Phase II Non-Randomized Three Arm Trial of Induction Chemotherapy with *nab*-Paclitaxel and Cisplatin **(AP: Arms 1 and 3)** or Single Agent *nab*-Paclitaxel **(A: Arm 2)** as Induction Therapy followed by Definitive Concurrent Chemoradiation for Locally Advanced Squamous Cell Carcinoma of the Head and Neck (HNSCC): **"*The APA Trial*"**

HRPO #: 201510013
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Study Drugs: *nab*-Paclitaxel
Cisplatin
Cetuximab

ClinicalTrials.gov #: NCT02573493

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Protocol Revision History

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Amendment #2 Version	**08/24/16**
Amendment #3 Version	**11/23/16**
Amendment #4 Version	**04/24/17**
Amendment #5 Version	**07/02/18**
Amendment #6 Version	**01/29/19**
Amendment #7 Version	**03/18/19**
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Amendment #9 Version	**10/04/19**
Amendment #10 Version	**03/25/2020**

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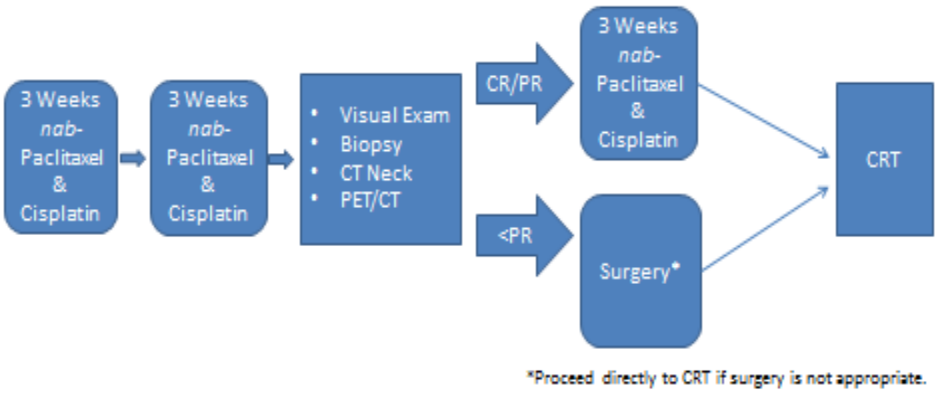
Principal Investigator Signature Page

Site Principal Investigator:		
	Signature of Investigator	Date
	Printed Name of Investigator	
	By my signature, I agree to personally supervise the conduct of this study and to ensure its conduct in compliance with the protocol, informed consent, IRB/HRPO procedures, the Declaration of Helsinki, ICH Good Clinical Practices guidelines, and the applicable parts of the United States Code of Federal Regulations or local regulations governing the conduct of clinical studies.	

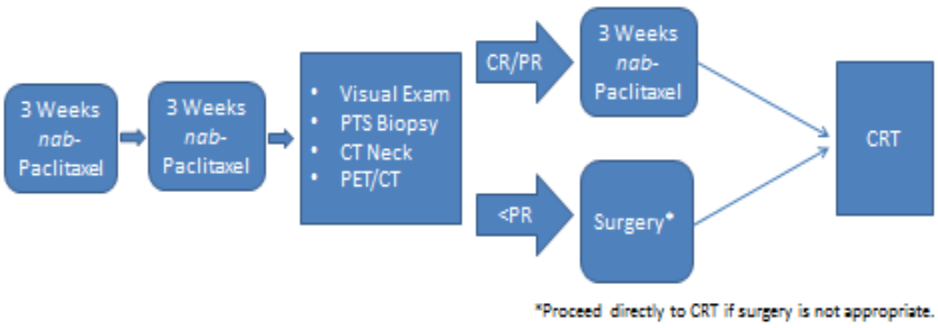
Phase II Non-Randomized Three Arm Trial of Induction Chemotherapy with *nab*-Paclitaxel and Cisplatin **(AP: Arms 1 and 3)** or Single Agent *nab*-Paclitaxel **(A: Arm 2)** as Induction Therapy followed by Definitive Concurrent Chemoradiation for Locally Advanced Squamous Cell Carcinoma of the Head and Neck (HNSCC): ***"The APA Trial"***

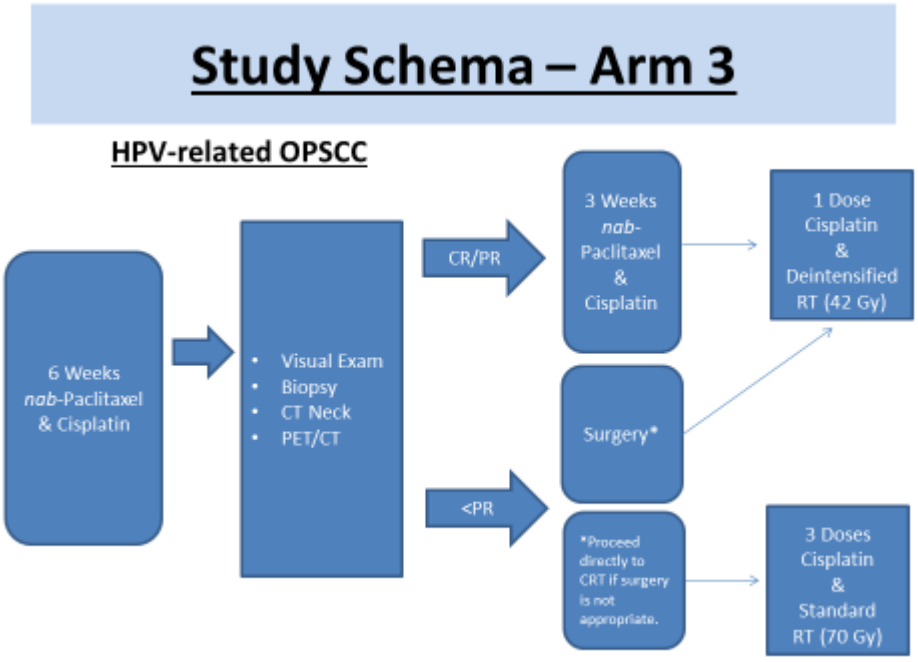
SCHEMA

Study Schema – Arm 1 (AP)



Study Schema – Arm 2 (A)




Study Schema – Arm 3
HPV-related OPSCC
6 Weeks nab-Paclitaxel & Cisplatin
Visual Exam
Biopsy
CT Neck
PET/CT
CR/PR
<PR
3 Weeks nab-Paclitaxel & Cisplatin
Surgery*
*Proceed directly to CRT if surgery is not appropriate.
1 Dose Cisplatin & Deintensified RT (42 Gy)
3 Doses Cisplatin & Standard RT (70 Gy)

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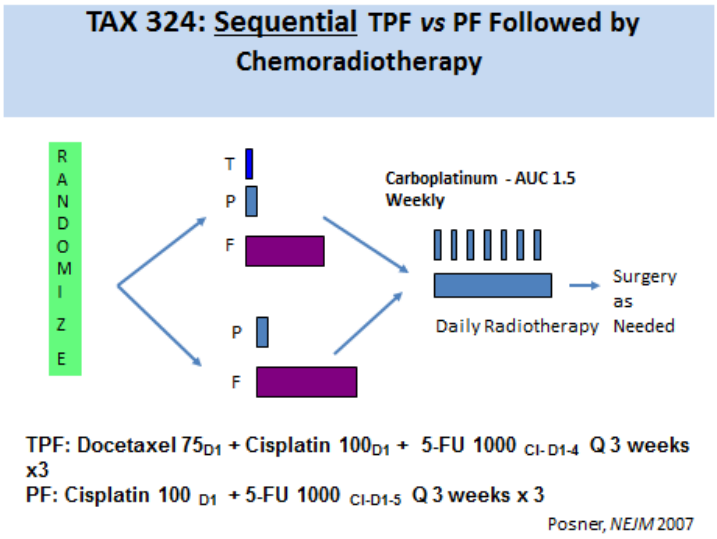
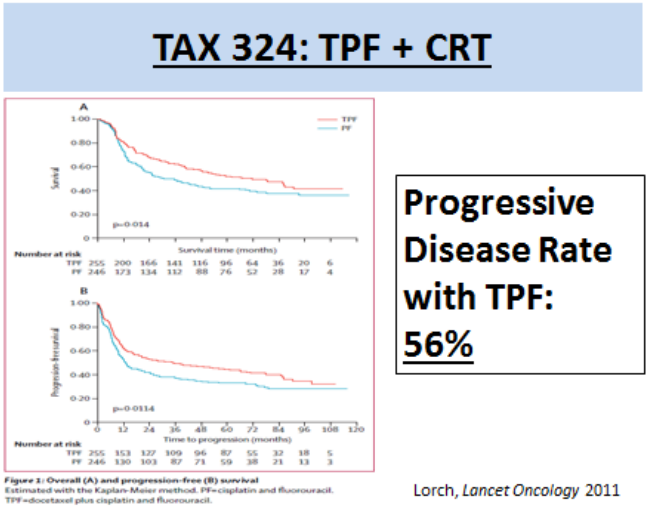
1.0 INTRODUCTION AND BACKGROUND

1.1 Introduction

50,000 new cases of head and neck squamous cell carcinoma (HNSCC) are diagnosed in the USA each year[1]. Most patients present with locally advanced disease and are treated with definitive concurrent chemoradiation therapy (CRT). We, and others, have investigated the addition of induction chemotherapy (IC) to complement CRT particularly in patients with bulky disease.

TPF (docetaxel, cisplatin and 5-FU) emerged as the standard IC regimen after it was compared to PF and shown to be superior (TAX-323 and TAX-324 trials)[2,3,4] as shown:





TAX 324: TPF + CRT

Oropharynx

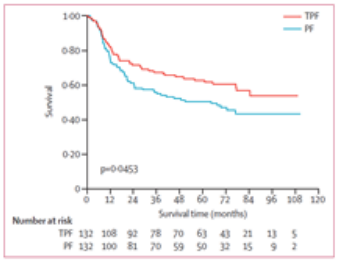


Figure 3: Overall survival for patients with oropharyngeal cancer
Estimated with the Kaplan-Meier method. PF=cisplatin and fluorouracil. TPF=docetaxel plus cisplatin and fluorouracil.

Larynx and Hypopharynx

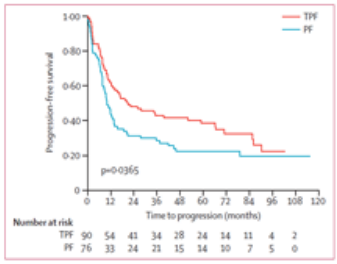


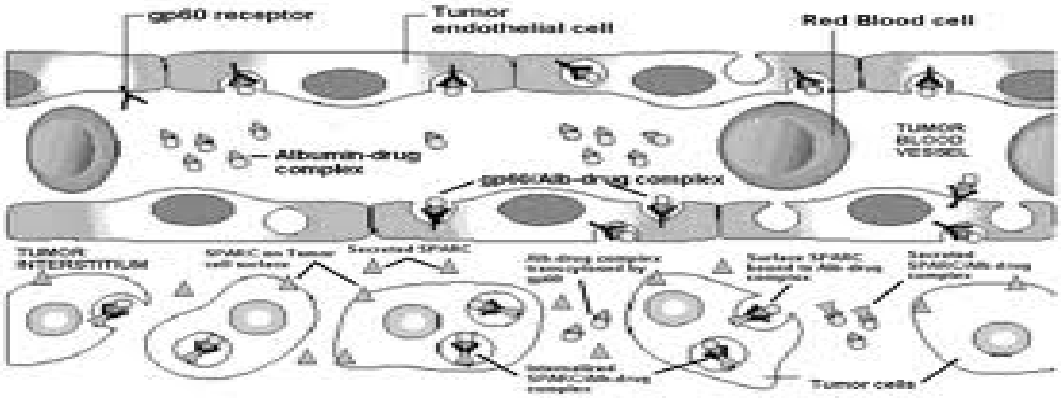
Figure 2: Progression-free survival for patients with hypopharyngeal and laryngeal primary tumour sites
Estimated with the Kaplan-Meier method. PF=cisplatin and fluorouracil. TPF=docetaxel plus cisplatin and fluorouracil.

Cremophor-based paclitaxel appears to have similar benefit to docetaxel[5].

However, the relapse rate (RR) after TPF and CRT was **56%** in the TAX-324 trial[3,4] and 24% in the Paradigm trial[6]. A complete response (CR) at the primary tumor site (PTS) following two cycles of IC is a surrogate prognostic marker for favorable survival free of disease recurrence following subsequent definitive RT-based therapy[7,8]. The likelihood of CR at the PTS after two cycles of TPF was only **14%**[9]. The risk of grade 3-4 adverse events (AEs) with TPF was high (**83%**)[6]. These data establish three important endpoints (RR, PTS CR rate, and grade 3-4 AEs) that future clinical trials of IC should improve upon.

