$ 6cm)
- > 10 pack year history tobacco use

Response Stratified grouping

Patients will be assigned to Radiation alone or CRT/TFHX based on response to induction chemotherapy. TFHX will consist of 14-day cycles of paclitaxel (100 mg/m^2 Day 1 over 1 hour), 5FU (continuous infusion at 600 mg/m^2/day $\times$ 5 days), and hydroxyurea (500 mg PO BID day 0-5, 11 doses/cycle) with twice daily radiation (150 cGy per fraction).

No therapy on days 6-14. Supportive care should be administered as specified in Section 5.

Group A/Low Dose Arm (LDA) – Radiation only:

Patients who have **low risk** disease and > 50% reduction of tumor by RECIST with induction chemotherapy will receive 50Gy radiation alone.

Group B/Intermediate Dose Arm (IDA) – Low dose CRT (3 cycles TFHX):

Patients who have **low risk** disease and < 50% but $\geq$ 30% reduction of tumor by RECIST with induction chemotherapy will receive 45 Gy in 3 cycles TFHX.

OR

Patients who have **high risk** disease and $\geq$ 50% reduction of tumor by RECIST with induction chemotherapy will receive 45 Gy in 3 cycles TFHX.

Group C/Standard Dose Arm (SDA) – Standard dose CRT (5 cycles TFHX):

Patients who have **low risk** disease and < 30% reduction of tumor by RECIST with induction chemotherapy will receive 75 Gy in 5 cycles TFHX.

OR

Patients who have **high risk** disease and < 50% reduction of tumor by RECIST with induction chemotherapy will receive 75 Gy in 5 cycles TFHX.

OR

Any patient who has progressive disease will receive 75 Gy in 5 cycles TFHX.

Cisplatin based CRT may be used in Group C/Standard Dose Arm as a fallback option, after approval by the PI (Dr. Vokes).

Expected AEs and appropriate dose modifications for nab- paclitaxel, carboplatin, 5-FU, hydroxyurea, and radiation are described in sections 6.1 and 6.2 and Appendix B and C. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

Patients with intermediate or regular dose arm will receive chemoradiation for 3.5-5 weeks as per Chemotherapy should be administered during all 3 weeks of radiotherapy.

Day 0		
	P.M.:	start hydroxyurea at 500 mg PO q 12 hours × 6 days (11 doses). The first daily dose of hydroxyurea on Days 1 – 5 is given 2 hours prior to the first fraction of daily radiotherapy.
	6:00 P.M.:	start continuous infusion of 5-FU at 600 mg/m^2/day × 5 days (120 hours).
Day 1 – 5		dexamethasone 20 mg PO (IV) in am Day 1, 1 hr prior to paclitaxel famotidine 20 mg PO (IV) in am Day 1, 1 hr prior to paclitaxel diphenhydramine 50 mg PO (IV) in am Day 1, 30 mins prior to paclitaxel Start paclitaxel 100 mg/m^2 after first RT fraction on day 1 of each cycle. Paclitaxel should be administered in 250 ml 0.9% NaCl over 60 minutes. Radiation therapy is administered twice daily at 150 cGy per fraction.
Days 6 – 13:		No chemoradiotherapy. **Patients should be seen once on an outpatient basis during these non-treatment days to monitor for toxicity.**

For each cycle: Administer 5 μg/kg subcutaneously (SQ) of G-CSF (filgrastim) daily, beginning on Day 6 through Day 12 at a minimum of 24 hours after completion of 5-FU in patients who develop grade 3 neutropenia or who have neutropenia ≥ grade 2 on Day 0 of any cycle. In these patients, G-CSF should be utilized in all subsequent cycles. G-CSF can be utilized prophylactically from the start of chemoradiotherapy in all cycles at the discretion of the treating physician.

Chemoradiotherapy cycles are repeated every 14 days until the completion of radiotherapy.

As an alternative the option to use Cisplatin based chemoradiotherapy can be approved on a case by case basis for high risk patients. Cisplatin based CRT will be given analogous to the EPIC HN and RTOG 0522 trials, albeit without cetuximab, and with the respective field adjustements as outlined below. Use of Cisplatin based CRT requires prior PI approval (please email/call Dr. Vokes).

5.5.1 Radiation Therapy Guidelines

1. All patients will have a complete dental evaluation prior to the start of radiation therapy, ideally prior to the start of chemotherapy.

2. Treatment approaches will use Intensity Modulated Radiotherapy (IMRT) and, in selected cases, 3D conformal radiotherapy will be used alone or in combination with IMRT. In both instances the physician will attempt to deliver an even dose to the target tissue and minimize doses to surrounding normal structures. The use of customized blocks or multileaf collimation for field shaping is strongly recommended.

3. **Localization requirements:** All patients will be immobilized and simulated in the treatement position prior to the start of induction chemotherapy and after induction chemotherapy within 1-2 weeks after the last cycle of chemotherapy. A contrast enhanced CT with immobilization is required for planning. Slice thickness should be optimally 3mm and no greater than 5 mm. The pre- and post-chemotherapy scans will be fused to define the targets below. Patients must be reproducibly immobilized. Radio-opaque markers may be used whenever possible to delineate the surgical scars, extent of nodal disease, skin involvement, and any gross disease.

4. **Target volumes:** Appropriate field sizes will be determined at the time of simulation to treat gross disease and areas of potential microscopic disease.

Three target volumes will be defined on each CT slice: GTV, PTV1 and PTV2. GTV will be all gross tumor identified by physical exam, additional clinical information and radiographic studies before induction chemotherapy. The GTV will be expanded by 1.5 cm to create PTV1. PTV1 can be modified at the discretion of the treating physician for the constraints of normal tissue tolerance and to avoid extension beyond the skin.

PTV2 will include PTV1 plus the next echelon of uninvolved but at risk lymph nodes that include the nodal stations at risk for microscopic spread as described in the tables below. In general, the pre-induction chemotherapy scan is used to define the primary tumor GTV and the post-induction chemotherapy volume is used to define the nodal volume GTV. PTV2 may not differ significantly from PTV1 if the required GTV expansion includes the next nodal station at risk. For tumors that cross midline in the oral cavity or oropharynx (e.g. tumors involving the soft palate and base of tongue), PTV 2 may include contralateral level 2 LN. PTV2, can be modified at the discretion of the treating physician to achieve dose contraints for normal tissue tolerance and to avoid extension beyond the skin. The inclusion of the retropharyngeal lymph nodes in PTV2 will be at the discretion of the attending radiation oncologist. Reasonable attempts should be made to provide an adequate treatment volume without encroaching on critical organs (e.g. spinal cord) or extending to the skin.

5. Field Size: Appropriate field sizes will be determined at the time of simulation to treat gross disease and areas of potential microscopic disease. Initial field size and arrangement will be at the discretion of the attending radiation oncologist. The optimal field arrangement will be determined based on the treatment planning techniques employed. All fields must be treated during each treatment session.

6. **Treatment technique:** Blocking will be individualized for each patient. Either custom Cerrobend blocks or multileaf collimator will be acceptable.

   Intensity modulated Radiotherapy: Optimal IMRT planning will depend on the planning system employed. We anticipate the optimal plan will use 7 to 11 gantry positions. Acceptable plans will encompass the PTV with the 95% isodose line. No more than 1% of the PTV should receive less than 95% of the prescribed dose. Plans should be reviewed to insure that any part of the PTV getting less than 95% of the prescribed dose is at the edge of the volume. In no case should a central area of the PTV receive less than 95% of the prescribed dose. No more than 1% of the PTV should receive more than 110% of the prescribed dose.

   3D Conformal Radiotherapy: The neck should be treated with opposed lateral fields using a half-field technique. The lower neck should be treated with an anterior field prescribed to a depth of 3 cm. Opposed fields for the lower neck are permitted in order to improve PTV coverage and increase homogeneity.

Wedges, tissue compensators or segmented fields should be used to insure uniformity of PTV coverage. Electron boosts of the posterior neck are permitted to limit the dose to the spinal cord. Electron fields shall be prescribed to the depth of maximum dose with the energy and field size chosen so that the target volume is encompassed within 90% of the prescribed isodose line. A cord block is permitted on the anterior or lateral fields provided it dose not block tumor. Feathering the match line is permitted in cases where a cord block would block tumor. For 3D techniques, acceptable plans will encompass the PTV within the 95% isodose line. The dose variation in the PTV will be +7% and -5% of the prescription point dose.

7. **Dose Fractionation:** Isodose calculations in the axial, sagittal, or coronal planes are required. In addition, dose volume histograms for the GTV and the spinal cord are required.
    i. **Group A:** Radiation will be delivered in 200 cGy daily fractions to a total dose of 5000 cGy. No chemotherapy will be delivered with radiation. Radiation will be delivered for 5 consecutive weeks.
    ii. Group B: Each cycle of treatment will consist of 5 consecutive days of radiation with 150 cGy given bid (300 cGy per day and 1500 cGy per week) in conjunction with chemotherapy. Three total cycles of chemoradiation will be delivered. Ideally, PTV1 and PTV2 will be treated with the first two cycles and PTV1 will be treated with the third cycle. Chemoradiation will be given on an alternating weekly basis. There should be a minimum of 6 hours between fractions. All fields will be treated each day. In the case of mechanical failure or a holiday, one day of BID radiotherapy can be replaced with a single QD fraction of 200 cGy. Accordingly, the final cumulative dose will be slightly less. Ideally, the dose to PTV1 will be 45 Gy and PTV2 will be 30 Gy.
    iii. **Group C (with THFX):** Each cycle of treatment will consist of 5 consecutive days of radiation with 150 cGy given bid (300 cGy per day and 1500 cGy per week) in conjunction with chemotherapy. Five total cycles of chemoradiation will be delivered. Ideally, PTV1 and PTV2 will be treated with the first 3 cycles and PTV1 will be treated with the final 2 cycles. Chemoradiation will be given on an alternating weekly basis. There should be a minimum of 6 hours between fractions. All fields will be treated each day. In the case of mechanical failure or a holiday, one day of BID radiotherapy can be replaced with a single QD fraction of 200 cGy. Accordingly, the final cumulative dose will be slightly less. Ideally, the dose to PTV1 will be 70-75 Gy and PTV2 will be 45-54 Gy.
    iv. **Group C (with concurrent cisplatin):** PTV1 and PTV2 will be treated with to 54 Gy in 1.8 Gy fraction/day. For the last 12 treatment days, PTV1 will be boosted an additional 18 Gy in 1.5 Gy fraction/day given at least 6 hours after the 1.8 Gy fraction.

8. **Normal Tissue Constraints/Dose Volume Histograms:** The dose limit to the spinal cord will vary depending upon the technique used. Attempts should be made to limit the spinal cord dose to < 30 Gy for Low and Intermediate Risk Groups. For High Risk Groups, attempts should be made to limit the spinal cord dose to < 40 Gy with conventional 3D radiation treatment. Doses should be limited to 46 Gy with IMRT techniques and reduced fraction size to the spinal cord.