1.2 Rationale for Adding *Nab*-Paclitaxel to IC in HNSCC

Improved antitumor activity and increased intratumoral paclitaxel accumulation occurred with nanoparticle albumin-bound paclitaxel (*nab*-paclitaxel) compared to cremophor-based paclitaxel in nude mice bearing several human tumor xenografts[10]. In contrast to cremophor-based paclitaxel, *nab*-paclitaxel resulted in higher tumor response rates in breast cancer[11]. The improved efficacy may be in part due to the high tumor expression of *S*ecreted *P*rotein *A*cidic and *R*ich in *C*ysteine (SPARC), a protein that plays a role in albumin receptor-mediated endothelial transport[12,13].

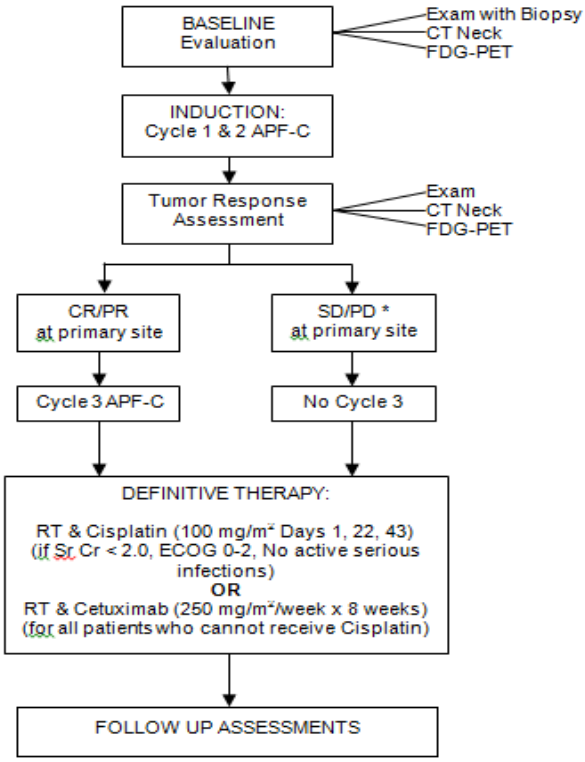


SPARC expression is common in tumor and stromal cells of HNSCC but not in adjacent normal oral mucosa[13,14], and is correlated with tumor response to *nab*-paclitaxel in patients with HNSCC[15]. Although *nab*-paclitaxel acts in a dose-dependent but SPARC saturable manner, stromal-derived SPARC does not influence accumulation of nab-paclitaxel delivered at therapeutic doses in a PDA mouse model[16].

Nab-paclitaxel uptake by tumor cells is also mediated by macropinocytosis, in contrast to cremophor-based paclitaxel[17]. Ras and PI3K pathway activation stimulates macropinocytosis[18]as does EGFR activation. Ras or PI3K pathway activation occurs in the majority (67%) of HNSCC[19-25]. Based on these data, *nab*-paclitaxel may be a more effective anti-tumor agent than cremophor-based paclitaxel in the treatment of HNSCC.

1.3 APF-C as Induction Chemotherapy followed by CRT

In a recent phase II trial performed at Washington University and supported by Celgene (protocol # ABX218/HRPO# 08-0911), we assessed the feasibility and efficacy of a novel induction chemotherapy regimen of *nab*-paclitaxel, cisplatin, 5-FU + cetuximab (**APF-C**) given to patients with locally advanced HNSCC who were subsequently treated with definitive CRT[26]Thirty patients were enrolled over 12 months. The schema for the APF-C regimen is shown below:



APF-C*
Abraxane – 100 mg/m^2
Days 1, 8 & 15
Cetuximab – 250 mg/m^2
Days 1, 8 & 15
Cisplatin – 75 mg/m^2
Day 1
5-FU – 750 mg/m^2 per day
Days 1-3

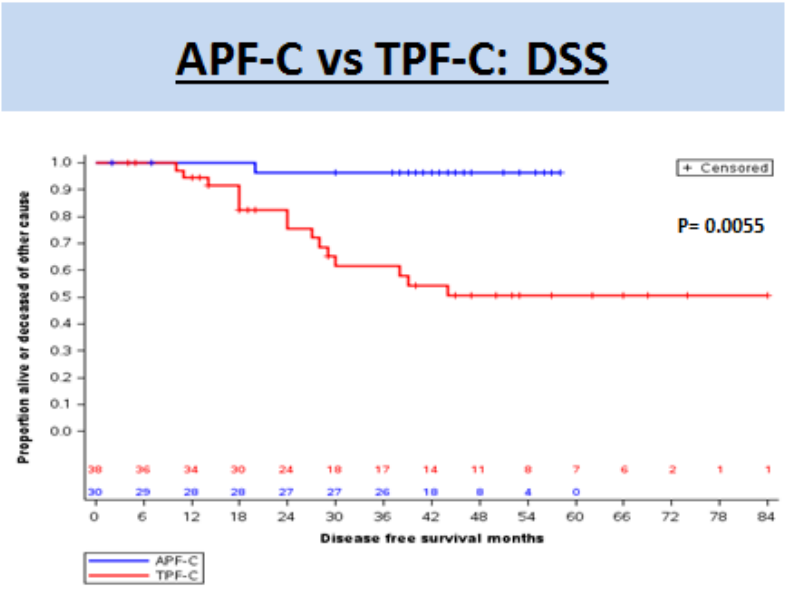
*Every three week cycles

*SD = Stable Disease; PD = Progressive Disease. The protocol permitted resection followed by appropriate adjuvant (C)RT in these patients; however, no primary resections were performed because CR or PR occurred in all patients following ACCF.

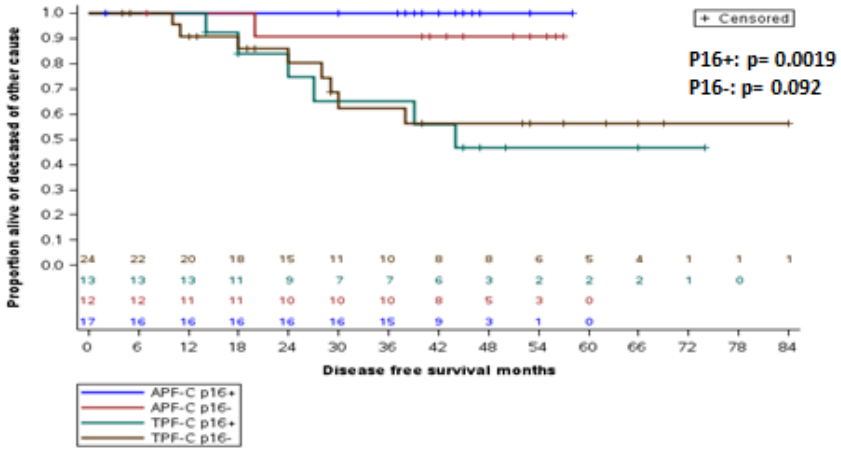
Most patients had bulky primary tumor and nodal disease (74% T3 or T4 and 79% ≥ N2b). By clinical examination, **53%** of patients achieved CR at the PTS following 2 cycles of APF-C as shown:

The risk of serious adverse events (grades 3-4) during APF-C was **39%**. The relapse rate with APF-C followed by CRT was only **13%**, with a median follow-up of 49 months (range: 30-65).

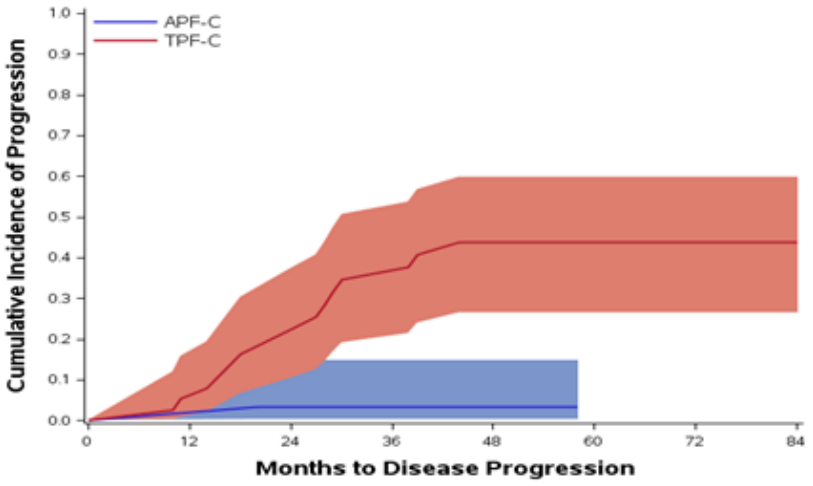
We then compared the outcomes of the 30 patients treated on the APF+C protocol with a similar historical control group of 38 patients treated at our institution with TPF + cetuximab as induction chemotherapy followed by definitive CRT. APF-C was superior to TPF-C overall (2 yr DSS 96.7% vs 77.6%, respectively, p=0.004) and in both p16 positive OPSCC and p16 negative HNSCC[27], as shown:

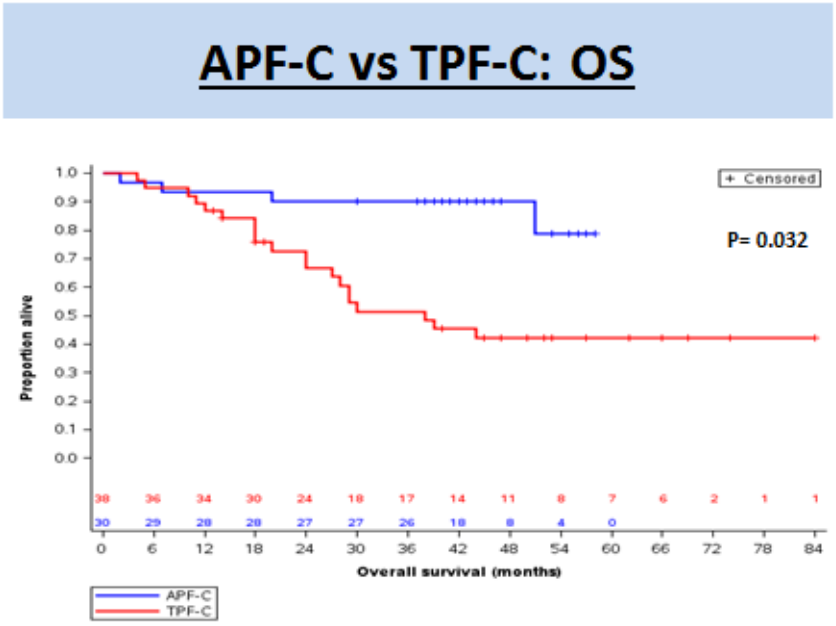


APF-C vs TPF-C: DSS Stratified for p16 Status



APF-C vs TPF-C: Death due to Disease

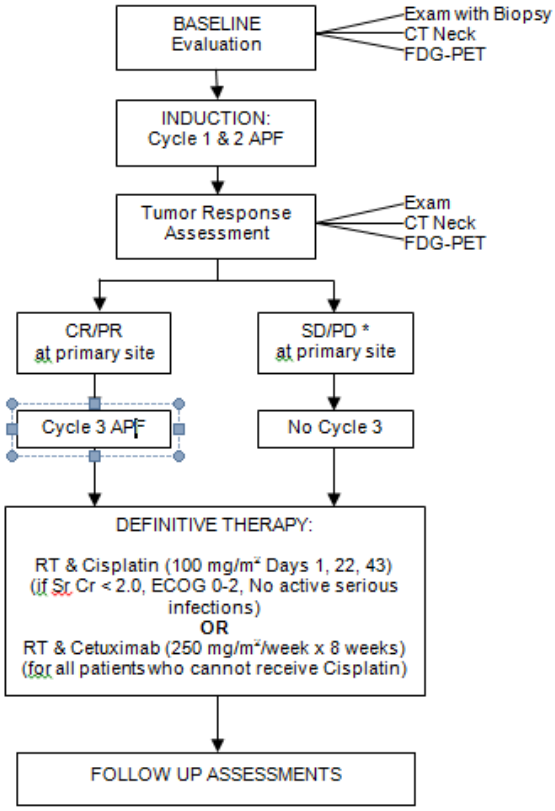




1.4 ACF as Induction Chemotherapy followed by CRT

Compared to TPF, APF-C included two therapeutic changes: *nab*-paclitaxel was substituted for docetaxel and cetuximab was added. The second generation of this novel IC regimen eliminated cetuximab from the APF-C regimen to isolate the treatment effects of *nab*-paclitaxel when given with cisplatin and 5-FU (APF)[28]. APF (protocol # AX-HN-PI-0005/HRPO#201202113) was an institutional trial supported by Celgene.

APF was developed to explore the effect of removing cetuximab on efficacy and to reduce the risk of grade 3-4 AEs (39% during APF-C). Cetuximab was deleted from the APF-C regimen since its benefit during IC was unclear. The schema for APF followed by CRT is shown:



APF*

nab-Paclitaxel – 100 mg/m^2
Days 1, 8 & 15
Cisplatin – 75 mg/m^2
Day 1
5-FU – 750 mg/m^2 per day
Days 1-3

*Every three week cycles

The results of the APF trial were compared to the APF-C trial. Unexpectedly, we found that APF was more effective than APF-C as judged by the PTS CR rate: **77%** with APF and 53% with APF-C. PTS CR rates were higher with APF even when stratified for T classification and p16 status. Relapse rate with APF was only **3%**; however, median follow-up was early (11 [6-21] months).