9. Surrounding critical normal structures should be outlined for study purposes, including the brainstem, spinal cord, superior/middle constrictor muscles, optic nerves/chiasm, parotid glands, temporo-mandibular (T-M) joints and cochlea, oral cavity, mandible, eyes, lens, brachial plexus, esophagus (including postcricoid pharynx) and glottic larynx. The normal tissues will be contoured and considered as solid organs. DVH's must be generated for relevant critical normal structures, any corresponding PRVs, and the unspecified tissues. Institutions that use PRVs must clearly define them as such. Dose constraints are given below:

   Ultimate inclusion of the normal structures and exceptions from the above guidelines will be made at the discretion of theattending Radiation Oncologist.

10. **Special situations:** 3D conformal treatment techniques may be preferable to IMRT in certain situations. Some large primary tumors and some large neck nodes may extend up to the skin. In these situations it may not be possible to add a sufficient margin to the GTV to account for variability in the patient set up. In this situation 3D conformal treatment techniques may be preferable to IMRT.

Detailed Site by Site Instructions for Nodal Planning Target Volume 2 Delineation:

Lateralized Base of Tongue

	Adenopathy Level											
	Ipsilateral						Contralateral					
Involved Nodes	IA	IB	II	III	IV	V	IA	IB	II	III	IV	V
PTV2												
Ipsilateral	IB, II	IA, II	IB, III	II, IV	II, III SCV[1]	II, III	IA, IB, II	II	II	II	II	II
Contralateral	IA	II	II	II	II	II	IB	II	IB	II, IV	II, III SCV	II, III

[1] SCV = supraclavicular lymph nodes

Base of Tongue Crossing Midline

	Adenopathy Level	
	Ipsilateral	Contralateral

Involved Nodes	IA	IB	II	III	IV	V	IA	IB	II	III	IV	V
PTV2												
Ipsilateral	IB, II	IA, II	IB, III	II, IV	II, III, SCV	II, III	IA, IB, II	II	II	II	II	II
Contralateral	IA	II	II	II	II	II	IB	IA, II	IB, III	II, IV	II, III, SCV	II, III

Soft Palate

	Adenopathy Level											
	Ipsilateral						Contralateral					
Involved Nodes	IA	IB	II	III	IV	V	IA	IB	II	III	IV	V
PTV2												
Ipsilateral	IB, II	IA, II	IB, III	II, IV	II, III, SCV	II, III	IA, IB, II	II	II	II	II	II
Contralateral	IA	II	II	II	II	II	IB	IA, II	IB, III	II, IV	II, III, SCV	II, III

Lateralized Tonsil

	Adenopathy Level											
	Ipsilateral						Contralateral					
Involved Nodes	IA	IB	II	III	IV	V	IA	IB	II	III	IV	V
PTV2												
Ipsilateral	IB, II	IA, II	IB, III	II, IV	II, III, SCV	II, III	IA, IB, II	II	II	II	II	II
Contralateral	IA	---	---	---	---	---	IB	IA, II	IB, III	II, IV	II, III, SCV	II, III

Tonsil with base of tongue invasion

	Adenopathy Level											
	Ipsilateral						Contralateral					
Involved Nodes	IA	IB	II	III	IV	V	IA	IB	II	III	IV	V
PTV2												
Ipsilateral	IB, II	IA, II	IB, III	II, IV	II, III, SCV	II, III	IA, IB, II	II	II	II	II	II
Contralateral	IA	II	II	II	II	II	IB	II	IB, III	II, IV	II, III,	II, III

											SCV	

Oropharynx involving Larynx

	Adenopathy Level											
	Ipsilateral						Contralateral					
Involved Nodes	IA	IB	II	III	IV	V	IA	IB	II	III	IV	V
PTV2												
Ipsilateral	IB, II	IA, II	III	II, IV	II, III, SCV	II, III	IA, IB, II	II	II	III	III	II
Contralateral	IA	II	II	II	II	II	IB	IA, II	IB, III	II, IV	II, III, SCV	II, III

Oropharynx involving oral cavity (lateralized)

	Adenopathy Level											
	Ipsilateral						Contralateral					
Involved Nodes	IA	IB	II	III	IV	V	IA	IB	II	III	IV	V
PTV2												
Ipsilateral	IB, II	IA, II	IA, IB, III	IA, IB, II, IV	IA, IB, II, III, IV, SCV	IA, IB, II, III	IA, IB, II	IA, IB, II	IA, IB, II	IA, IB, II	IA, IB, II	IA, IB, II
Contralateral	IA, IB	---	---	---	---	---	IB, II	IA, II	IA, IB, III	IA, IB, II, IV	IA, IB, II, III, SCV	II, III

Oropharynx involving oral cavity (crosses midline)

	Adenopathy Level											
	Ipsilateral						Contralateral					
Involved Nodes	IA	IB	II	III	IV	V	IA	IB	II	III	IV	V
PTV2												
Ipsilateral	IB, II	IA, II	IA, IB, III	IA, IB, II, IV	IA, IB, II, III, IV, SCV	IA, IB, II, III	IA, IB, II	IA, IB, II	IA, IB, II	IA, IB, II	IA, IB, II	IA, IB, II
Contralateral	IB,	IB,	IB,	IB,	IB, II	IB	IB,	IA,	IA,	IA,	IA,	II,

	II	II	II	II		, II	II	II	IB, III	IB, II, IV	IB, II, III, SCV	III

Oropharynx involving Nasopharynx

	Adenopathy Level											
	Ipsilateral						Contralateral					
Involved Nodes	IA	IB	II	III	IV	V	IA	IB	II	III	IV	V
PTV2												
Ipsilateral	IB, II, VA	IA, II, VA	IB, III, VA	II, IV, VA	II, III, VA, SCV	II, III	IA, IB, II, VA	II, VA	II, VA	II, VA	II, VA	II, VA
Contralateral	IA	II	II	II	II	II	IB, VA	IA, II, VA	IB, III, VA	II, IV, VA	II, III, SCV , VA	II, III, VA

5.6 Supportive Guidelines

- Antiemetics will be ordered at the discretion of the attending physician.
- Use of growth factor support (G-CSF) on days 16/17/18), see above
- A double lumen venous access device (e.g., Port-a-Cath®) is recommended prior to initiation of therapy.
- Use of a feeding device is recommended for high-risk patients. Placement of a feeding device is left to the discretion of the treating physician/investigator. Commonly applied criteria for feeding device placement include
    i. Loss of > 10% of body weight from the start of therapy
    ii. Dehydration or inability to maintain adequate oral hydration
    iii. Inability to maintain intake of ≥ 25 kcal/kg of ideal body weight
- During chemoradiotherapy patients should receive instructions for oral hygiene and prescriptions to include:
    i. Oral nystatin or fluconazole (100mg QD)
    ii. Viscous lidocaine HCl (Xylocaine®) solution) and/or Grade I mouthwash 10ml QID, swish and spit

Table: Grade I mouthwash

Lidocaine, Viscous (2%)	50 mL
Diphenhydramine elixir (12.5 mg/5 mL)	50 mL
Sodium bicarbonate injection	100 mL
Normal saline irrigation	500 mL
Total volume	700 mL

iii. Normal saline mouthwash 10ml QID swish and spit

iv. Natural Care Gel (or similar product) BID during chemoradiotherapy and TID during rest week.

v. Vigilon (or similar product) to be applied to open wounds during chemoradiotherapy.

vi. Silvadene cream to open wounds followed by zinc oxide cream and then Telfa dressings BID during rest week (N.B.: discontinue Silvadene and zinc oxide creams 1 day prior to radiotherapy).

vii. Aquaphor (or similar brand) cream to lips PRN.

viii. Adequate analgesia is essential to maintain oral intake and patient comfort. Narcotic analgesics are usually necessary and should be used at the physician/investigator discretion.

ix. Therabite for trismus if appropriate.

x. Replacement for electrolyte imbalances when applicable.

- Prior to discharge of the patients after a cycle of chemoradiation, a CBC and platelet count, and determination of serum electrolytes, including creatinine will be performed.

- **A visit to the treating physician is strongly recommended between cycles of chemoradiation (i.e., days 6-14)**

- Use of intravenous home hydration is strongly recommended in patients with inadequate oral intake: normal saline 1000ml IV QD during rest week (days 6-14).

- If Hgb < 10, patients should generally be transfused an amount sufficient to increase Hgb to $\geq$ 10. The Hgb level should be maintained > 11 mg/dl for the duration of chemoradiotherapy in all patients.

- The use of peg-filgrastim is described in section 6 and G-CSF (filgrastim) is described in section 5.2.

- The use of amifostine during chemoradiotherapy is **not** permitted

5.7 Surgical Guidelines

Following chemoradiotherapy, patients will undergo surgical evaluation, and pathologic response evaluation will be considered. This may include either surgery or biopsy. Particular focus will be on the first 50% of patients in groups A and B.

Simple excision (e.g., transoral laser excision or TORS) of the primary lesion may be performed if it can be accomplished while preserving organ function. Modified or selective neck dissection may also be performed.

Curative intent surgery should typically NOT be performed prior to study enrollment, and study enrollment can only proceed with RECIST 1.1. measurable disease is present.

5.8 Post-therapy follow-up

Every subject should be followed clinically until taken off study. After the 30-day follow-up evaluations, patients should undergo clinical and radiographic disease evaluation every 3 months in year 1, every 6 months in years 2 and 3, and annually in years 4 and 5. Radiographic assessment should include imaging of the head and neck and chest. Laboratory evaluation should consist of at least a CBC, serum electrolytes, serum creatinine, liver enzymes (AST, ALT, alkaline phosphatase), serum calcium, and serum albumin. TSH should be measured at least annually.A PET scan is required within 3 months after treatment. If nodal disease persists, a lymph node dissection must be performed. Otherwise, neck dissections are at the discretion of the treating physician. This schedule can be altered according to the physician's discretion. Suspicion of progressive disease should be evaluated by radiographic studies whenever possible.

5.9 Duration of Therapy

In the absence of treatment delays due to adverse events, treatment may continue for 14-20 weeks or until one of the following criteria applies:

- Disease progression.

- Intercurrent illness that prevents further administration of treatment.

- Unacceptable adverse event(s).

- Patient decides to withdraw from the study.

- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investiga

5.10 Late Toxicity Assessment

5.10.1 Schedule

Swallowing function and speech will be assessed pretreatment or within 3 weeks of starting treatment, post-induction/pre-CRT as clinically indicated, on treatment as clinically indicated and then 1, 6 and 12 months post treatment.

5.11.2 Assessment of Late Toxicity

Performance measures will be assessed by determining swallowing function and speech. Voice will be assessed as a simple yes/no response from patients as to whether their voice has returned to normal. Swallowing will be determined by patients' ability to swallow table food. A formal swallow evaluation will be done on patients experiencing dysphagia. Additionally, late toxicity will be determined by evaluating presence and degree of xerostomia, and dental decay, osteoradionecrosis, as well as the presence of G-tube dependency, tracheostomy placement, and dysphagia.