Why would APF be superior to APF-C in HNSCC? EGFR is overexpressed in nearly all HNSCC. Macropinocytosis, the process whereby large molecules like albumin are taken up by cells, is increased by EGFR activation. Cetuximab, an EGFR inhibitor, may down regulate macropinocytosis, which could decrease tumor cell uptake of *nab*-paclitaxel. Cetuximab also reduces the fraction of tumor cells in "S" phase, during which tumor cells are particularly vulnerable to taxanes.

Although APF may be more effective than APF-C, the risk of grade 3-4 AEs during APF was 40%.

1.5 A Comparison of Four Taxane-based IC Regimens

Comparison of Four Taxane-based Induction Chemotherapy Regimens

Outcome	TPF*	TPF-C**	APF-C***	APF****
PTS CR Rate (%)	14	34	53	77
DSS (%)		78	97	97
OS (%)	52	47	87	97
Relapse Rate (%)	56	45	13	3
Grade 3-4 AEs during Induction (%)	83		39	40
Median F/U mos (range)	72	52 (13-84)	49 (30-65)	11 (6-21)

* Posner, TAX 324, NEJM 2007 & Lancet Oncol 2011.
** Kuperman, ProcASCO 2007.
*** Adkins, Cancer 2013
**** Ley, ProcASCO 2014

In summary, PTS CR rates were lowest with TPF and highest with APF, as was DSS and OS. Relapse rate was highest with TPF and lowest with APF. Grade 3-4 AEs were highest with TPF and lowest with APF. However, grade 3-4 AEs during IC remain disturbingly high (40%) even with APF. Given the extraordinarily high efficacy of APF, our next generation of *nab*-paclitaxel IC regimens will explore reducing the rate of grade 3-4 AEs by sequentially deleting 5-FU (**AP**: *nab*-paclitaxel and cisplatin) and then deleting cisplatin (**A**: *nab*-paclitaxel alone).

1.6 "The APA Trial"

We hypothesize that *nab*-paclitaxel is the most effective and least toxic agent in the APF regimen. The efficacy of 5-FU during IC is unclear in the absence of controlled trials, but 5-FU does increase the risk of stomatitis, diarrhea, and neutropenia. 5-FU will not be used in the two arms of the APA trial. Cisplatin, historically the most effective agent in the treatment of HNSCC, resulted in a 27% risk of renal AEs during APF. Cisplatin will be a component of Arm 1 but not Arm 2 of the APA trial. Arm 1 will include patients with good performance status and vital organ function. Arm 2 will include patients with poorer performance status and vital organ function.

In this trial, our objectives are to determine the efficacy and toxicity of IC with *nab*-paclitaxel + cisplatin (Arm 1: AP) and with *nab*-paclitaxel (Arm 2: A) alone in patients with HNSCC, and to compare these data to APF. We also hypothesize that the high anti-tumor efficacy of nab-paclitaxel in HNSCC is due to the upregulation of macropinocytosis, a result of the frequent presence of Ras and PI3K (and EGFR) activation in this cancer.

The following highlights the key elements of the APA trial:

- Two arm, open label, phase II trial of induction chemotherapy with either *nab*-paclitaxel and cisplatin (Arm 1: AP) or *nab*-paclitaxel alone (Arm 2: A) followed by CRT in HNSCC.
- ARM 1 - AP
    - Six weeks of nab-paclitaxel (100 mg/m^2/week) and cisplatin (75 mg/m^2 days 1 and 22) followed by primary tumor site (PTS) assessment (by visual exam, biopsy
    - CT Neck and FDG-PET/CT)
    - If CR/PR, three more weeks of nab-paclitaxel and cisplatin followed by CRT
    - If <PR, move directly to CRT if not surgical candidates.
    - CRT includes high dose bolus (100 mg/m^2 x 3) cisplatin and IMRT
- ARM 2 – A
    - Six weeks of nab-paclitaxel (100 mg/m^2/week) followed by primary tumor site (PTS) assessment (by visual exam, biopsy, CT Neck and FDG-PET/CT)
    - If CR/PR, three more weeks of nab-paclitaxel followed by CRT
    - If <PR, move directly to CRT if not surgical candidates.
    - CRT includes cetuximab (400 mg/m^2 x 1 then 250 mg/m^2 x 7) and IMRT
- Primary efficacy endpoint of CR rate at the PTS with the objective to have each arm non-inferior to the PTS CR rate with APF (77%)
- Secondary adverse events (Grade 3-4) endpoint
    - Arm 1 at least 25% lower than the risk of Grade 3-4 AE's during APF (40% decreased to 30%).
    - Arm 2 at least 50% lower than the risk of Grade 3-4 AE's during APF (40% decreased to 20%).

1.7 Amendment to Add Arm 3:

1.7.1 Synopsis

In this amendment, Arm 3 will be added to the protocol. Arm 3 will include only patients with HPV-related OPSCC, who have a favorable prognosis with AP + CRT. However, these patients experience a high rate of serious acute toxicity, mainly mucositis, during and after CRT. In Arm 3, treatment will include AP as induction chemotherapy followed by de-escalated CRT. Our primary hypothesis is that de-escalated CRT will reduce the median percent weight loss (a quantifiable surrogate of mucositis) by 50% compared to what occurred with full dose CRT in patients treated on Arm 1 of this protocol.

1.7.2 Rationale for Arm 3

Our preliminary analysis of Arm 1 (AP + CRT; n=28 patients) showed preservation of all key efficacy endpoints: the CR rate at the PTS after 2 cycles of AP was 70.4% and the relapse rate was 3.6%. These data compare favorably to our historical

experience with APF followed by CRT where the CR rate at the PTS after two cycles of APF was 77% and the relapse rate was 3%. However, **64% of patients on Arm 1 experienced grades 3-4 AEs during CRT. Mucosal toxicity was the most troublesome AE during CRT, resulting in a median weight loss of 13.1% (95%CI: 5% - 23.2%).**

Given the significant rate of grades 3-4 AEs during CRT, along with the very low rate of relapse, further refinement of AP + CRT is indicated to reduce the AE burden and maintain the low relapse rate. De-escalation of radiation is a strategy likely to lower the AE risk of AP + CRT.

In this amendment, we retain the AP + CRT backbone but de-escalate the dose of RT from 70 Gy to 42 Gy. We also plan to administer one dose (vs three) of cisplatin during RT. With these modifications, we hypothesize: a 50% decrease in the median percent weight loss during CRT. This novel treatment approach will be evaluated in patients with HPV-related OPSCC (Arm 3), a sub-group with a very favorable prognosis.

1.7.3 Unique Feature of Arm 3

Several ongoing trials are evaluating de-escalation of RT. The common theme of the non-surgical de-escalation trials is the use of RT doses $\geq$ 54 Gy. Another theme of these trials is restriction of this approach to HPV-related OPSCC, and only those patients with low risk disease (limited smoking history and not T4 or N2c/3 disease). In this amendment, we will distinguish our de-escalation approach from these trials by using a much lower dose of RT (42 Gy) and including all patients with HPV-related OPSCC (Arm 3).

1.7.4 Rationale for 42 Gy of RT

Like HPV-related OPSCC, anal canal SCC is also caused by HPV. CRT is the standard of care treatment for anal canal SCC. Surgery is only used as salvage therapy for LRR after CRT. The treatment plan for T2N0 disease is 42 Gy elective nodal and 50.4 Gy anal tumor planning target volumes (PTV) in 28 fractions and for T3-4N0-3 disease is 45 Gy elective nodal, 50.4 Gy for $\leq$ 3 cm or 54 Gy for > 3 cm metastatic nodal and 54 Gy anal tumor in 30 fractions[29]. In contrast to anal SCC, the dose of RT given is 70 Gy. Also, in anal SCC the planned cumulative dose of cisplatin given during CRT is 140 mg/m^2; whereas, in HNSCC the cumulative dose of cisplatin is much higher (300 mg/m^2). **These data suggest that the doses of CRT given for HPV-related OPSCC may be more than needed to cure this cancer.**

The most important message from the studies of CRT in anal SCC is a radiation dose of only 42 Gy is effective in eliminating low volume disease. We hypothesize that a radiation dose of 42 Gy would also eliminate disease in patients with HPV-related OPSCC. In the non-operative setting, the idea way to test this

hypothesis is in patients with HNSCC who undergo induction chemotherapy to reduce disease volume before applying de-escalated RT. In our amendment, we hypothesize the use of induction chemotherapy (AP) will permit reduction of RT to 42 Gy

There is precedent for using induction chemotherapy as a platform to de-escalate RT. ECOG 1308 used the strategy of induction chemotherapy (cisplatin, paclitaxel and cetuximab) followed by 54Gy of RT (with cetuximab) and found excellent results (2-year PFS and OS rates were 80% and 94%, respectively) and lower rates of swallowing difficulties[30].

1.7.5 Expected Reduction of Toxicity by De-escalation of RT Dose from 70 Gy to 42 Gy

The Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) study[31] summarized the latest understanding of organ specific dose/volume/outcome data. **Based on QUANTEC, reduction of the RT dose from 70 Gy to 42 Gy would substantially decrease the toxicity burden.** The organs related to swallowing function include the pharyngeal constrictors, larynx, and esophagus. For the pharyngeal constrictors, a mean radiation dose of less than 50 Gy reduces the risk of symptomatic dysphagia and aspiration from 100% (with 70 Gy) to less than 20%. For the larynx, a mean dose of < 50 Gy reduces the risk of aspiration from 100% to less than 30%, and the risk of laryngeal edema is less than 20% with a mean dose of less than 44 Gy. For the esophagus, if the volume receiving 50 Gy is less than 40%, the risk of grade 2 or above toxicity is no more than 30%. It is important to understand that the normal tissue complication probability (NTCP) with RT dose curve is exponential in shape, meaning that a dose of 42 Gy would markedly reduce normal tissue risk relative to 50 Gy in the QUANTEC data above, and relative to the 70 Gy standard dose for HNSCC in the non-operative setting.

1.7.6 Hypotheses of the Amendment

1. De-escalation of RT from 70 Gy (our current standard in Arms 1 and 2 of the APA protocol) to 42 Gy and reduction of the number of doses of cisplatin given during RT from three to one will result in a significant decrease in acute toxicity of CRT, measured by median percent weight loss.

2. The relapse risk of this overall therapy will not exceed 25% in Arm 3.

2.0 STUDY ENDPOINTS

2.1 Primary Objectives

1. Arm 1 and 2: To determine the complete response (CR) rate by clinical exam at the primary tumor site following two cycles of Arm 1: AP or Arm 2: A given over 6 weeks (with the objective to have each arm non-inferior to the PTS CR rate with APF [77%]).
2. Arm 3: To determine the median percent weight loss in patients with HPV-positive OPSCC who are treated with AP.

2.2 Secondary Objectives

1. Arm 3: To determine the complete response (CR) rate by clinical exam at the primary tumor site following two cycles of AP given over 6 weeks (with the objective to have it be non-inferior to the PTS CR rate with APF [77%]).
2. To document the clinical partial response (PR) rate at the primary tumor site and the clinical CR and PR rates at the involved regional nodes following two cycles of Arm 1: AP, Arm 2: A, and Arm 3: AP(for HPV-related OPSCC).
3. To document the anatomic tumor response as assessed by CT scan using RECIST 1.0 criteria following two cycles of Arm 1: AP, Arm 2: A, and Arm 3: AP(for HPV-related OPSCC).
4. To document and quantify Ki-67 expression by IHC and histologic tumor response in primary tumor tissue obtained at baseline and following two cycles of AP or A and correlate these results with clinical primary tumor site response to Arm 1: AP or Arm 2: A, or Arm 3: AP(for HPV-related OPSCC).
5. To document and grade AE's with Arm 1: AP, Arm 2: A, or Arm 3: AP (for HPV-related OPSCC) and to compare to those observed with APF with the objective that Arm 1 will be at least 25% lower than the risk of Grade 3-4 AE's during APF (40% decreased to 30%) and Arm 2 will be at least 50% lower than the risk of Grade 3-4 AE's during APF (40% decreased to 20%).
6. To determine the overall survival (OS), disease-free survival (DFS), and progression-free survival (PFS) of these patient populations.
7. To document the measures of Quality of Life (QOL) at baseline, during treatment, and through one year after completion of treatment for all arms.
8. To compare response rate, OS, DFS, and PFS of Arm 3 to Arm 1 (stratified for HPV status).
9. To compare the rate of grade 3-4 AEs during CRT in Arm 3 to Arm 1.
10. To compare the median absolute and percent weight loss during CRT in Arms 2 and 3, to Arm 1.