6.0 EXPECTED ADVERSE EVENTS, RISKS AND DOSE MODIFICATIONS

6.1 Expected Adverse Events

6.1.1 Nab-Paclitaxel

- Cardiovascular: ECG abnormal (60%; 35% in patients with a normal baseline). Edema /fluid retention (10%), hypotension (5%), cardiovascular events (grades 3/4: 3%; included chest pain, cardiac arrest, supraventricular tachycardia, thrombosis, pulmonary thromboembolism, pulmonary emboli, and hypertension)
- Dermatologic: Alopecia (90%)
- Gastrointestinal: Nausea (30%; grades 3/4: 3%), diarrhea (27%; grades 3/4: <1%), vomiting (18%; grades 3/4: 4%), mucositis (7%; grades 3/4: <1%)
- Hematologic: Neutropenia (80%; grade 4: 9%), anemia (33%; grades 3/4: 1%), myelosuppression (dose-related), bleeding (2%), neutropenic fever (2%), thrombocytopenia (2%; grades 3/4: <1%)
- Hepatic: AST increased (39%), alkaline phosphatase increased (36%), GGT increased (grades 3/4: 14%), bilirubin increased (7%)
- Neuromuscular & skeletal: Sensory neuropathy (71%; grades 3/4: 10%; dose dependent; cumulative), weakness (47%; severe 8%), myalgia/arthralgia (44%), peripheral neuropathy (grade 3: 10%)
- Ocular: Vision disturbance (13%; severe [keratitis, blurred vision]: 1%)
- Renal: Creatinine increased (11%; severe 1%)
- Respiratory: Dyspnea (12%), cough (7%)
- Miscellaneous: Infection (24%; primarily included oral candidiasis, respiratory tract infection, and pneumonia) Hypersensitivity reaction (4%, includes chest pain, dyspnea, flushing, hypotension; severe: <1%)

6.1.2 Carboplatin

- Dermatologic: Alopecia (includes other agents in combination with carboplatin)

- Endocrine & metabolic: Hypomagnesemia, hypokalemia, hyponatremia, hypocalcemia; less severe than those seen after cisplatin (usually asymptomatic)
- Gastrointestinal: Nausea, vomiting, stomatitis, diarrhea, anorexia
- Hematologic: Myelosuppression is dose related and is the dose-limiting toxicity; thrombocytopenia is the predominant manifestation, with a reported incidence of 37% in patients receiving 400 mg/m^2 as a single agent and 80% in patients receiving 520 mg/m^2; leukopenia has been reported in 27% to 38% of patients receiving carboplatin as a single agent (nadir: ~21 days following a single dose)
- Hepatic: Alkaline phosphatase increased, AST increased (usually mild and reversible)
- Otic: Hearing loss at high tones (above speech ranges, up to 19%); clinically-important ototoxicity is not usually seen
- Renal: Increases in creatinine and BUN have been reported; most of them are mild and they are commonly reversible; considerably less nephrotoxic than cisplatin
- Neuromuscular & skeletal: Peripheral neuropathy (4% to 6%; up to 10% in older and/or previously-treated patients)
- <1% (Limited to important or life-threatening): Neurotoxicity, urticaria, rash, nephrotoxicity, secondary malignancies, anaphylaxis, malaise, hypertension

5-Fluorouracil

Common toxicities include:

- Gastrointestinal – diarrhea, mucositis, nausea, and vomiting
- Hematologic – myelosuppression
- Dermatologic – photosensitivity, skin dryness, hand-foot syndrome, increased pigmentation of skin, increased pigmentation of veins used for infusion, nail changes

Less commonly observed toxicities include

- Cardiac – myocardial ischemia, arrhythmias
- Allergic reactions
- Neurologic – acute cerebellar syndrome, disorientation, headache
- Eye – lacrimal duct stenosis, lacrimation, photophobia, and visual changes

5-FU may cause birth defects and should not be used in pregnant women. It is a known radiation sensitizer and may potentiate side effects of radiation.

Paclitaxel

Common toxicities include

- Myleosuppression
- Anemia

- Alopecia
- Myalgias and arthralgias
- Peripheral neuropathy
- Nausea and vomiting (usually mild)
- Diarrhea
- Mucositis
- Hypersensitivity reaction - fever, facial flushing, chills, shortness of breath, or hives after Taxol is given. The majority of these reactions occur within the first 10 minutes of an infusion. Notify your healthcare provider immediately (premedication regimen has significantly decreased the incidence of this reaction).

Less common side effects

- Peripheral edema
- Abnormal liver function tests
- Hypotension
- Skin reactions/darkening of the skin
- Nail changes/discoloration
- Electrocardiogram (ECG) abnormalities with bradycardia, heart block, bundle branch block, and ventricular tachycardia,

The following are less common side effects (occurring in 10-29%) for patients receiving Taxol:

- Swelling of the feet or ankles (edema).
- Increases in blood tests measuring liver function. These return to normal once treatment is discontinued. (see liver problems).
- Low blood pressure (occurring during the first 3 hours of infusion).
- Darkening of the skin where previous radiation treatment has been given (radiation recall - see skin reactions).
- Nail changes (discoloration of nail beds - rare) (see skin reactions)

Hydroxyurea

Common side effects include:

- Myelosuppression (mainly leukopenia)
- Nausea, vomiting
- Diarrhea or constipation
- Stomatitis

It may aggravate the inflammation of mucous membranes secondary to irradiation.

Less common side effects include:

- Dysuria or impairment of renal tubular function
- Rare neurologic disturbances, e.g., headaches, dizziness, disorientation, hallucination and convulsion.

Cisplatin

Common side effects include:

- Nausea and vomiting
- Renal toxicity
- Electrolyte wasting (magnesium, calcium, potassium)
- Myelosuppression
- Anemia

Less common side effects include:

- Peripheral neuropathy
- Hearing loss
- Anorexia
- Dysguesia, metallic taste
- Elevated liver function tests
- Alopecia
-

Filgrastim

Toxicities, warnings, and drug interactions are specified in Sections 6.

Radiation

Radiation to the head and neck will cause skin irritation, dry mucous membranes due to salivary gland dysfunction, mucositis and stomatitis. The concomitant administration of chemotherapy will aggravate these side effects. Long-term side effects include myelitis, osteoradionecrosis, hoarseness, hypothyroidism, trismus, swallowing dysfunction, and fibrosis of soft tissues.

6.2 Dose modifications

This study will utilize the CTC (NCI Common toxicity Criteria) Version 2.0 for toxicity and Adverse Event reporting. A copy of the CTC Version 2.0 can be downloaded from the CTEP home page (http://ctep.info.nih.gov).

6.2.1 Chemotherapy

During Induction Chemotherapy

No more than two dose modifications should be allowed for any patient. If a patient requires a third dose-reduction study treatment should be discontinued. If such a patient is clinically benefiting from treatment, and, if the physician believes the toxicity

will be alleviated sufficiently with dose modification, further treatment will be permitted at the discretion of the Principal Investigator in consultation with Celgene Corporation, U.S. Medical Affairs. In no case should the two cycles of induction chemotherapy be given over a period exceeding ten (10) weeks.

Hematologic toxicity

- If ANC are <1,500 cells/mm^3 or platelets <100,000 cells/mm^3 on Day 1 of Cycle 2, 3 repeat counts once or twice a week. Administer cycle 2,3 with 1 dose reduction of the starting doses of carboplatin and albumin-bound paclitaxel.
- Day 8, 15 of each cycle should only be held for ANC < 500 or PET< 50,000.
- A delay in therapy of up to 3 weeks is permitted for count recovery. (please use table for dose reductions)
- If ANC are <1,500 or platelets <100,000 on day 8 of cycle 1 or day 8 of cycle 2, reduce all subsequent doses of nab-paclitaxel and carboplatin (If any) to one dose reduction of the previous dose. Withhold treatment until counts recover to an absolute neutrophil count of at least 500 cells/mm^3 and a platelet count of at least 50,000 cells/mm^3 on days 8 or 15 of the cycle. Growth factor support should then be used with subsequent cycles.
- Patients should not begin a new cycle of treatment unless the ANC is ≥1000 cells/mm^3, the platelet count is ≥100,000 cells/mm^3.

Dose Modification

Dose modification

Adverse Drug Reaction	Occurrence	Weekly ABRAXANE Dose (mg/m^2)	Every 3-Week Carboplatin Dose (AUC mg•min/mL)
Neutropenic Fever (ANC less than 500/mm^3 with fever >38°C) OR Delay of next cycle by more than 7 days for ANC less than 1500/mm^3 OR ANC less than 500/mm^3 for more than 7 days	First	75	4.5
	Second	50	3
	Third	Discontinue Treatment	
Platelet count less than 50,000/mm^3	First	75	4.5
	Second	Discontinue Treatment	

Neurotoxicity (Peripheral)

- Withhold albumin-bound paclitaxel for grade 3-4 peripheral neuropathy. Resume albumin-bound paclitaxel and carboplatin at reduced doses (see table) when peripheral neuropathy improves to Grade 1 or completely resolves.

Severe sensory Neuropathy – Grade 3 or 4	First	75	4.5
	Second	50	3
	Third	Discontinue Treatment	

Ototoxicity:

For grade 3 ototoxicity discontinue carboplatin.

Hypersensitivity

Albumin-bound paclitaxel (Nab-paclitaxel):

For grade 3 reactions manage the reaction according to institutional guidelines. For subsequent doses, use steroid and anti-histamine pretreatment and increase the infusion time to 60 minutes. For documented grade 4 hypersensitivity reactions, manage the reaction according to institutional guidelines and discontinue nab-paclitaxel.

Liver

Nab-Paclitaxel:

- Mild impairment (AST or ALT <10 times ULN and bilirubin ≤1.25 times ULN): No adjustment required.
- Moderate impairment (AST or ALT <10 times ULN and bilirubin 1.26-2 times ULN): Reduce dose to 75 mg/m^2.
- Severe impairment: AST or ALT <10 times ULN and bilirubin 2.01-5 times ULN: Reduce dose to 50 mg/m^2. May increase up to 75mg/m^2 in subsequent cycles if liver impairment improves to either moderate or mild impairment (based on individual tolerance).
- AST or ALT >10 times ULN or bilirubin >5 times ULN: Discontinue nab-paclitaxel.

No dose adjustment required for Carboplatin

Other: (mucositis)

- For all other grade ≥ 2 toxicities (except alopecia, nausea, vomiting, fatigue and anorexia), reduce carboplatin and albumin-bound paclitaxel by 25% for all subsequent doses during induction.
- In the event of recurrent grade 3 or 4 toxicity attributed to chemotherapy (excluding transaminase elevation, nausea, vomiting, and alopecia) reduce carboplatin and nab-Paclitaxel by a further 25% during induction.

During Concurrent Chemoradiotherapy

Other Dose Modifications and Adverse Event Management

Hematologic Dose Modifications for Hydroxyurea:

Neutropenia:

If the absolute neutrophil count (ANC) is between 500 and 1000 on day 0 – 5 of each cycle, decrease hydroxyurea to 50% of the full dose. On subsequent cycles, a reduced starting dose of hydroxyurea should be used.

For ANC of ≤ 500/μl on Day 0 – 5 of any cycle, omit hydroxyurea, and administer 600 mg/m^2/day of 5-FU and radiotherapy only. On subsequent cycles, a reduced starting dose of hydroxyurea by 50% should be used.