3.0 PATIENT ELIGIBILITY

3.1 Inclusion Criteria

ARMS 1 and 3 – AP	ARM 2 - A
1. Diagnosis of selected Stage III or IVa/b HNSCC. Arm 1: T2-T4 primary tumors. Arm 3: T1-T4 primary tumors. Although most of these patients will have regional nodal disease, patients with no nodal disease will also be eligible.	1. Diagnosis of selected Stage III or IVa/b HNSCC. T2-T4 primary tumors. (Patients with T1 tumors will be excluded). Although most of these patients will have regional nodal disease, patients with no nodal disease will also be eligible.
2. Arm 1: Presence of disease at the oropharynx, hypopharynx, or larynx sub-sites. Arm 3: Presence of disease at the oropharynx sub-sites, which is HPV-related as verified by p16, a surrogate marker of HPV, or HPV ISH or PCR.	2. Presence of disease at the oropharynx, hypopharynx, or larynx sub-sites.
3. Presence of measurable disease defined as lesions that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 10 mm with CT scan.	3. Presence of measurable disease defined as lesions that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 10 mm with CT scan.
4. At least 18 years of age.	4. At least 18 years of age.
5. Women of childbearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control, abstinence) prior to study entry, for the duration of study participation, and for 3 months after completing treatment. Should a woman become pregnant or suspect she is pregnant while participating in this study, she must inform her treating physician immediately.	5. Women of childbearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control, abstinence) prior to study entry, for the duration of study participation, and for 3 months after completing treatment. Should a woman become pregnant or suspect she is pregnant while participating in this study, she must inform her treating physician immediately.
6. Able to understand and willing to sign an IRB-approved written informed consent document.	6. Able to understand and willing to sign an IRB-approved written informed consent document.
	7. ECOG performance status ≤ 3.
	8. Adequate bone marrow and organ function as defined below: a. ANC: ≥ 1500/mcL. b. Platelets: ≥ 100,000/mcL.

7. ECOG performance status ≤ 1. 8. Adequate bone marrow and organ function as defined below: a. ANC: ≥ 1500/mcL. b. Platelets: > 100,000/mcL. c. Hemoglobin > 9.0 g/dL d. Total bilirubin ≤ 1.5 mg/dL e. AST/ALT/alkaline phosphatase: ≤ 2.5 x ULN. f. Serum creatinine: < 1.5 mg/dL or calculated GFR ≥ 75 cc/min. CrCl by Cockcroft-Gault will be used to estimate GFR. g. Pulmonary: no requirement for supplemental oxygen and no evidence of moderate-severe COPD by PFTs.	c. Hemoglobin > 9.0 g/dL d. Total bilirubin ≤ 2.0 mg/dL e. AST/ALT/alkaline phosphatase: ≤ 5x ULN. f. Calculated GFR >30 cc/min. CrCl by Cockcroft-Gault will be used to estimate GFR. g. Pulmonary: patients with a requirement for supplemental oxygen or evidence of moderate-severe COPD by PFTs are permitted to enroll.

9. If a patient fully meets criteria for Arm 1, but has profound hearing loss and the physician feels that the patient should not receive cisplatin, the patient will be eligible for Arm 2.

10. If a patient fully meets criteria for Arm 1, but has a history of solid organ or bone marrow transplant, the patient will be eligible for Arm 2 (due to contraindications of cisplatin with medications the patient is taking due to the transplant).

3.2 Exclusion Criteria

1. Prior chemotherapy, prior EGFR targeted therapy, or prior radiation therapy for HNSCC.

2. Disease at the nasopharyngeal, sinus, oral cavity, or other sub-site not specified in Section 3.1 as eligible.

3. Diagnosis of unknown primary squamous cell carcinoma of the head and neck.

4. History of prior invasive malignancy diagnosed within 3 years prior to study enrollment; exceptions are malignancies with a negligible risk of metastasis or death (e.g., expected 5-year OS > 90%) that were treated with an expected curative outcome, such as squamous cell carcinoma of the skin, in-situ carcinoma of the cervix uteri, non-melanomatous skin cancer, carcinoma in situ of the breast, or incidental histological finding of prostate cancer (TNM stage of T1a or T1b).

5. Receiving any other investigational agents.

6. History of allergic reactions attributed to compounds of similar chemical or biologic composition to any of the agents used in this study.

7. Taking cimetidine or allopurinol. If currently taking either of these medications, patient must discontinue for one week before receiving treatment with *nab*-paclitaxel.

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

9. Pregnant and/or breastfeeding. A negative serum or urine pregnancy test is required at screening for all female patients of childbearing potential.

10. Known to be HIV-positive on combination antiretroviral therapy because of the potential for pharmacokinetic interactions with the study agents. In addition, these patients are at increased risk of lethal infections when treated with marrow suppressive therapy. Appropriate studies will be undertaken in patients receiving combination antiretroviral therapy when indicated.

11. Peripheral neuropathy > grade 1.

3.3 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this trial.

4.0 REGISTRATION PROCEDURES

Patients must not start protocol intervention prior to registration through the Siteman Cancer Center.

The following steps must be taken before registering patients to this study:

1. Confirmation of patient eligibility by Washington University
2. Registration of patient in the Siteman Cancer Center database
3. Assignment of unique patient number (UPN)

Once the patient has been entered in the Siteman Cancer Center database, the WUSM coordinator will forward verification of enrollment and the UPN via email.

4.1 Confirmation of Patient Eligibility

Confirm patient eligibility by scanning and emailing the information listed below to the research coordinator listed in the *Siteman Cancer Center Clinical Trials Core Protocol Procedures for Secondary Sites* packet at least one business day prior to registering patient:

1. Your name and contact information (telephone number, fax number, and email address)
2. Your site PI's name, your institution name, and the registering MD's name
3. Patient's race, sex, and DOB
4. Three letters (or two letters and a dash) for the patient's initials
5. Currently approved protocol version date
6. Copy of signed consent form (patient name may be blacked out)
7. Planned date of enrollment
8. Completed eligibility checklist, signed and dated by a member of the study team
9. Copy of appropriate source documentation confirming patient eligibility

4.2 Patient Registration in the Siteman Cancer Center OnCore Database

Registrations may be submitted Monday through Friday between 8am and 5pm CT. Urgent late afternoon or early morning enrollments should be planned in advance and coordinated with the WUSM research coordinator. Registration will be confirmed by the research coordinator or his/her delegate by email within one business day. Verification of eligibility and registration should be kept in the patient chart.

Patients at all sites must be registered through the Siteman Cancer Center OnCore database at Washington University.

4.3 Assignment of UPN

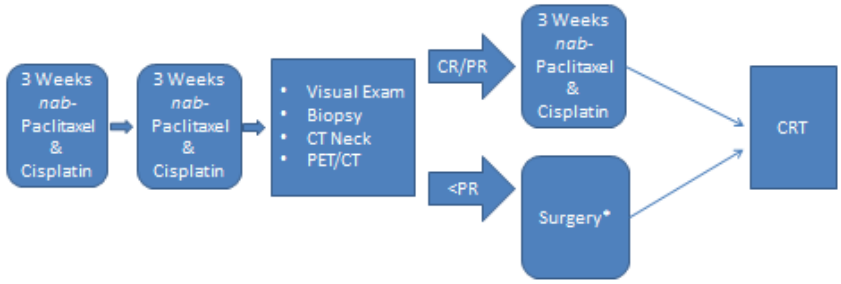
Each patient will be identified with a unique patient number (UPN) for this study. Patients will also be identified by first, middle, and last initials. If the patient has no middle initial, a dash will be used on the case report forms (CRFs). All data will be recorded with this identification number on the appropriate CRFs.

5.0 TREATMENT PLAN AND SCHEDULED ASSESSMENTS

5.1 Summary of Treatment Plan

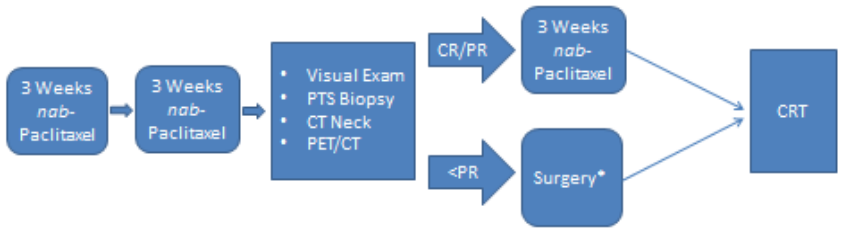
One cycle of induction chemotherapy is 21 days.

Study Schema – Arm 1 (AP)

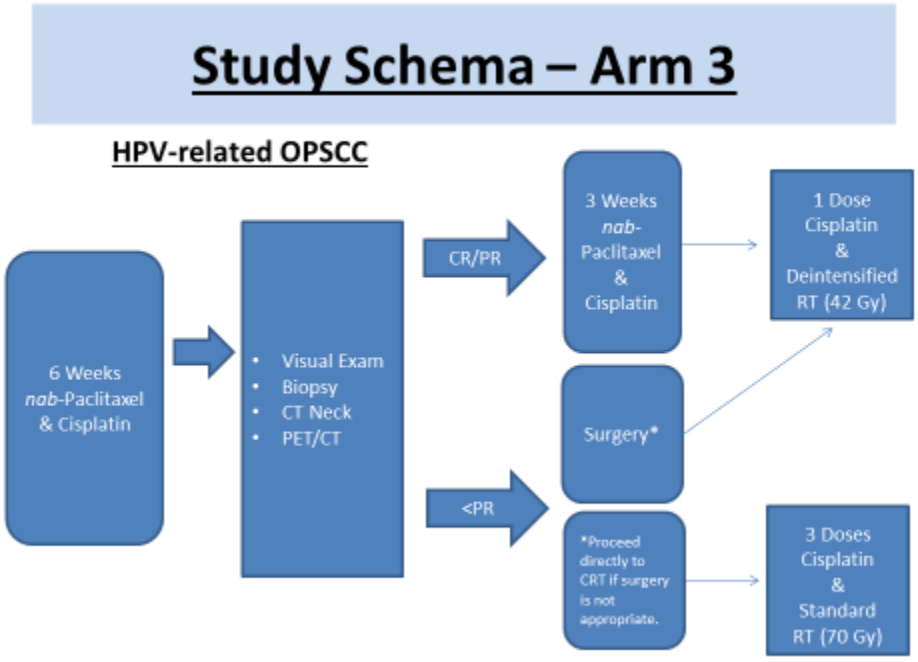


*Proceed directly to CRT if surgery is not appropriate.

Study Schema – Arm 2 (A)



*Proceed directly to CRT if surgery is not appropriate.



5.2 Evaluations for Toxicity and Response

All patients who receive any study treatment are evaluable for toxicity. Patients are evaluated from first receiving study treatment until a 10-year follow-up after the conclusion of treatment, or death.

All patients are evaluable for disease response unless they come off study prior to completion of Cycle 2 and have not had any disease assessment.

5.3 General Concomitant Medication and Supportive Care Guidelines

Primary prophylaxis with G-CSF or Neulasta is not permitted; however it can be used in a non-prophylactic setting following neutropenia (see Section 7.1.7). Use of erythropoietin is not permitted.

Patients may not take cimetidine or allopurinol while receiving *nab*-Paclitaxel or for at least 7 days prior to initiating treatment with *nab*-Paclitaxel.

Concurrent treatment with bisphosphonates is allowed.

5.4 Women of Childbearing Potential

Women of childbearing potential (defined as a sexually mature woman who (1) has not undergone hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries) or (2) has not been naturally postmenopausal for at least

24 consecutive months (i.e. has had menses at any time during the preceding 24 consecutive months)) must:

(1) Either commit to true abstinence from heterosexual contact (which must be reviewed on a monthly basis), or agree to use, and be able to comply with, effective contraception without interruption, 28 days prior to starting treatment (including dose interruptions) and while on study medication or for a longer period if required by local regulations following the last dose of study treatment; and
(2) Have a negative serum pregnancy test result at screening and agree to ongoing pregnancy testing during the course of the study, and after the end of study therapy. This applies even if the subject practices true abstinence from heterosexual contact.

Male subjects must practice true abstinence or agree to use a condom during sexual contact with a pregnant female or a female of childbearing potential while participating in the study, during dose interruptions, and for 6 months following discontinuation of study treatment, even if he has undergone a successful vasectomy.

Please note that true abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

If a patient is suspected to be pregnant, the study agent should be immediately discontinued. In addition a positive urine test must be confirmed by a serum pregnancy test. If it is confirmed that the patient is not pregnant, the patient may resume dosing.

If a female patient or female partner of a male patient becomes pregnant during therapy or within 3 months after the last dose of the study agent, the investigator must be notified in order to facilitate outcome follow-up.

5.5 Duration of Therapy

If at any time the constraints of this protocol are considered to be detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, the protocol therapy should be discontinued and the reason(s) for discontinuation documented in the case report forms.

In the absence of treatment delays due to adverse events, treatment may continue until completion of all planned therapy or until one of the following criteria applies:

- Documented and confirmed disease progression
- Death
- Adverse event(s) that, in the judgment of the investigator, may cause severe or permanent harm or which rule out continuation of study drug
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Suspected pregnancy
- Serious non-compliance with the study protocol

- Lost to follow-up
- Patient withdraws consent
- Investigator removes the patient from study
- The Siteman Cancer Center decides to close the study

Patients who prematurely discontinue treatment for any reason will be followed as indicated in the study calendar.