Thrombocytopenia:

For a platelet count of 50,000/μl to 74,000/μl on Day 0 – 5 of each cycle, decrease hydroxyurea to 50% of full dose. On subsequent cycles, a reduced starting dose of hydroxyurea may be used.

For a platelet count ≤ 50,000/μl on Day 0 – 5 of any cycle, omit hydroxyurea, and administer 600 mg/m^2/day of 5-FU and radiotherapy only. On subsequent cycles, a reduced starting dose of hydroxyurea by 50% should be used.

Hematologic Dose Modifications for Paclitaxel:

Dose Level	Paclitaxel (mg/m^2)

0	100
–1	75
-2	50

Discontinue Paclitaxel if further dose reduction is required.

Neutropenia and Thrombocytopenia:

For ANC ≤ to 1000 or platelet count of 50-74 on day 0-5 of each cycle: decrease paclitaxel by one dose level.

For ANC </= 500 or platelet count of less than 50 on day 0-5 of any cycle: hold paclitaxel for that cycle and decrease by one dose level in subsequent cycles.

Mucositis, Dysphagia, Dermatitis, Diarrhea

Treatment cycles should not be delayed for mucositis, dysphagia, dermatitis or diarrhea.

For grade 4 mucositis, dysphagia, and dermatitis exceeding 7 days duration or persisting on Day 1 of a subsequent cycle, decrease 5-FU to 500 mg/m^2/day.

For grade 4 diarrhea exceeding 7 days duration or persisting on Day 1 of a subsequent cycle, decrease 5-FU to 500 mg/m^2/day.

Doses will not be increased again on subsequent cycles.

Nephrotoxicity

Grade 2 renal toxicity – administer 50% dose hydroxyurea

Grade 3, 4 renal toxicity – Hold hydroxyurea

Hepatotoxicity on day 0: Grade 3, 4 – Hold hydroxyurea and adjust paclitaxel per package insert

Peripheral neuropathy:

For Grade 2 peripheral neuropathy, decrease paclitaxel by one dose level per CRT dosing schedule (see hematologic toxicity chart).

For Grade 3 or greater peripheral neuropathy, discontinue paclitaxel.

Other Non-hematological Toxicity

Chemoradiotherapy should not be interrupted for non-hematologic toxicity except as judged necessary on a case-by-case basis by the treating radiation, medical oncologists, and Principal Investigator.

In the presence of a persisting fever ≥ 38C or other clinically apparent infection a cycle can be postponed for 1 week or interrupted (if treatment cycle has already started) if this is necessary in the opinion of the treating medical and radiation oncologists.

Cutaneous vasculitic toxicities, including vasculitic ulcerations and gangrene, have occurred in patients with myeloproliferative disorders during therapy with hydroxyurea. These vasculitic toxicities were reported most often in patients with a history of, or currently receiving, interferon therapy. Due to potentially severe clinical outcomes for the cutaneous vasculitic ulcers reported in patients with myeloproliferative disease, hydroxyurea should be discontinued if cutaneous vasculitic ulcerations develop.

Geriatric Use: Elderly patients may be more sensitive to the effects of hydroxyurea, and may require a lower dose regimen. This drug is known to be excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Cisplatin

Renal Toxicity

CrCl 46-60 – 25% dose reduction

CrCl 31-45 – 50% dose reduction

Myelosuppression

If the absolute neutrophil count (ANC) is < 1000 on day 1 of each cycle, hold cisplatin and when count recover > 1000 ANC, then decrease cisplatin 25%. On subsequent cycles, a reduced starting dose of cisplatin should be used.

Peripheral neuropathy

If Grade 2 neuropathy on day 1 of each cycle, then decrease cisplatin 25%. On subsequent cycles, a reduced starting dose of cisplatin should be used.

If Grade 3 or greater neuropathy on day 1 of each cycle, hold cisplatin and when neuropathy recovers to grade 2 or better, then decrease cisplatin 25%. On subsequent cycles, a reduced starting dose of cisplatin should be used.

General Toxicity Information

Any other significant toxicity that is felt to be potentially drug related should be discussed between the PI and the treating physician and dose reduction can be implemented for the benefit and safety of the patient.

Radiotherapy should not be interrupted for non-hematologic toxicities except when judged necessary on a case-by-case basis by the treating radiation and medical oncologist in consultation with the PI.

All interruptions or changes to study drug administration must be recorded.

It will be documented whether or not each patient completed the clinical study. If for any patient either study treatment or observations were discontinued the reason will be recorded. Reasons that a patient may discontinue participation in a clinical study are considered to constitute one of the following:

1. adverse event(s)

2. abnormal laboratory value(s)
3. abnormal test procedure result(s)
4. disease progression
5. protocol violation
6. subject withdrew consent
7. lost to follow-up
8. administrative problems
9. death

7.0 AGENT FORMULATION AND PROCUREMENT

7.1 Nab-paclitaxel

Classification:
Antineoplastic Agent, Antimicrotubular; Natural Source (Plant) Derivative; Taxane Derivative

Mode of Action:
Albumin-bound paclitaxel nanoparticle formulation. Paclitaxel promotes microtubule assembly by enhancing the action of tubulin dimers, stabilizing existing microtubules, and inhibiting their disassembly, interfering with the late G_2 mitotic phase, and inhibiting cell replication. May also distort mitotic spindles, resulting in the breakage of chromosomes. Paclitaxel may also suppress cell proliferation and modulate immune response.

How Supplied:
Injection, powder for reconstitution: Abraxane®: 100 mg [contains albumin (human)]

Storage:
Store in vials in original cartons at room temperature (20oC-25oC; 68oF to 77oF). Retain in the original package to protect from bright light.

Stability:
Unopened vials of nab-paclitaxel are stable until the date indicated on the package when stored at the above temperature in the original package. Reconstituted vials of albumin-bound paclitaxel may be refrigerated at 2oC to 8oC (38oF to 46oF) for a maximum of 8 hours and should be protected from bright light

Dose Specifics:
Albumin-bound paclitaxel 100mg/m2 IV over 30, minutes on day 1 and 8 of each 21-day cycle (total of 2 cycles)

Preparation:
Reconstitute each vial with 20 mL of 0.9% sodium chloride injection, USP injected over at least 1 minute. Direct the NaCl onto the inside wall of the vial, and not directly onto the lyophilized cake, as this will result in foaming. Following reconstitution, allow the vial to sit for a minimum of 5 (five) minutes to ensure proper wetting of the lyophilized cake/powder. Gently swirl and/or invert the vial slowly for at least 2 minutes until complete dissolution of any cake/powder occurs.

Rapid agitation or shaking will result in foaming. If foaming or clumping occurs, stand solution for at least 15 minutes until foam subsides. The reconstituted suspension should appear milky and homogeneous without visible particulates. If unsuspended powder is visible, the vial should be gently inverted again to ensure complete resuspension, prior to use. Each ml of reconstituted product will contain 5 mg of paclitaxel. Withdraw the desired volume and inject the suspension into an empty sterile PVC container.

Route of Administration
Albumin-bound paclitaxel will be administered as an IV infusion over 30 minutes. On days when carboplatin is given, albumin-bound paclitaxel will be administered first. Filters are not required for preparation or administration of albumin-bound paclitaxel. If filters are used as part of institutional procedures, the pore size must be ≥ 15 micron.

Drug Return and Destruction
Study drug will be disposed of as per the University of Chicago Medical Center Investigational Pharmacy drug destruction policy/procedure. The following information must be recorded on the site's pharmacy drug accountability log:

Quantity of vials destroyed.
Expiration date
Lot number.

The pharmacist must document that the study drug was destroyed in accordance with their institution's drug destruction policy or SOP. A drug destruction memo and the site's drug destruction SOP/policy should be sent to Celgene Medical Operations Dept. A copy of the drug destruction memo should be retained at the clinical site. In the event of study completion or termination, a copy of all pharmacy records (drug dispensing log, drug accountability log and any destruction memos) must be mailed to Celgene Medical Operations.

a) Supplier

Celgene Corporation
86 Morris Avenue

Summit, NJ 07901

Industry Contact:

Martha Kennedy
Manager, Medical Operations
Celgene Corporation
400 Connell Drive, 7th Floor
Connell Corporate Park
Berkeley Heights, NJ 07922
Mobile: 908-723-6919
Fax: 908-673-2779
Email: Mkennedy@celgene.com

b) Drug Distribution

ABRAXANE® will be distributed by Celgene Corporation. No supplies will be shipped to any site until regulatory approval has been obtained. Investigational sites will be supplied with ABRAXANE® upon identification and screening of a potential trial subject.

Upon identification of a potential subject, sites must fax a completed Drug Request Form to Celgene Corporation. Allow at least 5 working days for drug shipment. There are no shipments on Fridays or holidays.

For re-supply of drug, please complete and fax the Drug Request Form to Celgene Corporation at 908-673-2779.

c) Drug Return and Destruction

If the investigational site does not have a policy, procedure or SOP detailing the process to follow for study drug destruction, the study drug must then be returned to Celgene using the Drug Return Form provided in the package containing the study drug. The following information must be recorded on the site's pharmacy drug accountability log: quantity of vials to be returned, expiration date and lot number. A copy of the Drug Return Form and the study drug should be returned to Celgene Clinical Supplies Dept. using the mailing address on the packaging slip that came with the original study drug order. A copy of the Drug Return Form should be retained at the clinical site. In the event of study completion or termination, a copy of all pharmacy records (drug dispensing log, drug accountability log and any destruction memos) must be mailed to Celgene Medical Operations.

If the investigational site has a policy, procedure or SOP detailing the process to follow for study drug destruction, the pharmacist or designee can choose to destroy the study drug on site. The following information must be recorded on the site's pharmacy drug accountability log: quantity of vials destroyed, expiration date and lot number. The pharmacist must document that the study drug was destroyed in accordance with their institution's drug destruction policy or SOP. A drug destruction memo and the site's drug destruction SOP/policy should be sent to Celgene Medical Operations Dept. A copy of the drug destruction memo should be retained at the clinical site. In the event of study completion or termination, a copy of all pharmacy records (drug dispensing log, drug accountability log and any destruction memos) must be mailed to Celgene Medical Operations.

7.2 Carboplatin

Carboplatin: supplied commercially as a sterile lyophilized powder available in single-dose vials containing 50 mg, 150 mg and 450 mg of carboplatin. Each vial contains equal parts by weight of carboplatin and mannitol. Please refer to package insert for information on preparation.

Side effects: listed in section 9.3. Please refer to the package insert for full prescribing information.

Preparation: Immediately before use, the content of each vial must be reconstituted with either sterile water for injection, USP, 5% dextrose in water, or 0.9% sodium chloride injection, USP to produce a carboplatin concentration of 10 mg/ml. When prepared as directed, carboplatin solutions are stable for 8 hours at room temperature. Since no antibacterial preservative is contained n the formulation, it is recommended that carboplatin solutions be discarded 8 hours after dilution.

Storage and Stability: Unopened vials of carboplatin are stable for the life indicated on the package when stored at controlled room temperature and protected from light.