5.6 Duration of Follow-up

Patients will be followed according to the schedule specified in Section 5.11. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

5.7 Baseline Assessment

The baseline assessment will include the following tests or procedures and must occur within 28 days (PET scan within 42 days) of enrollment:

1. Clinical examination to document extent of primary tumor by laryngoscopy performed in the office or in the operating room (depending on the ease of the exam and the primary tumor site) and palpable involved regional neck nodes. Size of the primary tumor and involved regional neck nodes will be determined based on visual and palpable assessments and will be dictated in the ENT assessment note The neck node measurements will be performed clinically by the treating medical oncology physician and dictated in his/her assessment note.
2. Whenever possible, evaluation by a radiation oncologist before initiation of induction chemotherapy should be performed. A significant response to induction therapy sometimes complicates post-response tumor contouring. Assessment for a CT simulation scan prior to induction therapy may be made on a case by case basis.
3. Documentation of site of primary tumor (oropharynx, hypopharynx, or larynx), location and level of clinically involved neck nodes (right or left neck, Level I-V), T stage (1-4), N stage (0-3), and overall clinical stage (3-4b by AJCC Cancer Staging Manual Sixth Edition).
4. Documentation of demographic information, including gender (M/F), age (years), height (cm), weight (Kg), and BSA (m^2).
5. Documentation of baseline patient symptoms using NCI-CTCAE version 3.0.
6. Documentation of ECOG performance status (ECOG-Appendix 1).
7. Completion of QOL questionnaire (Appendices 5 and 6).
8. Documentation of Comorbidity Index (Comorbidity Scoring – Appendix 4).
9. Laboratory evaluations: CBC, CMP, Magnesium, PT/PTT, serum pregnancy test if patient is a female of childbearing potential. (Please note that the pregnancy test must be performed within 7 days of start of study treatment.)
10. EKG.
11. CT scan (IV contrast preferred) to document and measure the extent of the primary tumor size and involved regional neck nodes using RECIST 1.0 (Appendix 2).

12. FDG-PET/CT scan (whole body) to document and measure the FDG avidity at the primary tumor site and at the involved regional neck nodes.
13. Document and quantify Ki-67 expression in primary tumor biopsy specimens using standard IHC techniques (Section 7.0). Tissue biopsies (punch, incisional, or core needle biopsy) from the primary tumor site will be obtained during the laryngoscopy. If a biopsy is not feasible for financial reasons or safety concerns, at the Primary Investigator's discretion, the biopsy may be forgone.
    i. If the participant is enrolled in Washington University's TAP protocol (head and neck bank, HPRO #201102323), tissue that has been banked may be accessed in lieu of fresh biopsy at baseline.
14. Pulmonary Function Tests (PFTs): spirometry, lung volumes, DLCO.

5.8 Induction Chemotherapy Regimen

1. Physical examination and weight (kg) on Days 1, 8, and 15 of Cycle 1, and on Day 1 of each subsequent cycle.
2. Documentation of performance status (ECOG) on Days 1, 8, and 15 of Cycle 1, and on Day 1 of each subsequent cycle.
3. Documentation of patient symptoms using NCI-CTCAE version 3.0 on Days 1, 8, and 15 of Cycle 1, and on Day 1 of each subsequent cycle.
4. CBC on Days 1, 8, and 15 of each cycle.
5. STAT CMP, STAT magnesium on Day 1 of each cycle.
6. Arm 1 only: Hydration consisting of 1L IVF NS (also recommended 10 meq KCL/L + 8 meq $MgSO_4$/L) over 60 minutes before and after cisplatin on Day 1 of each cycle. 2L IVF NS over 120 minutes on Days 2 and 3 of each cycle recommended.
7. Antiemetic premedication (recommended) on Day 1 (Arms 1, 3, and 4) Palonosetron 0.25 mg, dexamethasone 20 mg, and aprepitant 150 mg IV and on Days 2-4 dexamethasone 4-8 mg po bid.
8. Antiemetic premedication (recommended) on Days 8 and 15 (Arm 1 and 3); on Days 1 8, and 15 (Arm 2) of each cycle: granisetron 1 mg.
9. Arms 1-3: Administration of *nab*-Paclitaxel 100 mg/m^2 IVPB over 30 minutes on Days 1, 8, and 15 of each cycle.
10. Arms 1 and 3 only - administration of cisplatin 75 mg/m^2 IVPB over 60 minutes on Day 1 of each cycle.

Following the completion of Cycle 2 treatment (between Days 16 and 21), the following assessments will be performed to direct the patient's next therapy:

1. Assessment of primary tumor site will be done by laryngoscopy performed in the office or in the operating room. The primary tumor response to the first two cycles of induction will be assessed using visual categorical response. The percent change from baseline will be dictated in the ENT physician's clinical exam note.

Visual Categorical Outcomes	
CR	Complete resolution – 100% decrease/minimal residual mucosal abnormality
PR	99-50% decrease

SD	49-0% decrease
PD	Any increase

2. Assessment of involved regional neck nodes by physical examination. The involved neck node response to the first two cycles of induction will be assessed using visual categorical response. The neck node measurements will be performed clinically by the treating medical oncology physician and dictated in his/her assessment note.
3. Assessment of clinical overall response using visual categorical response based on data from items 1 and 2 above. Overall response is determined as the lesser of the primary site and neck node responses (i.e., Primary Site – CR; Neck Nodes – PR; Overall Response – PR)
4. CT scan (IV contrast preferred) to document and measure the extent of the primary tumor size and involved regional neck nodes. RECIST 1.0 will be used to determine response at the primary tumor site, at the involved regional neck nodes and the radiographic overall tumor response.
5. FDG-PET/CT scan (whole body) to document and measure the FDG avidity at the primary tumor site and at the involved regional neck nodes.
6. Biopsy of the primary tumor site for routine surgical pathology and documentation and quantification of Ki-67 expression in primary tumor biopsy specimens using standard IHC techniques (Section 7.0). Tissue biopsies (punch, incisional, or core needle biopsy) from the primary tumor site will be obtained during the laryngoscopy (or former location of primary tumor if tumor is no longer visible). If a biopsy is not feasible for financial reasons or safety concerns, at the Primary Investigator's discretion, the biopsy may be forgone.

Arms 1 and 2: If disease response shows CR or PR at the primary tumor site (by clinical examination using visual categorical response) and does not show radiographic (CT) or FDG-PET/CT evidence of disease progression, s/he may initiate Cycle 3 of induction, followed immediately by definitive radiation and concurrent chemotherapy (See Section 5.9.1 and 5.9.2). If the patient shows SD or PD, or if the patient experiences an unacceptable toxicity unlikely to resolve in the face of a reasonable dose delay (at the discretion of the Primary Investigator) s/he should receive definitive radiation and concurrent chemotherapy if not a surgical candidate. If the patient is a surgical candidate, they will receive surgery followed by CRT (See Section 5.9.1 and 5.9.2).

Arm 3: If disease response shows CR or PR at the primary tumor site (by clinical examination using visual categorical response) and does not show radiographic (CT) or FDG-PET/CT evidence of disease progression, s/he may initiate Cycle 3 of induction, followed immediately by de-intensified radiation (42Gy) and one dose of cisplatin or 6 doses of cetuximab (see section 5.9.3 or 5.9.4). Patients with SD or PD after 2 cycles of AP will either 1) undergo surgery (if a surgical candidate) followed by CRT with 42 Gy RT and abbreviated cisplatin or cetuximab (see section 5.9.3 or 5.9.4) or 2) if not a surgical candidate, the patient will be treated with standard definitive radiation (70Gy) and 3 cycles of Cisplatin or 8 doses of Cetuximab (See Section 5.9.1 and 5.9.2).

5.9 Definitive Radiation and Concurrent Chemotherapy

5.9.1 ARM 1 ONLY - Concurrent Cisplatin

Cisplatin is the preferred chemotherapy to be given during radiation for patients on ARM 1. Cisplatin will begin 1 to 35 days after the completion of Cycle 3. The first dose of cisplatin will be given during the initial 5 days of definitive radiation therapy, the second on approximately Day 22 of radiation, and the third on approximately Day 43 of radiation.

Criteria to receive the first dose of cisplatin include:

- creatinine clearance $\geq$ 60 cc/min
- ECOG performance status 0-2
- no active serious infections

Patients who do not meet these criteria will not receive cisplatin during radiation therapy but will be permitted to receive cetuximab concurrently with radiation therapy (ARM 1 patients only)(see Section 5.9.2). During radiation therapy, patients who receive cisplatin cannot be switched to cetuximab.

Procedures for cisplatin therapy during definitive radiation therapy are as follows:

1. Antiemetics premedication (recommended) prior to each dose of cisplatin: palonosetron 0.25 mg IVPB, dexamethasone 10 mg IVPB and aprepitant 150 mg IVPB.
2. Hydration consisting of 1L IVF NS (also recommended: 10 meq KCL/L + 8 meq $MgSO_4$/L) over 60 minutes before and after cisplatin on the day of dosing. 2L IVF NS over 60 minutes on the two days following cisplatin dosing.
3. Administration of cisplatin at 100 mg/m^2 IVPB over 60 minutes on approximately radiation Days 1, 22, and 43.
4. Physical examination and weight (kg) will be performed on each day of cisplatin administration.
5. Documentation of ECOG performance status will be done on each day of cisplatin administration.
6. Documentation of patient symptoms using NCI-CTCAE version 3.0 will be done on each day of cisplatin administration.
7. CBC, STAT CMP and STAT magnesium on each day of cisplatin administration.
8. Patient to complete QOL questionnaire prior to starting radiation and at the last week of radiation.

5.9.2 ARM 2 and selected patients in ARM 1 - Concurrent Cetuximab

Concurrent cetuximab will be given to all patients in ARM 2. In Arm 1, concurrent cetuximab will only be given to those patients who do not meet the criteria for receiving cisplatin as specified in Section 5.4.1 (Arm 1). Cetuximab will begin 1 to 35 days after the completion of Cycle 3 of IC.

Procedures for cetuximab during definitive radiation therapy are as follows:

1. Premedications (recommended): diphenhydramine 50 mg IVPB, solucortef 100 mg IVPB, and albuterol inhalation (2.5 mg by nebulizer or inhaler) prior to each dose of cetuximab.
2. Cetuximab will be started 7 days (+/- 3 days) before starting definitive radiation therapy to the head and neck. The initial (loading) dose of cetuximab will be 400 mg/m^2 IVPB. The recommended process for administering the loading dose is to give a test dose of 100 mg for one hour, followed by an hour of observation, followed by giving the remainder of the dose over 2 hours, followed by another hour of observation. Do not give cetuximab on the same day as *nab*-paclitaxel.
3. Subsequently, cetuximab will be given weekly at a dose of 250 mg/m^2 IVPB over 60 minutes (followed by an hour of observation) for seven additional doses concurrently with radiation therapy.
4. Hydration consisting of 1L IVF NS over 60-90 minutes before cetuximab on the day of dosing.
5. Weight (kg) will be taken weekly starting with the loading dose of cetuximab.
6. Physical examination and documentation of ECOG performance status will be performed on Weeks 1, 5, and 8 starting with the loading dose of cetuximab.
7. Documentation of patient symptoms using NCI-CTCAE version 3.0 will be done weekly starting with the loading dose of cetuximab.
8. CBC, STAT CMP and STAT magnesium will be drawn on Weeks 1, 5, and 8 starting with the loading dose of cetuximab.
9. Patient to complete QOL questionnaire prior to starting radiation and at the last week of radiation.

5.9.3 ARM 3 ONLY – Concurrent Cisplatin

Cisplatin will begin 1 to 35 days after the completion of Cycle 3 of induction chemotherapy. Cisplatin will be given as <u>one dose</u> during the initial 5 days of definitive radiation therapy. (Unless receiving definitive therapy following SD or PD after 2 cycles of induction treatment).

Criteria to receive cisplatin include:

- creatinine clearance <u>≥</u> 60 cc/min
- ECOG performance status 0-2
- no active serious infections

Patients who do not meet these criteria will receive cetuximab with radiation therapy.

Procedures for cisplatin therapy during definitive radiation therapy are as follows:

1. Antiemetics premedication (recommended) prior to cisplatin: palonosetron 0.25 mg IVPB, dexamethasone 10 mg IVPB and aprepitant 150 mg.
2. Hydration consisting of 1L IVF NS (also recommended: 10 meq KCL/L + 8 meq $MgSO_4$/L) over 60 minutes before and after cisplatin on the day of dosing. 2L IVF NS over 60 minutes on the two days following cisplatin dosing.
3. Administration of cisplatin at 100 mg/m^2 IVPB over 60 minutes on Day 1 (in initial 5 days of RT) **only**.
4. Physical examination and weight (kg) will be performed on the day of cisplatin administration,on day 22 of radiation therapy, and at the 2 week short term follow-up visit. Weight (kg) will also be collected at the last day of RT (no physical exam required that day).
5. Documentation of ECOG performance status will be done on the day of cisplatin administration, on day 22 of radiation therapy, and at the 2 week short term follow-up visit.
6. Documentation of patient symptoms using NCI-CTCAE version 3.0 will be done on the day of cisplatin administration, on day 22 of radiation therapy, and at the 2 week short term follow-up visit.
7. CBC, STAT CMP and STAT magnesium on the day of cisplatin administration and on day 22 of radiation therapy.
8. CBC, STAT BMP and STAT magnesium at the 2 week short term follow-up visit.
9. Patient to complete QOL questionnaire prior to starting radiation, at the last week of radiation, and at the 2 week short term follow-up visit.

5.9.4 ARM 3 ONLY – SELECTED PATIENTS – Concurrent Cetuximab

In Arm 3, concurrent cetuximab will **only** be given to those patients who do not meet the criteria for receiving cisplatin as specified in Section 5.9.3. Cetuximab will begin 1 to 35 days after the completion of Cycle 3 of IC.

Procedures for cetuximab during definitive radiation therapy are as follows:

1. Premedications (recommended): diphenhydramine 50 mg IVPB, solucortef 100 mg IVPB, and albuterol inhalation (2.5 mg by nebulizer or inhaler) prior to each dose of cetuximab.
2. Cetuximab will be started 7 days (+/- 3 days) before starting definitive radiation therapy to the head and neck. The initial (loading) dose of cetuximab will be 400 mg/m^2 IVPB. The recommended process for administering the loading dose is to give a test dose of 100 mg for one hour, followed by an hour of observation, followed by giving the remainder of the dose over 2 hours, followed by another hour of observation. Do not give cetuximab on the same day as *nab*-paclitaxel.

3. Subsequently, cetuximab will be given weekly at a dose of 250 mg/m^2 IVPB over 60 minutes for **five** additional doses concurrently with radiation therapy. (Unless receiving definitive therapy following SD or PD after 2 cycles of induction treatment)
4. Hydration consisting of 1L IVF NS over 60-90 minutes before cetuximab on the day of dosing.
5. Weight (kg) will be taken weekly starting with the loading dose of cetuximab through completion of radiation therapy and at the two week short term follow-up visit.
6. Physical examination and documentation of ECOG performance status will be performed on day of loading dose of cetuximab, on day 22 of radiation therapy, and at the 2 week short term follow-up visit. Weight (kg) will also be collected on the first and last day of RT (no physical exam required that day)
7. Documentation of patient symptoms using NCI-CTCAE version 3.0 will be done weekly starting with the loading dose of cetuximab.
8. CBC, STAT CMP and STAT magnesium on Week 1 (loading dose of cetuximab) and on day 22 of radiation therapy.
9. CBC, STAT BMP and STAT magnesium at the 2 week short term follow-up visit.
10. Patient to complete QOL questionnaire prior to starting radiation, at the last week of radiation, and at the 2 week short term follow-up visit.

5.10 Definitive Radiation Therapy (Arms 1 and 2 Only)

Prior to starting radiation therapy and at the last week of radiation therapy, the patient will be asked to complete QOL questionnaire.

5.10.1 Overview

It is strongly recommended that radiation therapy begin within 21 to 42 days (and no later than 56 days) after the start of Cycle 3. Intensity modulated radiation therapy (IMRT) is to be used exclusively for this study. Definitive IMRT will be delivered once per day Monday through Friday per routine clinical practice using. The total dose to the gross disease will be 7000 cGy in 35 fractions of 200 cGy each over 7 weeks. A dose of 6300 cGy in 35 fractions is optional and may be delivered to areas considered to be at intermediate risk. Additional regions in the ipsilateral and contralateral neck at risk for microscopic disease in the cervical lymph nodes will receive 5600 cGy in 35 fractions. See Appendix 3 for contouring guidelines.

5.10.2 CT Simulation

As per routine practice, computed tomography (CT) will be the primary image platform for targeting and treatment planning. Prior to the scan, the patient will be given IV contrast according to institutional protocols (provided the patient has normal renal function and no allergies to contrast). The patient will be positioned

supine on the CT simulator table (head toward the gantry). The head will be placed on a clear plastic headrest so as to have the neck slightly extended. Alternatively, a custom head/shoulder mold may be used for immobilization. An immobilization mask will then be fashioned. A CT dataset will be acquired from the top of the head through 5 cm below the clavicular heads with no more than 5 mm axial slices. Three localization marks will be drawn and wired on the patient's immobilization mask at the angle of the mandible bilaterally and midline. These marks will serve to establish an internal reference from which an isocenter is placed midline, midplane, at the level of the angle of the mandible. If a CT simulation scan was performed prior to induction therapy, a repeat CT simulation scan will be performed in the same immobilization device after induction therapy and electronic fusion of the images will be performed.

5.10.3 Virtual Simulation and Contouring

The CT scan will be exported to a commercially available virtual simulation software package. Guidelines for clinical treatment volumes to be contoured for each head and neck sub-site along with current institutional treatment guidelines are shown in Appendix 3. Guidelines for delineating each lymph node level will be based on the international consensus for delineation of head and neck lymph nodes (http://www.rtog.org/hnatlas/main.html; reproduced in Appendix 3). These guidelines were derived in part from Washington University School of Medicine institutional data, and are consistent with routine clinical practice at Washington University.

An example case of a T3N2BM0, stage IVA tonsil cancer is outlined in the table below. Current treatment guidelines for this case including dose levels are represented with CTV1, CTV2, and CTV3.

CTV1	CTV2 (Optional)	CTV3
[GTVp + GTVn] + 1.5 cm minimum concentric margin excluding bone and air	Adjacent LN Levels minimum 1.5 cm cranial-caudad dimension	IN (II-V) + BRPLN + CN (IIb-IV) Exclusive of CTV1 and CTV2
Dose 70 Gy/35 fx	Dose 63 Gy/35 fx	Dose 56 Gy/35 fx

Key: GTVp = GTV primary tumor; GTVn = GTV nodal tumor; IN = ipsilateral neck; CN = contralateral neck; roman numbers relate to the level system of naming lymph node regions; BRPLN = bilateral retropharyngeal lymph nodes).

Normal structure and treatment volume contours will be delineated in a manner consistent with routine clinical practice. Refer to appendix 4 for specific guidelines.

5.10.4 IMRT Optimization

The image and contour data will be exported to the TomoTherapy Hi Art System (TomoTherapy Inc., Madison WI), where treatment planning and IMRT optimization will be performed. For patients being treated on a Varian System

(Varian Medical Systems, Inc.), treatment planning will be completed on a compatible platform (i.e. Varian's Eclipse Treatment Planning System, or the ADAC Pinnacle treatment planning system).

5.10.5 Treatment Field Arrangement

With tomotherapy, a continuous helical treatment field is used with dynamic multileaf collimator fluence modulation. The system calculates the optimized collimator leaf delivery pattern (treatment sinogram) that most closely approximates the prescribed constraints. Planned dose deposition is calculated using a collapsed-cone convolution superposition technique that addresses three-dimensional scatter and inhomogeneities.

The Varian System employs up to ten co-planar fields with static or dynamic multileaf collimation. As with tomotherapy, the treatment planning system calculates the optimized collimator leaf delivery pattern that most closely approximates the prescribed constraints and prescription goals.

5.10.6 Dose, Energy and Prescription Parameters

External beam radiation with 6 MV photons will be delivered in 200 cGy daily fractions (Monday through Friday), 35 fractions over 7 weeks to a total dose of 7000 cGy.

Prescription Coverage Goals
99% of clinical treatment volumes should receive at least 93% of the respective prescription dose (i.e. 99% of PTV 7000 should be covered by 6510 cGy; 99% of PTV 6300 covered by 5859 cGy; and 99% of PTV 5600 covered by 5208 cGy).

No more than 5% of the volume "Skin" should receive more than the prescription dose (70 Gy) and hotspots must be within the PTV.

Photons with energy of 6 MV will be utilized for IMRT on the helical tomotherapy and Trilogy units.

5.10.7 Normal Structure Dose Limit Guidelines

Dose limit guidelines for normal structures are as follows:

Structure	**Volume**	**Dose Guideline (Gy)**	**Dose Mean (Gy)**
Critical Structures			
Spinal Cord + 8 mm	1 cc	50	
Spinal Cord	0.1 cc	45	
Brainstem	1%	60	
	0.1 cc	60	
Brain	1%	60	

	5 cc	65	
Optic nerve*	1%	60	
	0.1 cc	60	
Optic chiasm	1%	60	
	0.1 cc	60	
Eye*			45
Normal Structures			
Retina*	1%	50	35
Lens*			2
Oral cavity			35
Larynx			45
Mandible	5%	73.5	
Skin	5%	70	
Partial esoph	2 cc	54	
Middle Ear*			45
Parotid glands*	20 cc	20	26

*Paired structures. Dose constraints apply to one such structure and are equivalent for the contralateral side.

Priority for Above Dose Constraints

1. Critical Structures
2. PTV Prescription Goals
3. Salivary Glands
4. Other Structures

5.10.8 Treatment Plan Evaluation

The plan will be reviewed by the treating physician prior to treatment in order to ensure that all parameters have been met. Isodose curves and dose volume histograms (DVH) will be analyzed.

Criteria for plan evaluation will include:

- Isodose Curves:
  The 95% isodose line must be generally conformal to the PTV with visually acceptable tumor coverage and visually acceptable critical structure avoidance.
  The 110% isodose line must not include any critical structure volumes.
  The 4200 cGy isodose line must not encroach on the "Spinal cord + 8 mm" for patients planned on the Helios system. The 5000 cGy isodose line must not encroach on the "Spinal cord + 8 mm" for Tomotherapy plans.
  The 2600 cGy isodose line should spare parotid glands when possible.

- Dose Volume Histograms (DVHs):
  No more than 20% of any PTV should exceed 110% of the prescribed dose.
  DVH from PTVs must meet all prescription parameters.
  Normal structure DVHs should meet constraint parameters as listed above.

5.10.9 Daily Radiation Treatment

Patients will receive external beam radiation treatment delivered either by helical tomotherapy or by the Trilogy™ System once a day, five days a week, for 7 weeks as per routine clinical practice.

5.10.10 Quality Assurance

Treatment plan physics review and QA are required for each patient in accordance with current institutional standards for IMRT.

Daily set-up error will be minimized by the following clinically approved and commercially available patient setup techniques: immobilization mask, standard skin/mask alignment marks, and daily on-board imaging.

Per routine practice, daily megavoltage helical CT scans will be acquired on the tomotherapy unit and compared with planning CT overlay.

For patients treated on the Trilogy™ System, daily orthogonal port films or cone beam CT images will be aligned with the digitally reconstructed radiographs or 3D CT data set from the planning CT scan based on bony anatomy.

These setup scans will be performed immediately prior to each treatment and the appropriate shifts will be made at that time.

5.11 Definitive Radiation Therapy (Arm 3 Only—CR or PR after 2 cycles of induction therapy OR SD/PD after 2 cycles of induction therapy and received surgery)

5.11.1 Overview

It is strongly recommended that radiation therapy begin within 28 to 49 days (and no later than 56 days) after the start of Cycle 3. Intensity modulated radiation therapy (IMRT) is to be used exclusively for this study. Definitive IMRT will be delivered once per day Monday through Friday per routine clinical practice except for one BID treatment during the course of therapy. If patient logistics prohibit the one BID treatment, once daily treatments throughout will be acceptable. The total dose to the gross disease will be 4200 cGy in 21 fractions of 200 cGy over 4 weeks. Additional regions in the ipsilateral and contralateral neck at risk for microscopic disease in the cervical lymph nodes will receive 3780 cGy in 21 fractions of 180 cGy each. See Appendix 3 for contouring guidelines.

5.11.2 CT Simulation

As per routine practice, computed tomography (CT) will be the primary image platform for targeting and treatment planning. Prior to the scan, the patient will be given IV contrast according to institutional protocols (provided the patient has

normal renal function and no allergies to contrast). The patient will be positioned supine on the CT simulator table (head toward the gantry). The head will be placed on standard or customized plastic headrest so as to have the neck slightly extended. Alternatively, a custom head/shoulder mold may be used for immobilization. An immobilization mask will then be fashioned. A CT dataset will be acquired from the top of the head through 5 cm below the clavicular heads with no more than 5 mm axial slices. Three localization marks will be drawn and wired on the patient's immobilization mask at the angle of the mandible bilaterally and midline. These marks will serve to establish an internal reference from which an isocenter is placed midline, midplane, at the level of the angle of the mandible. If a CT simulation scan was performed prior to induction therapy, a repeat CT simulation scan will be performed in the same immobilization device after induction therapy and electronic fusion of the images will be performed.

5.11.3 Virtual Simulation and Contouring

The CT scan will be exported to a commercially available virtual simulation software package. Guidelines for clinical treatment volumes to be contoured for each head and neck sub-site along with current institutional treatment guidelines are shown in Appendix 3. Guidelines for delineating each lymph node level will be based on the international consensus for delineation of head and neck lymph nodes (http://www.rtog.org/hnatlas/main.html; reproduced in Appendix 2). These guidelines were derived in part from Washington University School of Medicine institutional data, and are consistent with routine clinical practice at Washington University.

An example case of a T3N2BM0, stage IVA tonsil cancer is outlined in the table below. Current treatment guidelines for this case including dose levels are represented with CTV1 and CTV2.