Administration: Administer over 1⁄2 hour after completing the paclitaxel infusion. The Calvert Equation (Dose=AUC (CC+25) will be used to achieve the desired dose where CC = Wt*(140-age)/72/creatinine (if female use 85%).

7.3 Fluorouracil

5-Fluorouracil (Adria, OH): commercially available as 10 ml ampules containing 500 mg/10 ml. No dilution is necessary for administration, but it may be further diluted in D5W or normal saline. It is stored at room temperature and is stable for 24 hours. It will be administered by intravenous continuous infusion. Please refer to the package insert for full prescribing information.

7.4 Hydroxyurea

Hydroxyurea (Bristol-Myers Squibb, Princeton, NY): commercially available as 500 mg capsules. It is stored at room temperature and will be administered orally. Please refer to the package insert for solution preparation and expected AE. Please refer to the package insert for full prescribing information.

7.5 Paclitaxel

Chemistry: Paclitaxel is a natural product with antitumor activity. The chemical name for paclitaxelis 5,20- Epoxy- 1,2 hexahydroxytax- 11- en 9- one 4, 10 diacetate 2- benzoate 13- ester with *(2R,3S)*- N- benzoyl- 3- phenylisoserine. Paclitaxel is a white to off- white crystalline powder with the empirical formula C47H51NO14 and a molecular weight of 853.9. It is extremely lipophilic and melts at around 216- 217°C. Paclitaxel is highly insoluble in water.

Mechanisms of Action: Microtubules have been demonstrated to be very strategic targets for antineoplastic agents; however, few antimicrotubule agents have been discovered and encompassed into standard chemotherapeutic regimens. Paclitaxel, a diterpenoid plant product extracted from the bark of the western yew *(Taxus brevifolia)*, has a unique mechanism of action. Unlike other antimicrotubule agents in clinical use *(e.g. colchicine, vincristine, and vinblastine)* that shift the equilibrium between microtubules and tubulin subunits toward microtubule disassembly, paclitaxel promotes assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization. These microtubules are stable even when treated with low temperatures or calcium, conditions that usually promote disassembly. This unusual stability results in the inhibition of the normal dynamic reorganization of the microtubule network that is essential for vital interphase and mitotic cellular functions. In addition, paclitaxel induces abnormal arrays or "bundles" of microtubules during mitosis.

Human Toxicology: The dose limiting toxicities and MTD of paclitaxel administered on a variety of schedules to patients with solid neoplasms were previously evaluated in phase I trials. In these studies, paclitaxel was infused over 1, 3, 6, and 24 h, but severe acute reactions, characterized by bronchospasm, hypotension, stridor, tachy- and bradyarrhythmias, and death, resulted in the temporary discontinuation of all trials. These reactions were attributed to paclitaxel's Cremophor vehicle, since identical reactions were observed with other drugs formulated with it and when the vehicle alone was administered to animals. Since a higher incidence of these acute reactions was observed with shorter durations of infusion, studies that used shorter infusions were permanently discontinued, and trials that evaluated longer infusion durations *(24 h)* were resumed using antiallergic pre- medications consisting of corticosteroids, H1- and H2- histamine antagonists. These modifications were associated with a marked reduction in the incidence of acute reactions. Neutropenia was the major dose- limiting toxicity for paclitaxel in phase I solid tumor trials. In addition, a sensory neuropathy, characterized by a glove- and- sock distribution of numbness and paresthesias, was

observed at higher doses. Nausea and vomiting, myalgias, mucositis, total- body alopecia, diarrhea, and phlebitis were also observed.

Pharmaceutical Data:
Formulation: Paclitaxel *(TAXOL®)* for Injection Concentrate is a clear colorless to slightly yellow viscous solution. It is supplied as a solution in a nonaqueous medium. It is intended for dilution with a suitable parenteral fluid prior to intravenous infusion. Paclitaxel is available in 30 mg *(5mL)* vials. Each mL of sterile non- pyrogenic solution contains 6 mg paclitaxel, 527 mg of Cremophor®EL *(polyoxyethylated castor oil)* and 49.7% *(v/v)* dehydrated alcohol, USP.

Storage and Stability: Unopened vials of Paclitaxel for Injection Concentrate are stable until the date indicated on the package when stored under refrigeration, 2°- 8°C *(36°47° F)*. Refrigeration is not required for shipping. Freezing does not adversely affect the concentrate. Solutions for infusion which are prepared as recommended are stable at ambient temperature and lighting for up to 27 hours.

Administration: Paclitaxel should be given after the patient has received the appropriate premedication as per institutional standards. Paclitaxel: supplied in 5 ml vials containing 30 mg of drug (6mg/ml). Please refer to the package insert for information on preparation and for full prescribing information.
Drug interactions: There is a potential for interaction with Ketoconazole, which might interfere with paclitaxel metabolism.

Contraindications: Known hypersensitivity to either paclitaxel or Cremaphor EL.

7.6 Cisplatin

Formulation: Cisplatin is a sterile aqueous solution, each mL containing 1 mg cisplatin and 9 mg sodium chloride. Cisplatin is supplied in multidose vials of 50 mg and 100 mg cisplatin. Please refer to package insert for information on preparation.

NOTE: Aluminum reacts with cisplatin causing precipitate formation and loss of potency; therefore, needles or intravenous sets containing aluminum parts that may come in contact with the drug must not be used for the preparation or administration of cisplatin.

Storage: Store at 15° to 20°C. Do not refrigerate. Protect unopened container from light. The cisplatin remaining in the amber vial following initial entry is stable for 28 days protected from light or for 7 days under fluorescent room light.

Side effects are listed in section 9.4. Please refer to the package insert for full prescribing information.

Availability: Cisplatin is commercially available from Bristol Laboratories Oncology Products.

7.7 Filgrastim (Neupogen®) Drug Information

Packaging and Formulation

G-CSF (Filgrastim) is commercially available. Filgrastim is a sterile, clear, colorless, preservative-free liquid for parenteral administration, containing Filgrastim at a specific activity of 1.0 ± 0.6 x 10^8 U/mg (as measured by a cell mitogenesis assay). The product is available in single use vial form and prefilled syringe. The single use vial contains 480 mcg Filgrastim at a fill volume of 1.6 mL. The formulation is: 480 mcg of Filgrastim (r-methHuG-CSF), containing acetate (0.94 mg), sorbitol (80.0 mg), Tween® 80 (0.004%), sodium (0.056 mg) in water for injection, USP q.s. ad (1.6 mL). The single use prefilled syringe contains 0.6 mg Filgrastim at a fill volume of 0.8 mL. The formulation is: 480 mcg of Filgrastim (r-methHuG-CSF), containing acetate (0.472 mg), sorbitol (40.0 mg), Tween® 80 (0.004%), sodium (0.028 mg) in water for injection, USP q.s. ad (0.8 mL).

Storage Conditions and Stability

Filgrastim should be stored in the refrigerator at 2° to 8°C (36° to 46°F). Avoid shaking. Prior to injection, Filgrastim may be allowed to reach room temperature for a maximum of 24 hours. Any vial or pre-filled syringe left at room temperature for greater than 24 hours should be discarded. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit; if particulate or discoloration are observed, the container should not be used. At a concentration of 5 mcg/ml or greater in D5W, filgrastim is stable for 7 days at room or refrigerator temperatures. At dilutions from 5 to 15 mcg/ml, albumin in a final concentration if 2mg/ml should be added to protect against adsorption to plastic materials. Addition of albumin is unnecessary when the drug is diluted to a concentration greater than 15 mcg/ml in D5W. Dilutions in D5W are stable in glass bottles, polyvinyl chloride, polyolefin or polypropylene bags and IV sets, and Travenol Infusors.

Dilution of Neupogen® to a final concentration of less than 5 mcg/mL is not recommended at any time. Do not dilute with saline at any time because the product may precipitate.

Preparation and Administration

If using the vial, draw the appropriate dose into a syringe for subcutaneous injection. If using the pre-filled syringe, select the appropriate pre-filled syringe for subcutaneous injection. Inject only the appropriate dose, discard the unused drug. Incompatibilities: Normal saline.

Adverse Reactions

The following events are associated with Filgrastim and meet the regulatory definition of “expected”. The only consistently observed clinical toxicity described with Filgrastim is medullary bone pain. Other clinical adverse events that have been described include skin rash, and cutaneous vasculitis. Since commercial introduction of Neupogen®, there have been rare reports of allergic-type reactions. Biochemical abnormalities that may occur include increases in alkaline phosphatase, uric acid, and lactate dehydrogenase.

Overdosage

The maximum amount of Filgrastim that can be safely administered has not been determined. Efficacy was demonstrated at doses of 4 to 8 mcg/kg/day in the phase 3 study of nonmyeloablative chemotherapy. Patients in bone marrow transplant studies received up to 138 mcg/kg/day without toxic effects, although there was a flattening of the dose response curve above daily doses of greater than 10 mcg/kg/day.

In Fligrastim clinical trials of cancer patients receiving myelosuppressive chemotherapy, WBC > 100,000/mm^3 have been reported in less than 5% of patients, but were not associated with any reported adverse clinical effects.

In cancer patients receiving myelosuppressive chemotherapy, discontinuation of Filgrastim therapy usually results in a 50% decrease in circulating neutrophils within 1 to 2 days, with a return to pretreatment levels in 1 to 7 days.

Toxicity/Warnings

Filgrastim is contraindicated inpatients with known hypersensitivity to *E coli*-derived proteins, pegfilgrastim, Neupogen®, or any other component of the product.

Rare cases of splenic rupture have been reported following the administration of colony-stimulating factors, including Filgrastim, for peripheral blood progenitor cell (PBPC) mobilization in both healthy donors and patients with cancer. Some of these cases were fatal. Individuals receiving Filgrastim who report abdominal or shoulder tip pain, particularly healthy donors receiving Filgrastim for PBPC mobilization, should be evaluated for an enlarged spleen or splenic rupture.

Adult respiratory distress syndrome (ARDS) has been reported in neutropenic patients with sepsis receiving Filgrastim, and is postulated to be secondary to an influx of neutrophils to sites of inflammation in the lungs. Neutropenic patients receiving Filgrastim who develop fever, lung infiltrates, or respiratory distress should be evaluated for the possibility of ARDS. In the event that ARDS occurs, Filgrastim should be discontinued until resolution of ARDS and patients should receive appropriate medical management for this condition.

Allergic-type reactions occurring on initial or subsequent treatment have been reported in < 1 in 4000 patients treated with Filgrastim. These have generally been characterized by systemic symptoms involving at least 2 body systems, most often skin (rash, urticaria, facial edema), respiratory (wheezing, dyspnea), and cardiovascular (hypotension, tachycardia). Some reactions occurred on initial exposure. Reactions tended to occur within the first 30 minutes after administration and appeared to occur more frequently in patients receiving Filgrastim IV. Rapid resolution of symptoms occurred in most cases after administration of anti-histamines, steroids, bronchodilators, and/or epinephrine. Symptoms recurred in more than half the patients who were rechallenged.