CTV1	CTV2
[GTVp + GTVn] + 1.0 to1.5 cm minimum concentric margin excluding bone and air with aid of preop imaging with/without fusion	IN (II-V) + BRPLN + CN (IIb-IV) Exclusive of CTV1.
Dose 4200 cGy/21 fx	Dose 3780 cGy/21 fx

Key: GTVp = GTV primary tumor; GTVn = GTV nodal tumor; IN = ipsilateral neck; CN = contralateral neck; roman numbers relate to the level system of naming lymph node regions; BRPLN = bilateral retropharyngeal lymph nodes).

Normal structure and treatment volume contours will be delineated in a manner consistent with routine clinical practice. Refer to appendix 3 for specific guidelines.

5.11.4 IMRT Optimization

The image and contour data will be exported to the Varian Eclipse platform where IMRT optimization will be performed.

5.11.5 Treatment Field Arrangement

The Varian System employs up to ten co-planar fields with static or dynamic multileaf collimation. The treatment planning system calculates the optimized collimator leaf delivery pattern that most closely approximates the prescribed constraints and prescription goals.

5.11.6 Dose, Energy and Prescription Parameters

External beam radiation with 6 MV photons will be delivered in 200 cGy daily fractions (Monday through Friday), 21 fractions over 4 1/2 weeks to a total dose of 4200 cGy.

Prescription Coverage Goals
99% of clinical treatment volumes should receive at least 95% of the respective prescription dose (i.e. 99% of PTV 4200 should be covered by 3990 cGy and; 99% of PTV 3780 cGy covered by 3591 cGy).

No more than 5% of the volume "Skin" should receive more than the prescription dose (42 Gy) and hotspots must be within the PTV.

Photons with energy of 6 MV will be utilized

5.11.7 Normal Structure Dose Limit Guidelines

Dose limit guidelines for normal structures are as follows:

Structure	Volume	Dose Guideline (Gy)	Dose Mean(Gy)
Critical Structures			
Spinal Cord + 8 mm	1 cc	45	
Spinal Cord	0.1 cc	40	
Brainstem	1%	40	
	0.1 cc	40	
Brain	1%	40	
	5 cc	45	
Optic nerve*	1%	40	
	0.1 cc	42	
Optic chiasm	1%	40	
	0.1 cc	42	

Eye*			45
Normal Structures			
Retina*	1%	40	25
Lens*			2
Oral cavity			35
Larynx			42
Mandible	5%	45	
Skin	5%	45	
Partial esoph	2 cc	40	
Middle Ear*			45
Parotid glands*	20 cc	20	26

*Paired structures. Dose constraints apply to one such structure and are equivalent for the contralateral side.

Priority for Above Dose Constraints

1. Critical Structures
2. PTV Prescription Goals
3. Salivary Glands
4. Other Structures

5.11.8 Treatment Plan Evaluation

The plan will be reviewed by the treating physician prior to treatment in order to ensure that all parameters have been met. Isodose curves and dose volume histograms (DVH) will be analyzed.

Criteria for plan evaluation will include:

- Isodose Curves:
  The 95% isodose line must be generally conformal to the PTV with visually acceptable tumor coverage and visually acceptable critical structure avoidance.

  The 110% isodose line must not include any critical structure volumes.
  The 4200 cGy isodose line must not encroach on the "Spinal cord + 5 mm"
  The 2600 cGy isodose line should spare parotid glands when possible.

- Dose Volume Histograms (DVHs):
  No more than 20% of any PTV should exceed 110% of the prescribed dose.
  DVH from PTVs must meet all prescription parameters.
  Normal structure DVHs should meet constraint parameters as listed above.

5.11.9 Daily Radiation Treatment

Patients will receive external beam radiation treatment delivered by Varian linear accelerator once a day, five days a week, for 4 to 4 1/5 weeks as per routine clinical practice.

5.11.10 Quality Assurance

Treatment plan physics review and QA are required for each patient in accordance with current institutional standards for IMRT.

Daily set-up error will be minimized by the following clinically approved and commercially available patient setup techniques: immobilization mask, standard skin/mask alignment marks, and daily on-board imaging.

Per routine practice, daily cone beam CT scans will be acquired and compared with planning CT overlay.

These setup scans will be performed immediately prior to each treatment and the appropriate shifts will be made at that time.

5.12 Follow-Up Assessments

Follow-up assessments will be conducted at the following time points (actual follow up times may vary due to patient logistics and compliance):

- 2 weeks (+/- 1 week) following completion of definitive therapy (RT)
- 8 weeks (+/- 2 weeks) following completion of definitive therapy (RT)
- 16 weeks (+/- 2 weeks) following completion of definitive therapy (RT)
- 9, 12, 16, 20, 24, 28, 32, 36, 42, 48, 54, and 60 months (+/- 6 weeks) following completion of definitive therapy (RT) [ENT follow-up, including laryngoscopy procedures, will be conducted as standard of care after 12 months of follow-up]
- 72 months (+/- 3 months) following completion of definitive therapy (RT) and annually thereafter [ENT follow-up, including laryngoscopy procedures, will be conducted as standard of care after 12 months of follow-up]

Patients with progression will only be followed for survival and will not stay on the above follow-up schedule. Their follow-up schedules will then be at the discretion of the investigator.

5.12.1 Two Week (+/- 1 week) Assessment

1. Physical examination and weight (kg).
2. CBC
3. BMP
4. Assessment of clinical overall response using visual categorical response based on data from 4 and 5 above. Overall Response is determined as the lesser of the primary site and neck node responses (i.e. Primary Site – CR; Neck Nodes – PR; Overall Response = PR)

5.12.2 Eight Week (+/- 2 weeks) Assessment

1. Physical examination and weight (kg).

2. Documentation of ECOG performance status.
3. Documentation of patient symptoms using NCI-CTCAE version 3.0.
4. CBC, CMP, and magnesium.
5. CT Neck.

5.12.3 Sixteen Week (+/- 2 weeks) Assessment

1. Physical examination and weight (kg).
2. Documentation of ECOG performance status.
3. Documentation of patient symptoms using NCI-CTCAE version 3.0. Any adverse event determined by the PI to be possibly, probably, or definitely related to the research procedures should be reported to the clinical research coordinator to report according to Section 10.0.
4. Assessment of primary tumor site to be done by laryngoscopy performed in the office or in the operating room. The primary tumor response will be assessed using visual categorical response. The percent change from assessment one will be dictated in the ENT physician's clinical exam note.
5. Assessment of involved regional neck nodes by physical examination. The involved neck node response will be assessed using visual categorical response. The neck node measurements will be performed clinically by the treating medical oncology physician and dictated in his/her assessment note.
6. Assessment of clinical overall response using visual categorical response based on data from 4 and 5 above. Overall Response is determined as the lesser of the primary site and neck node responses (i.e. Primary Site – CR; Neck Nodes – PR; Overall Response = PR)
7. FDG-PET/CT scan (whole body) to document and measure the FDG avidity at the primary tumor site and at the involved regional neck nodes.

5.12.4 Nine to Sixty Month Assessments

1. Physical examination and weight (kg).
2. Documentation of ECOG performance status.
3. Completion of QOL questionnaire (to occur at 6 and 12 month visits only).
4. Documentation of patient symptoms using NCI-CTCAE version 3.0.
5. Assessment of primary tumor site to be done by laryngoscopy performed in the office. The primary tumor response will be assessed using visual categorical response. The percent change from last assessment will be dictated in the ENT physician's clinical exam note. [ENT follow-up, including laryngoscopy procedures, will be conducted as standard of care after 12 months of follow-up so will occur at some, but not all, long-term follow-up visits]
6. Assessment of involved regional neck nodes by physical examination. The involved neck node response will be assessed using visual categorical response. The neck node measurements will be performed clinically by the treating medical oncology physician and dictated in his/her assessment note.
7. Assessment of clinical overall response using visual categorical response, based on data from 5 and 6 above. Overall Response is determined as the lesser of the

primary site and neck node responses (i.e. Primary Site – CR; Neck Nodes – PR; Overall Response = PR)

8. CT scan of neck and chest (IV contrast preferred) to be done at 12, 18, 24, and 36 months (+/- 6 weeks) following completion of definitive therapy to document and measure the extent of the primary tumor size and involved regional neck nodes. RECIST 1.0 will be used to determine response at the primary tumor site, at the involved regional neck nodes and the radiographic overall tumor response.

5.12.5 Seventy-Two Month Assessment and Beyond

1. Physical examination and weight (kg).
2. Documentation of ECOG performance status.
3. Documentation of patient symptoms using NCI-CTCAE version 3.0.
4. Assessment of primary tumor site be done by laryngoscopy performed in the office. The primary tumor response will be assessed using visual categorical response. The percent change from last assessment will be dictated in the ENT physician's clinical exam note. [ENT follow-up, including laryngoscopy procedures, will be conducted as standard of care after 12 months of follow-up so will occur at some, but not all, long-term follow-up visits]
5. Assessment of involved regional neck nodes by physical examination. The involved neck node response will be assessed using visual categorical response. The neck node measurements will be performed clinically by the treating medical oncology physician and dictated in his/her assessment note.
6. Assessment of clinical overall response using visual categorical response, based on data from 4 and 5 above. Overall Response is determined as the lesser of the primary site and neck node responses (i.e. Primary Site – CR; Neck Nodes – PR; Overall Response = PR).

6.0 PHARMACEUTICAL INFORMATION

6.1 *nab*-Paclitaxel (Abraxane)

6.1.1 *nab*-Paclitaxel Description

nab-Paclitaxel is a novel biologically interactive albumin-bound paclitaxel combining a protein with a chemotherapeutic agent in the particle form. *nab*-Paclitaxel for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) (albumin-bound) is currently indicated for the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy.

Molecular formula: C47H51N014
Chemical name: 5β,20-Epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4,10-diacetate 2-benzoate 13 ester with (2*R*,3*S*)-*N*-benzoyl-3-phenylisoserine.

Molecular weight: 853.91.

6.1.2 Clinical Pharmacology

nab-Paclitaxel is an antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization. This stability results in the inhibition of the normal dynamic reorganization of the microtubule network that is essential for vital interphase and mitotic cellular functions. Paclitaxel induces abnormal arrays or "bundles" of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis.

6.1.3 Supplier

nab-Paclitaxel will be distributed by Celgene Corporation and labeled appropriately as investigational material for this study. Labels will bear Celgene's name and address, the protocol number, product name, dosage form and strength, medication identification/kit number, lot number, expiry date, dosing instructions, storage conditions, the quantity of IP contained, and require education statements and/or regulatory statements as applicable. No supplies will be shipped to any site until regulatory approval has been obtained. Investigational sites will be supplied with *nab*-Paclitaxel 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.

6.1.4 Dosage Form and Preparation

nab-Paclitaxel is supplied as a white to off-white sterile lyophilized powder for reconstitution with 20 mL of 0.9% Sodium Chloride. Each single-use 50 mL vial will contain paclitaxel (100 mg) and approximately 900 mg human albumin (HA) as a stabilizer. Each vial will be labeled according to country-specific regulatory requirements for labeling of investigational products.

1. Calculate the patient's body surface area at the beginning of the study and if the weight changes by > 10%.
2. Calculate the total dose (in mg) to be administered by multiplying study dose by BSA.
3. Calculate the total number of vials required by dividing the total dose by 100 (as there are 100 mg per vial) and rounding up to the next higher whole number.
4. Using sterile technique, prepare the vials for reconstitution.
5. Swab the rubber stoppers with alcohol.

6. Reconstitute each *nab*-Paclitaxel vial by injecting 20 mL of 0.9% Sodium Chloride Injection, USP or equivalent into each vial over a period of not less than 1 minute. DO NOT INJECT the 0.9% Sodium Chloride Injection, USP solution directly onto the lyophilized cake as this will result in foaming. Once the injection is complete, 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. Each ml of reconstituted product will contain 5 mg of paclitaxel.
7. Calculate the exact total dosing volume of 5 mg/ml suspension required for the patient by dividing the total dose by 5.
8. The reconstituted sample should be milky and homogeneous without visible particulates. If unsuspended powder is visible, the vial should be gently inverted again to ensure complete re-suspension prior to use.
9. Once the exact volume of reconstituted *nab*-Paclitaxel has been withdrawn from the vials, discard any excess solution left over in accordance with standard operating procedures.
10. Further dilution is not necessary. Inject the calculated dosing volume of reconstituted *nab*-Paclitaxel suspension into an empty sterile, standard PVC IV bag using an injection port. Inject perpendicularly into the center of the injection port to avoid dislodging plastic material into the IV bag.
11. Administer the calculated dosing volume of reconstituted Nab-Paclitaxel suspension by IV infusion over 30 minutes. The use of in-line filters is not recommended.
12. Following administration, the intravenous line should be flushed with sodium chloride 9 mg/ml (0.9%) solution for injection to ensure complete administration of the complete dose, according to local practice.
13. Use within 8 hours of reconstitution. If not used immediately, store reconstituted *nab*-Paclitaxel in a refrigerator for no longer than 8 hours.