Severe sickle cell crisis have been reported in patients with sickle cell disease (specifically homozygous sickle cell anemia, sickle/hemoglobin C disease, and sickle/□+ thalassemia) who received Filgrastim for PBPC mobilization or following chemotherapy. One of these cases was fatal.

PREGNANCY AND LACTATION

Since there are no adequate and well-controlled studies in pregnant women, the effect, if any, of Filgrastim on the developing fetus or the reproductive capacity of the mother is unknown.

It is not known whether Filgrastim is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Filgrastim is administered to a nursing woman.

DRUG INTERACTIONS

No formal drug interaction studies between pegfilgrastim and other drugs have been performed. Drugs which may potentiate the release of neutrophils, such as lithium, should be used with caution. Patients receiving lithium and Filgrastim should have more frequent monitoring of neutrophil counts.

Nursing Guidelines

Filgrastim should be kept in the refrigerator until needed and the vials or Pre-filled Syringe should not be shaken. The drug should be administered at the same time each day. Vials and Pre-filled Syringes of filgrastim are single-dose and the remaining drug should be discarded. Refer to protocol text for information regarding requirements for documentation of doses administered, temperatures, side effects, etc. Acetaminophen is the recommended analgesic for mild bone pain. Duration of therapy will be determined by the return of blood counts (WBC/ANC) to specific values.

8.0 CORRELATIVE/SPECIAL STUDEIS

8.1 Objective

It remains unclear what the histologic features of dying HNSCC are, and how to interpret tissue that has been obtained after chemotherapy. We will therefor combine the effort to assess pathologic response post induction chemotherapy with review of histology and correlative with radiologic and clinical assessment. Dr. Nicole Cipriani in the Univ. of Chicago pathology department will lead this effort. We will also evaluate tumors on surgery/biopsy post chemoradiotherapy.

Furthermore it remains unclear what the molecular and immunological determinants are that predict for improved responses for HPV-associated HNSCC. While largely descriptice, in order to accomplish such analysis we will collect tumor, blood, and saliva as part of our regular tissue banking effort on all patients.

Plasma, DNA and RNA will be extracted from patient samples and stored until further analysis.

8.2 Sample and Tissue Procurement

Archival tumor collection

All patients at the time of enrollment need to provide ≥10 5-micron uncstained slides for correlative analysis. Under extenuating circumstances the PI can waive this requirement, but it is expected that patients, who cannot fulfill this requirement undergo a new biopsy prior to enrollment on study.

Tissue Biopsy

Tumor biopsy will be performed prior to starting therapy or archival tissue will be obtained for all patients. At the time of surgical resection or biopsy, tissue in excess of what is necessary for diagnostic purposes will be obtained <15 min after removal from the patient. Tissues will be instantaneously frozen and stored anonymously with a unique barcode at -80C in a locked freezer in Biospecimen Shared Resource (Tissue Bank) at The University of Chicago. Additional alternative processing (e.g. tissue digestion, and cell suspension generation for flow analyses is also acceptable).

- Write study number, patient initials and date on plastic cryomold.
- Weigh or estimate sample weight and slice sample into less than 0.5 cm thick fragments.
- Place tissue into cryotube labeled with study number, patient initials and date filled with RNAlater reagent from Qiagen.

- Freeze over liquid nitrogen vapors or in -80 C freezer.

Blood Isolation

Blood will be obtained from all patients enrolled in the study for pharmacogenomics and biomarker evaluation. Investigation of the relevant polymorphisms will take place in germline DNA extracted from peripheral whole blood (10 ml) collected in EDTA (purple top) plastic vacutainer tubes (i.e. BD catalog #366643). Investigation of cytokine markers will be from peripheral blood (10 ml) collected in a red top vacutainer tubes. Blood should be stored at -80 C and sent to Biospecimen Shared Resource (Tissue Bank) at The University of Chicago for DNA extraction and serum isolation. Please label vacutainer with study number, patient initials and date of draw. DNA extraction for genotyping will be performed according to commercially available DNA isolation kits such as Qaigen. For isolation of serum, specimens will then remain at room temperature for 15 minutes and then centrifuged at room temperature at approximately 1000 x g for 5 minutes. The serum supernatant will be removed and stored at –80°C in 125µl aliquots. Isolated DNA will be store anonymously with a unique barcode at -80 C at the University at Chicago for future genotype analysis.

Patients will have blood samples for genotyping and serum analysis collected prior to induction chemotherapy. Samples for serum analysis will be collected prior to radiotherapy initiation, and then after the first week and at the completion of radiotherapy and will be collected at 2 months after radiotherapy.

8.3 Shipment

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

Dr. Mark Lingen (773-702-5548), email: mlingen@uchospitals.edu)
University of Chicago
FMI Dock/Lab Supply
5830 S. Ellis Ave
Room G-02
Chicago, IL 60637
Attn: Mary Jo Fekete (773 834 4593, email: mfekete@bsd.uchicago.edu)

N.B.: Samples must be shipped to arrive Monday to Thursday. Samples should not be shipped on holidays. Please notify Leslie Martin when sample has been shipped.

All participating institutions outside of the University of Chicago will be provided with a University of Chicago Federal Express Account assigned to this study.

Each sample must be accompanied with a list containing the following information:

Treating Physician Information
Patient name, Patient ID number, date of birth, sex
Diagnosis
Day started on clinical protocol (date consent signed)
Site of biopsy (if applicable)
Date and time of biopsy (if applicable)

On arrival, each sample will be assigned a PIN code. All subsequent handling of the tissue samples will be blinded to the investigators performing various tests, except for the clinical pathologists.

8.4 Correlative analysis

A number of exploratory analyses will be performed to better characterize factors contributing to treatment benefit or failure.

8.4.1 Biopsy samples after induction chemotherapy and/or chemoradiotherapy will be stained by immunohistochemical staining, and assessed histo-morphologically to descripe the characteristics of dying HPV(+) HNC. Analyses will be performed by Dr. Nicole Cipriani and colleagues. These analyses will be descriptive, but will be correlated with clinical outcome, i.e. amount of tumor shrinkage, failure after treatment, side effects etc.

8.4.2 For patients that fail therapy (and control samples for comparison), genetic analysis including the mutational spectrum, expression phenotype and other genetic profiling features will be examined in an exploratory manner. This may include profiling using next generation sequenting (e.g. Foundation medicine, or as outline in Seiwert et al ASCO 2013). Patients have the option to opt out of such genetic analyses in the consent form.

8.4.3 Using both archival or fresh tumor samples (tissue digest or fresh frozen/OTC tissue) we will analyze the immune microenvironment and CD8 Tumor infiltrating lymphocyte characteristics in a small number of patients in a descriptive fashion, comparing patients that fail therapy with tumors from control tumors. The analyses may include determination of CD8, PDL1, FOXP3, IDO, and other immune related markers that will be determined by immunohistochemistry, immunofluorescence, or flow

cytometry (cell digest). Analysis of the T cell receptor characteristics (e.g. TCR repertoire from blood and tumor tissue) will be performed by PCR, and next generation sequencing, or a similar technique. Analysis will be descriptive, but are aimed at identifiying high risk characteristics that lead to failure from therapy. Patients have the option to opt out of such genetic analyses in the consent form.

9.0 STUDY CALENDAR

Baseline evaluations are to be conducted within 1 week prior to start of protocol therapy. Scans and x-rays must be done 6 weeks prior to starting therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

		Induction Chemotherapy			Radiotherapy/Chemoradiotherapy*								
	Pre-study	C1	C2 &3	Surgery	Pre-RT	RT-C1*	RT-C2*	RT-C3*	RT-C4*	RT-C5*	30 day follow-up	3 months post-radiotherapy	Every 3-4 months f/u up to 2 years post-radiotherapy
Induction chemotherapy		X	X										
Radiotherapy/CRT*						X*	X*	X*	X*	X*			
Concurrent Chemotherapy*						X		X		X			
Biopsy***/surgery[1]	X***			X***							X[1]		
CT or PET/CT**	X				(X)*							X	X (as indicated
MR/CT of head and neck	X				(X)*						X		
Blood/Tissue for correlatives	X/X			X/X	X	X				X	X	X	
Informed consent	X												
Demographics	X												
Medical history	X												
Concurrent meds	X	X----------X											
Physical exam	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X												
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X
Performance status	X	X	X	X	X	X	X	X	X	X	X	X	X
CBC w/diff, plts	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse event evaluation	X	X----------X									X	X	X
Tumor measurements	X				X							X	X
□-hCG	X												
HPV testing	X												

* RT-C = radiation therapy cycle

1 – Surgery 4-8 weeks following CRT, or when clinically indicated (should only be performed post RT/CRT completion).

For Group A – every cycle is 1 week and treatment will continue until the target dose (50Gy is reached)

For Groups B and C - the TFHX regimen (week-on week-off) will be used. Every cycle (RT-C) is two weeks (one week on treatment, one week off treatment). Patient should be seen during their off weeks as indicated in the schedule. Treatment should continue until the respective dose is reached (typically Group B = 3 cycles, Group C = 5 cycles). For Cisplatin based CRT please refer to the respective publication (Ang RTOG0522 ASCO 2012).

**MRI or CT of the head and neck can be substituted for PET/CT after induction chemotherapy.
*** Biopsy should be performed in no adequate archival tissue is available pre-study. After induction a second biopsy should be performed.

10.0 MEASUREMENT OF EFFECT

For the purposes of this study, patients should have a baseline PET/CT scan for initial documentation of objective response. Scans will also be obtained before induction chemotherapy, before chemoradiation and at 12 weeks post-chemoradiation.

Response and progression will be evaluated in this study using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST v1.1)

Committee [Therasse et al]. Changes in only the largest diameter (unidirectional measurement) of the tumor lesions are used in the RECIST v1.1 criteria. Note: Lesions are either measurable or non-measurable using the criteria provided below.

10.1 Response Criteria

Will follow RECIST [Therasse et al].

10.2 Progression-Free and Overall Survival

10.2.1 Progression-Free: From the date of registration to the date of progressive disease (as defined in 9.3.3) or death.

10.2.2 Overall Survival time: From the date of registration to the date of death or date of last patient contact if censored.

10.2.3 Distant failure free survival: From the data of registration to the date of distant progression or death.

10.2.4 Assessment of Local/Distant Failure: If disease progression is documented, patients should have full assessment of sites of failure (i.e. local and distant). Local failure should be assessed by radiographic imaging and otolaryngology examination. Distant failure should be assessed by radiographic imaging. Further assessment of local and distant failure can be performed if warranted by patient symptoms.

11.0 REGULATORY AND REPORTING REQUIREMENTS

Adverse events (AEs) will use the descriptions and grading scales found in the revised NCO Common Toxicity Criteria (CTC). This study will utilize the CTC version 3.0 for adverse event reporting. All appropriate treating areas will have access to a copy of the CTC version 3.0. A copy of the CTC version 3.0. A copy of the CTC version 3.0 can be downloaded from the CTEP web site (http://cetp.cancer.gove/reporting/ctc.html).

SAE Reporting Wording

Adverse events must be reported to regulatory authorities according to the definitions and timelines specified in the local laws and regulations.

Serious events are defined as any untoward medical occurrence that at any dose results in:

- Death
- Initial or prolonged inpatient hospitalization
- A life-threatening situation (where the patient is at immediate risk of death).
- Severe or permanent disability.
- Congenital anomaly.
- Or, is significant for any other reason.

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

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

Serious adverse events occurring after a patient is discontinued from the study will NOT be reported unless the investigator feels that the even may have been caused by the study drug or a protocol procedure. Study-specific clinical outcomes of death because of disease progression are exempt from serious adverse event reporting, unless the investigator deems them related to use of the study drug. Hospitalization for study drug administration is not a serious adverse event.

In general, serious adverse events assessed as clearly being due to disease progression and not due to study drugs(s) should be excluded from adverse event

reporting. However, in cases where the specificity or severity of an event is not consistent with the risk information, the even should be reported.

11.1 Expedited Adverse Event Reporting

11.1.1 Expedited Reporting Guidelines (including hospitalization defined in bullet 1 below):

Unexpected Event		Expected Event	
Grades 2-3 Attribution of possible, probable or definite	Grades 4 and 5 Regardless of attribution	Grades 1-3	Grades 4 and 5 Regardless of attribution
Expedited report within 5 working days. Grade 1 Adverse Event Expedited Reporting NOT required.	Reporting by phone to UC Clinical Trials Office within 24 hours. Expedited report to follow within 5 working days. Deaths to be reported by phone to UC Clinical Trials Office within 24 hours. Expedited report to follow within 48 hours. This includes all deaths within 30 days of the last dose of treatment with an investigational agent regardless of attribution. Any late death attributed to the agent (possible, probable or definite) should be reported within 48 hours of site's knowledge.	Adverse event expedited reporting NOT required.	Expedited report within 5 working days. This includes all deaths within 30 days of the last dose of treatment with an investigational agent regardless of attribution. Any late death attributed to the agent (possible, probably or definite) should be reported within 48 hours of site's knowledge.

For Hospitalization only – Any medical event equivalent to CTC Grade 3,4 or 5 which precipitated hospitalization (or prolongation of existing hospitalization) must be reported regardless of designation or unexpected and attribution.

Reporting a serious adverse events

Within 24 hours of knowledge of Serious Adverse Event:

Telephone reports to the University of Chicago Cancer Center Clinical Trials Office (773-834-0357) within 24 hours (or next business day) when investigator and/or research study nurse becomes aware of the event.

The following information is required when calling in the event:

- Reporter's Name and Telephone Number
- Patient Initials
- Patient Medical Record Number
- IRB Protocol Number
- PI of Study
- Treating Physician
- Date of Event
- Description of Event (including grade of the event and if the event required hospitalization).

Email is sent to the research nurse, treating physician and PI of the study informing them that SAE notification has been received.

Serious adverse events (SAE) are defined above. The investigator must inform Celgene in writing using a Celgene SAE form or MEDWATCH 3500A form of any SAE within 24 hours of being aware of the event. The written report must be completed and supplied to Celgene by facsimile within 24 hours/1 business day. The initial report must be as complete as possible, including an assessment of the causal relationship between the event and the investigational product(s), if available. Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up report. A final report to document resolution of the SAE is required. The Celgene tracking number (AX-CL-HN-PI-004235) and the institutional protocol number should be included on SAE reports (or on the fax cover letter) sent to Celgene. A copy of the fax transmission confirmation of the SAE report to Celgene should be attached to the SAE and retained with the patient records.

If this is a multicenter trial, suggest including language indicating that participating study sites must report SAEs to Celgene as described and within 24 hours of awareness. Participating sites should also report SAEs to the primary study site.

Celgene Drug Safety Contact Information:
Celgene Corporation
Global Drug Safety and Risk Management
Connell Corporate Park
300 Connell Dr. Suite 6000
Berkeley Heights, NJ 07922
Fax:(908) 673-9115
E-mail: drugsafety@celgene.com

Within 5 working days of knowledge of Serious Adverse Event:

A completed MedWatch form (FDA form 3500A) must be sent to the University of Chicago Cancer Center Clinical Trials Office (fax number 773-702-8855) within **5 working days of event occurrence**. If the event occurred at the University of Chicago, the University of Chicago's IRB Adverse Event Form must also be filled out. The UC IRB Serious and Unexpected Adverse Event form is available on-line at: http://ors/IRB/AEserious.pdf. The UC IRB Fatal/Life-Threatening Event form is available on-line at: http://ors/IRB/AEfatal.pdf. This form must be typed. Once the forms are completed, the PI will then review, sign and place in QA coordinator's box.

Once the appropriate SAE documents have been received, the University of Chicago Cancer Center Clinical Trials Office submits these to the IRB and a copy will be forwarded to the appropriate Research Nurse.

A list of agent specific expected adverse events can be found in the protocol.

11.1.2 Forms

The UC IRB Serious and Unexpected Adverse Event form is available on-line at: http://ors/IRB/AEserious.pdf. The UC IRB Fatal/Life-Threatening Event form is available on-line at: http://ors/IRB/AEfatal.pdf. The MedWatch form is available at http://www.fda.gov/medwatch/SAFETY/3500A.pdf.

All serious, related adverse events will be reported and documented on Form FDA 3500 A (Med Watch Form) and forwarded directly to Aventis Pharmaceuticals Global Pharmacovigilance and Epidemiology Department. This includes serious, related, labeled (expected) and serious, related, unlabeled (unexpected) adverse experiences.

11.2 Patient registration and data submission

11.2.1 Registration

All patients must be registered with the University of Chicago Head and Neck Data Manager prior to the commencement of treatment. Confirm all selection criteria listed in Section 3.0, and then call the Data Manager with the following information:

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

11.2.2 Data Submission

On Study: Submit specific registration packet and source documentation prior to registration.

Weekly: Fax weekly flow sheets and toxicity reporting forms by noon of Friday of each week for review at the weekly Head and Neck Oncology Conference.

Evaluations: At each evaluation as specified in the protocol, complete the extent of disease form, specify response (CR, PR, SD PD) on the weekly flow sheet and submit source documentation of the response (CT, X ray physical exam).

Off-study: Submit a flow sheet documenting disease progression, second-line therapy and date of death.

11.3 Data and safety monitoring

For patients enrolled at the University of Chicago only, per University of Chicago Cancer Center Guidelines, this protocol will be classified as moderate risk. The patients enrolled to this study will be regularly discussed as a part of the weekly Head and Neck Oncology Conference. The discussion at this conference will include tumor response and toxicity. A Data and Safety Monitoring worksheet will also be completed at this conference and twenty percent of University of Chicago research charts will be audited annually.

Data and Safety Monitoring Board (DSMB) review will occur weekly at the HNC tumor board and DSMB HNC meeting.

12.0 STATISTICAL CONSIDERATIONS

12.1 Study Design/Endpoints

12.1.1 Study design

This Phase II study consists of a single arm trial to study the feasibility of chemoradiation de-intensification after induction chemotherapy for HPV-positive oropharyngeal cancers. All patients will be assessed for response to chemoradiation; acute/late mucosal, dermatologic, and salivary toxicity; progression free survival (PFS) and overall survival. Toxicities will be described.

12.1.2 Primary endpoint

To determine the two-year PFS rate with de-intensified chemoradiation after TPF induction chemotherapy.

12.1.3 Secondary endpoints

To determine the rate of pathologic complete response on post treatment biopsy/surgery with de-intensified chemoradiation after TPF induction chemotherapy.

To determine the rate of clinical complete response by PET after TPF induction chemotherapy and after de-intensified chemoradiation.

To determine overall survival and cancer specific survival.

To determine local/regional failure, time to distant failure, duration of response and failure patterns.

To determine the rates of acute toxicity with de-intensified chemoradiation as assessed by mucositis, xerostomia, anorexia, weight loss, dermatitis and G-tube placement.

To determine the rates of late toxicity with de-intensified chemoradiation as determined by xerostomia, dental decay, osteroradionecrosis, G-tube dependency, tracheostomy placement and dysphagia.

12.1.4 Laboratory Objectives

To evaluate histologic appearance of post-induction tumor tissue, as well as post-CRT (as available)
To collect blood and tissue samples for translational research detailed in section 2.4 and section 8.

To assess HPV and tumor reactive T cells in the tumor and circulating blood prior to induction chemotherapy, prior to radiation therapy, during radiation therapy and 2 months after radiation therapy.

12.2 Data analysis

12.2.1 Sample size/accrual rate

Sample Size: 61patients
Estimated monthly accrual: 3-5

12.2.2 Assumptions and hypothesis and sample size

We will employ a non-inferiority test in which the objective is to establish that the 2-year PFS rate is within an acceptable margin of that for carboplatin, paclitaxel, and cetuximab as part of the EPIC HN trial. We assume the true 2-year PFS rate for carboplatin, paclitaxel, and cetuximab is 85%, and set the non-inferiority margin at 11%, corresponding to 2-year PFS rate for carboplatin, nab-paclitaxel of at least 74%. We will test H_0: Δ<-11% vs. H_A: Δ>=-11%.

Using Power Analysis and Sample Size (PASS v11) software, n= 61 patients will provide 80% power to test this hypothesis using a (one-sided) type I error rate of 0.10. Essentially, H_0 will be rejected and the experimental regimen declared not materially inferior to EPIC-induction if the lower, one-sided 90% confidence limit for the 2-year PFS rate exceeds 74%, which will occur if 50 or more of the 61 patients are alive and progression-free at two years, i.e., if the *observed* PFS rate is at least 82%. (This calculation assumes that the true PFS rate for the experimental regimen is 85% and that all patients will be followed for a minimum of 2 years.) If dropouts occur, the PFS rate will be estimated using the Kaplan-Meier procedure and its standard error via Greenwood's formula, with corresponding (large-sample) confidence limit.

12.2.3 Statistical methods

Primary Endpoint

Progression-free survival (PFS) will be calculated for each patient as the time from enrollment until disease progression or death from any cause; patients still alive and progression-free will be censored as of the time of the last negative evaluation. If all patients are followed for two years, the PFS rate and confidence interval will be determined based on the exact binomial distribution. Otherwise PFS will be estimated using the Kaplan-Meier (65) method and a (large-sample) one-sided 90% confidence

interval will be derived for the PFS rate at two years to test the non-inferiority hypothesis. Median PFS will be estimated as described in Brookmeyer and Crowley (66).

Secondary Endpoints

Clinical and pathologic VVresponse rates will be determined and 95% confidence intervals obtained using the exact binomial distribution.

Kaplan-Meier curves will be generated for overall and cancer-specific survival; for the latter endpoint, patients dying from non-cancer related causes will be censored at the time of death. In addition, cumulative incidence curves (Gooley et al., 76) will be derived for the competing risks of cancer and non-cancer death. Time to local/regional failure and distant failure will similarly be assessed using Kaplan-Meier estimates and competing risks modeling. Duration of response will be determined as the time from response until disease progression or death among the subset of patients who respond, and estimated by Kaplan-Meier to accommodate potential censoring.

Toxicity rates will be summarized by type of toxicity, grade, and attribution. In particular, the incidence of acute (mucositis, xerostomia, anorexia, weight loss, dermatitis and G-tube placement) and late-term (xerostomia, dental decay, osteroradionecrosis, G-tube dependency, speech abnormalities, tracheostomy placement and dysphagia) toxicities will be estimated along with 95% confidence intervals.

Laboratory Objectives

Results of pathology/histologic review of post induction biopsy specimens will be descriptive and summeraize in tabular format.

Changes in reactive T cells over time will be assessed using mixed effects models and simple paired t-tests.

13.0 REFERENCES

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APPENDIX A

Performance status criteria

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

APPENDIX B

RTOG Early Toxicity Grading

Tissue	Grade 1	2	3	4
Skin	Follicular, faint or dull erythema / epilation / dry desquamation / decreased sweating	Tender or bright erythema, patchy moist desquamation / moderate edema	Confluent, moist desquamation other than skin folds, pitting edema	Ulceration, hemorrhage, necrosis
Mucous membrane	Injection / may experience mild pain not requiring analgesic	Patchy mucositis that may produce an inflammatory serosanguinous discharge / may experience moderate pain requiring analgesia	Confluent fibrinous mucositis / may include severe pain requiring narcotic	Ulceration, hemorrhage or necrosis
Eye	Mild conjunctivitis w/ or w/o scleral injection / increased tearing	Moderate conjunctivitis w/ or w/o keratitis requiring steroids and/or antibiotics / dry eye requiring artificial tears / iritis with photophobia	Severe keratitis with corneal ulceration / objective decrease in visual acuity or in visual fields / acute glaucoma / panophthalmitis	Loss of vision (uni or bilateral)
Ear	Mild external otitis with erythema, pruritus, secondary to dry desquamation not requiring medication. Audiogram unchanged from baseline	Moderate external otitis requiring topical medication / serous otitis media / hypoacusis on testing only	Severe external otitis with discharge or moist desquamation / symptomatic hypoacusis / tinnitus, not drug related	Deafness
Salivary gland	Mild mouth dryness / slightly thickened saliva / may have slightly altered taste such as metallic taste / these changes not reflected in alteration in baseline feeding behavior, such as increased use of liquids with meals	Moderate to complete dryness / thick, sticky saliva / markedly altered taste	(none)	Acute salivary gland necrosis
Pharynx & esophagus	Mild dysphagia or odynophagia / may require topical anesthetic or non-narcotic analgesics / may require soft diet	Moderate dysphagia or odynophagia / may require narcotic analgesics / may require puree or liquid diet	Severe dysphagia or odynophagia with dehydration or weight loss > 15% from pretreatment baseline requiring NG feeding tube, IV fluids, or hyperalimentation	Complete obstruction, ulceration, perforation, fistula
Larynx	Mild or intermittent hoarseness / cough not requiring antitussive / erythema of mucosa	Persistent hoarseness but able to vocalize / referred ear pain,	Whispered speech, throat pain or referred ear pain requiring narcotic / confluent	Marked dyspnea, stridor or hemoptysis with tracheostomy or intubation necessary

		sore throat, patchy fibrinous exudate or mild arytenoid edema not requiring narcotic / cough requiring antitussive	fibrinous exudate, marked arytenoid edema	
HEME	**1**	**2**	**3**	**4**
WBC	3.0 - < 4.0	2.0 - < 3.0	1.0 - < 2.0	< 1.0
Platelets	75 - < 100	50 - < 75	25 - < 50	<25 or spontaneous bleeding
Neutrophils	1.5 - < 1.9	1.0 - < 1.5	0.5 - < 1.0	< 0.5 or sepsis
Hgb / Hct	11 - 9.5 (28% - < 32%)	< 9.5 - 7.5 (< 28%)	< 7.5 - 5.0 (Packed cell transfusion required)	(none)

APPENDIX C

RTOG Late Toxicity Grading

Tissue	Grade 1	2	3	4
Skin	Slight atrophy; pigmentation change; some hair loss	Patch atrophy; moderate telangiectasia; total hair loss	Marked atrophy; gross telangiectasia	Ulceration
Subcutaneous tissue	Slight induration (fibrosis) and loss of subcutaneous fat	Moderate fibrosis but asymptomatic; slight field contracture; <10% linear reduction	Severe induration and loss of subcutaneous tissue; field contracture > 10% linear measurement	Necrosis
Mucous membrane	Slight atrophy and dryness	Moderate atrophy and telangiectasia; little mucous	Marked atrophy with complete dryness	Ulceration
Salivary glands	Slight dryness of mouth; good response on stimulation	Moderate dryness of mouth; poor response on stimulation	Complete dryness of mouth; no response on stimulation	Fibrosis
Spinal cord	Mild L'Hermitte's syndrome	Severe L'Hermitte's syndrome	Objective neurological findings at or below cord level treated	Mono, para quadraplegia
Brain	Mild headache; slight lethargy	Moderate headache; great lethargy	Severe headache; severe CNS dysfunction (partial loss of power or dyskinesia)	Coma
Eye	Asymptomatic cataract; minor corneal ulceration or keratitis	Symptomatic cataract; moderate corneal ulceration; minor retinopathy or glaucoma	Severe keratitis; severe retinopathy or detachment	Panophthalmitis / blindness
Larynx	Hoarseness; slight arytenoid edema	Moderate arytenoid edema; chondritis	Severe edema; severe chondritis	Necrosis
Esophagus	Mild fibrosis; slight difficulty in swallowing solids; no pain on swallowing	Unable to take solid food normally; swallowing semisolid food; dilatation may be indicated	Severe fibrosis; able to swallow only liquids; may have pain on swallowing; dilatation required	Necrosis / perforation fistula
Bone	Asymptomatic; no growth retardation; reduced bone density	Moderate pain or tenderness; growth retardation; irregular bone sclerosis	Severe pain or tenderness; complete arrest of bone growth; dense bone sclerosis	Necrosis / spontaneous fracture

APPENDIX D Docetaxel Hypersensitivity Reactions

Treatment should be discontinued for Grade 4 hypersensitivity reactions. There are no dose reductions for hypersensitivity reactions.

MANAGEMENT OF ACUTE HYPERSENSITIVITY

Severity of Symptoms	Treatment Guidelines
Mild symptoms: localized cutaneous reactions such as mild pruritus, flushing, rash	· consider decreasing the rate of infusion until recovery from symptoms, stay at bedside and monitor patient · then, complete Taxotere infusion at the initial planned rate
Moderate symptoms: any symptom that is not listed above (mild symptoms) or below (severe symptoms) such as generalized pruritus, flushing, rash, dyspnea, hypotension with systolic BP > 80 mm Hg	· interrupt Taxotere infusion · give diphenhydramine 50 mg IV with or without dexamethasone 10 mg IV; monitor patient until resolution of symptoms · resume Taxotere infusion after recovery of symptoms; depending on the physician's assessment of the patient, Taxotere infusion should be resumed at a slower rate, then increased incrementally to the initial planned rate*, (eg. infuse at a 4-hour rate for 3 minutes, then at a 2-h rate for 3 minutes, then at a 1-h rate for 3 minutes, then finally, resume at the initial planned rate.* · depending on the intensity of the reaction observed, additional oral or IV premedication with an antihistamine should also be given for the **next cycle** of treatment, and the rate of infusion should be decreased initially and then increased back to initial planned rate, *(eg. infuse at a 4-hour rate for 3 minutes, then at a 2-h rate for 3 minutes, then at a 1-h rate for 3 minutes, and finally, administer at the initial planned rate.)*
Severe symptoms: any reaction such as bronchospasm, generalized urticaria, systolic BP ≤ 80mm Hg, angioedema	· immediately discontinue Taxotere infusion · give diphenhydramine 50 mg IV with or without dexamethasone 10 mg IV and/or epinephrine as needed; monitor patient until resolution of symptoms · the same treatment guidelines outlined under moderate symptoms (i.e. the third and fourth bullets) should be followed.
Anaphylaxis (NCI grade 4 reaction)	· NO FURTHER STUDY DRUG THERAPY

Appendix E: Sample Transmission Form and Instructions

Protocol

The University of Chicago

Tissue and Blood Sample Collection Form

Clinician/Research Nurse: Please Fill Out

Tissue Samples

Patient Name: _____ UC MR # (if applicable): _____

Patient Protocol ID #:_____ Date Tissue Obtained: _____

Date of Birth: _____Attending Physician: _____

Site of Biopsy: _____ Institution: _____

Date consent was signed: _____ Diagnosis:_____

Pre/Post Therapy (Please circle) Day started on clinical protocol:_____

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

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

Blood Samples*

		date drawn	time	date shipped	
Pre-Therapy:	1 gold top/serum				(batched on dry ice)
Pre-therapy**	1 lavender top/DNA				(batched on dry ice)

*Please label tubes as serum.

**This can be drawn at any time but pre-therapy is preferred.

Researcher: Please Fill Out

Date Samples received: _____ Data entered into Database: **Yes** **No**

Name of Data Manager informed: _____ Date Informed:_____

Version Date: 05/20/2014;08/13/2014, 02/09/2015, 04/09/2015, 07/01/2015,01/04/2016, 05/18/2016 (PI-change)

Location in –80C freezer **-** _____

Approximate size of tissue: _____

Notes:

Questions or Problems? Please contact:
Leslie Martin, University of Chicago, 5841 S Maryland, MC 3083, Chicago, IL 60637
Phone 773-702-0119*, Pager 773-753-1880-9747, email:* lmartin@bsd.uchicago.edu

SHIPPING DIRECTIONS

All shipments must contain a completed Sample Identification form.

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

Leslie Martin: lmartin@.bsd.uchicago.edu

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

Leslie Martin
University of Chicago
FMI Dock/Lab Supply
5830 S. Ellis Ave
Room G-02
Chicago, IL 60637
Phone: 773-834-9814

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

Leslie Martin
University of Chicago
FMI Dock/Lab Supply
5830 S. Ellis Ave
Room G-02
Chicago, IL 60637
Phone: 773-834-9814

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

Leslie Martin
University of Chicago
FMI Dock/Lab Supply
5830 S. Ellis Ave
Room G-02
Chicago, IL 60637
Phone: 773-834-9814

APPENDIX F

Abbreviations

5-FU 5-Fluorouracil.

CDDP Cisplatin.

TPF Docetaxel, 5-FU, CDDP.

CT Computed Tomography.

GTV Gross Tumor Volume. Clinically detectable tumor volume.

CTV Clinical Tumor Volume. Encompasses the GTV plus area to account for microscopic extension or spread that is not clinically apparent.

CTV1 CTV encompassing the GTV plus a 7mm margin for microscopic extension.

CTV2 CTV encompassing the pre-chemotherapy volume, adjacent tissues at risk for microscopic extension plus lymph node echelons at a high risk for microscopic spread.

CTV3 CTV encompassing the lymph node echelons at a low risk for microscopic spread.

PTV Planning Tumor Volume. Encompasses the CTV plus a margin to account for setup error.

PTV1 CTV1 plus a 5mm margin.

PTV2 CTV2 plus a 5mm margin.

PTV3 CTV3 plus a 5mm margin.

LD Longest diameter.

CR Complete response.

PR Partial response.

SD Stable disease.

PD Progressive disease.