6.1.5 Storage and Stability

Unreconstituted *nab*-Paclitaxel should be stored at controlled room temperature (20° to 25°C or 68° to 77°F) in its carton. Retain in the original package to protect from bright light. Unopened vials of albumin-bound paclitaxel are stable until the date indicated on the package when stored at the above temperatures in the original package. Reconstituted albumin-bound paclitaxel should be used immediately, but may be refrigerated at 2ºC to 8ºC (38ºF to 46ºF) for a maximum of 8 hours if necessary. If not used immediately, each vial of reconstituted suspension should be replaced in the original carton to protect it from bright light. Discard any unused portion.

6.1.6 *nab*-Paclitaxel Drug Return and 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.

6.1.7 *nab*-Paclitaxel Premedication and Administration

Patients do not require premedication prior to *nab*-Paclitaxel administration, as hypersensitivity reactions are rare. In the unlikely event of a mild hypersensitivity reaction, premedication may be administered using the premedication regimen the institution typically uses for solvent based paclitaxel. In the rare event of a severe hypersensitivity reaction, discontinue *nab*-Paclitaxel. However, it is recommended that patients receive Granisetron 1mg prior to receiving *nab*-Paclitaxel.

NOTE: It is not a requirement to use filter needles in the preparation of, or in-line filters during the administration of *nab*-Paclitaxel. In any event, filters of pore-size less than 15 micrometers must not be used.

Albumin-bound paclitaxel should be administered by IV over 30 minutes.

6.2 Cisplatin (CDDP, Platinol-AQ®)

6.2.1 Cisplatin Description

Molecular formula: PtCl2H6N2
Molecular weight: 300.1.

6.2.2 Clinical Pharmacology

The mechanism of action of cisplatin has not been clearly elucidated. However the most likely mechanism of antitumor action of this drug resides in its ability to inhibit DNA synthesis, and to a lesser degree, RNA and protein synthesis. It has also been shown that Cisplatin binds to DNA and produces inter-strand cross-links. Also cisplatin is not phase-sensitive and its cytotoxicity is similar in all phases of the cell cycle. Additional information can be found in the package insert.

6.2.3 Supplier

Cisplatin is commercially available as 1 mg/mL in both 50 mL multiple dose vial and 100 mL multiple dose vial.

6.2.4 Dosage Form and Preparation

The stability of cisplatin in solution is dependent upon the chloride ion concentration present in the diluent. Cisplatin should be diluted into an IV solution containing NaCL at a minimum chloride ion concentration of 0.040 mol/L (0.2% NaCL). Needles, syringes, catheters and IV administrations sets containing aluminum must be avoided during preparation and administration due to cisplatin-aluminum reaction causing precipitation and loss of potency. Mannitol 12.5 to 25 gm may be added per institutional guidelines.

6.2.5 Storage and Stability

The dry, unopened vials should be stored at room temperature (15° -25° C). The unopened container should be protected from light and stored in the carton until contents are used. Do not refrigerate. 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.

6.2.6 Administration

Patients will receive cisplatin via IV infusion over 60 minutes. Adequate hydration must be maintained during and after administration as described in the treatment section. It is recommended that all patients should be premedicated with antiemetics.

6.3 Cetuximab (Erbitux) – with Radiation ARM 2 and selected ARM 1 or 3 patients

6.3.1 Cetuximab Description

Cetuximab is an anti-EGFR human-to-murine chimeric antibody.

6.3.2 Clinical Pharmacology

The epidermal growth factor receptor (EGFR, HER1, c-ErbB-1) is a transmembrane glycoprotein that is a member of a subfamily of type I receptor tyrosine kinases including EGFR, HER2, HER3, and HER4. The EGFR is constitutively expressed in many normal epithelial tissues, including the skin and hair follicle. Expression of EGFR is also detected in many human cancers including those of the head and neck, colon, and rectum.

Cetuximab binds specifically to the EGFR on both normal and tumor cells, and competitively inhibits the binding of epidermal growth factor (EGF) and other ligands, such as transforming growth factor-alpha. *In vitro* assays and *in vivo* animal studies have shown that binding of cetuximab to the EGFR blocks phosphorylation and activation of receptor-associated kinases, resulting in

inhibition of cell growth, induction of apoptosis, and decreased matrix metalloproteinase and vascular endothelial growth factor production. Signal transduction through the EGFR results in activation of wild-type KRAS protein. However, in cells with activating *KRAS* somatic mutations, the mutant KRAS protein is continuously active and appears independent of EGFR regulation.

In vitro, cetuximab can mediate antibody-dependent cellular cytotoxicity (ADCC) against certain human tumor types. *In vitro* assays and *in vivo* animal studies have shown that cetuximab inhibits the growth and survival of tumor cells that express the EGFR. No antitumor effects of cetuximab were observed in human tumor xenografts lacking EGFR expression. The addition of cetuximab to radiation therapy or irinotecan in human tumor xenograft models in mice resulted in an increase in anti-tumor effects compared to radiation therapy or chemotherapy alone.

6.3.3 Pharmacokinetics and Drug Metabolism

Cetuximab administered as monotherapy or in combination with concomitant chemotherapy or radiation therapy exhibits nonlinear pharmacokinetics. The area under the concentration time curve (AUC) increased in a greater than dose proportional manner while clearance of cetuximab decreased from 0.08 to 0.02 L/h/m^2 as the dose increased from 20 to 200 mg/m^2, and at doses >200 mg/m^2, it appeared to plateau. The volume of the distribution for cetuximab appeared to be independent of dose and approximated the vascular space of 2–3 L/m^2.

Following the recommended dose regimen (400 mg/m2 initial dose; 250 mg/m^2 weekly dose), concentrations of cetuximab reached steady-state levels by the third weekly infusion with mean peak and trough concentrations across studies ranging from 168 to 235 and 41 to 85 μg/mL, respectively. The mean half-life of cetuximab was approximately 112 hours (range 63–230 hours). The pharmacokinetics of cetuximab were similar in patients with SCCHN and those with colorectal cancer. Based on a population pharmacokinetic analysis, female patients with colorectal cancer had a 25% lower intrinsic clearance of cetuximab than male patients. Qualitatively similar, but smaller gender differences in cetuximab clearance were observed in patients with SCCHN. The gender differences in clearance do not necessitate any alteration of dosing because of a similar safety profile.

6.3.4 Supplier

Cetuximab is commercially available and is listed in the compendia as indicated for the therapy of SCCHN.

6.3.5 Dosage Form

Each single-use, ready to use 50-mL vial contains 100 mg of cetuximab at a concentration of 2 mg/mL and is formulated in a preservative-free solution containing 8.48 mg/mL sodium chloride, 1.88 mg/mL sodium phosphate dibasic

heptahydrate, 0.42mg/mL sodium phosphate monobasic monohydrate, and Water for injection, USP.

6.3.6 Storage and Stability

Cetuximab should be stored in a secure area according to local regulations. Store vials under refrigeration at 2° C to 8° C (36° F to 46° F). DO NOT FREEZE. Increased particulate formation may occur at temperatures at or below 0°C. This product contains no preservatives. Preparations of cetuximab in infusion containers are chemically and physically stable for up to 12 hours at 2° C to 8° C (36° F to 46° F) or up to 8 hours at controlled room temperature (20° C to 25° C; 68° F to 77° F). Discard any remaining solution in the infusion container after 8 hours at controlled room temperature or after 12 hours at 2° to 8° C. Discard any unused portion of the vial.

6.3.7 Safety Precautions

Appropriate mask, protective clothing, eye protection, gloves, and Class II vertical-laminar-airflow safety cabinets are recommended during preparation and handling. Opened vials must be disposed of at the investigational center as chemotherapy or biohazardous waste provided documented procedures for destruction are in place.

Cetuximab therapy should be used with caution in patients with known hypersensitivity to cetuximab, murine proteins, or any component of this product. It is recommended that patients wear sunscreen and hats and limit sun exposure while receiving cetuximab as sunlight can exacerbate any skin reactions that may occur.

6.3.8 Premedication

In an effort to prevent a hypersensitivity reaction, all patients will be premedicated with diphenhydramine hydrochloride 50 mg (or an equivalent antihistamine) IVPB given 30-60 minutes prior to the Cetuximab. Premedication will also include solucortef 100 mg IVPB and albuterol inhalation (by nebulizer or inhaler) according to standard of care procedures.

6.3.9 Preparation and Administration

Cetuximab must not be administered as an IV push or bolus. Cetuximab must be administered with the use of a low protein binding 0.22-micrometer in-line filter. Cetuximab is supplied as a 50-mL, single-use vial containing 100 mg of cetuximab at a concentration of 2 mg/mL in phosphate buffered saline. DO NOT SHAKE OR DILUTE. Adequate hydration must be maintained before administration as described in the treatment section

Cetuximab can be administered via infusion pump.

Infusion Pump:

- Draw up the volume of a vial using a sterile syringe attached to an appropriate needle (a vented spike or other appropriate transfer device may be used).
- Fill cetuximab into a sterile evacuated container or bag such as glass containers, polyolefin bags (e.g., Baxter Intravia), ethylene vinyl acetate bags (e.g., Baxter Clintec), DEHP plasticized PVC bags (e.g., Abbott Lifecare), or PVC bags.
- Repeat procedure until the calculated volume has been put in to the container. Use a new needle for each vial.
- Administer through a low protein binding 0.22-micrometer in-line filter (placed as proximal to the patient as practical).
- Affix the infusion line and prime it with cetuximab before starting the infusion.
- Maximum infusion rate should not exceed 5 mL/min.
- Use 0.9% saline solution to flush line at the end of infusion.
- The infusion rate of cetuximab must never exceed 10 mg/minute (5 mL/min). The infusion time of cetuximab should not exceed 4 hours. Patients must be continuously observed during the infusion for signs of anaphylaxis.

6.3.10 Patient Monitoring

Patients should be closely monitored for treatment-related adverse events, especially hypersensitivity reactions during the infusion and for one post-infusion observation hour. Vital signs (blood pressure, heart rate, and temperature) will be monitored and recorded prior to the administration of cetuximab, 1/2 hour into the infusion, at the completion of the infusion, and 1 hour post-infusion for the initial dose. During all subsequent administrations of cetuximab, vital signs will be monitored and recorded prior to administration of cetuximab and at the end of the infusion; however, it is recommended that the patient be observed for 1-hour post infusion.

7.0 DOSE MODIFICATIONS

At each of the scheduled visits noted in the study calendar, an assessment of adverse events (AE's) will be made by the treating physician with toxicity grading using the NCI CTCAE version 3. Patients without AEs will continue on study treatment as planned. Patients who develop grade 1-2 or selected grade 3 (nausea/vomiting/fatigue) AEs will be supported symptomatically and encouraged to continue on study treatment as planned. Modifications in their therapy may be necessary and will be detailed below. Management of specific AEs is noted below. **Omitted doses will not be made up at a later date.** Dosing interruptions are permitted in the case of medical/surgical events or logistical reasons not related to study therapy.

7.1 *nab*-Paclitaxel Dose Modifications

7.1.1 Dose Modification Table

Use this table as a guideline to determine any necessary dose modifications.

Dose Level	*nab*-Paclitaxel (mg/m^2)
Starting Dose	100
-1	80
-2	60

7.1.2 Administration of Study Drug to Patients with Abnormal Hematologic Function

nab-Paclitaxel dosing should not be administered at the start of each cycle until the absolute neutrophil count returns to $\geq 1.5 \times 10^9$ cells/L and the platelet count returns to $> 100 \times 10^9$ cells/L. For patients receiving weekly *nab*-Paclitaxel, patients must have an ANC $\geq 0.5 \times 10^9$ cells/L and platelets $> 50 \times 10^9$ cells/L for the Day 8 and Day 15 doses. If the ANC and platelets are not adequate for treatment on Day 8 and/or 15, the dose will be omitted and the total cycle length remains the same.

7.1.3 Administration of Study Drug to Patients with Abnormal Hepatic Function

For patients with mild hepatic impairment (total bilirubin > ULN and ≤ 1.5 x ULN and AST ≤ 10 x ULN), no dose adjustments are required regardless of indication. For patients with moderate hepatic impairment (total bilirubin between 1.5 x ULN and 5 x ULN), reduce nab-paclitaxel by one dose level. Do not administer nab-paclitaxel to patients with total bilirubin > 5 x ULN or AST > 10 x ULN regardless of indication as these patients have not been studied.

7.1.4 Peripheral Neuropathy

Peripheral neuropathy is dose- and schedule-dependent. The occurrence of grade 1 or 2 peripheral neuropathy does not generally require dose modification. If ≥ grade 3 peripheral neuropathy develops, withhold nab-paclitaxel until resolution to ≤ grade 1 followed by a dose reduction for all subsequent courses.

7.1.5 Hypersensitivity Reactions

Hypersensitivity reactions rarely occur, but severe and sometimes fatal hypersensitivity reactions, including anaphylactic reactions, have been reported. If they do occur, minor symptoms such as flushing, skin reactions, dyspnea, lower back pain, hypotension, or tachycardia may require temporary interruption of the

infusion. However, severe reactions, such as hypotension requiring treatment, dyspnea requiring bronchodilators, angioedema, or generalized urticaria require immediate discontinuation of study drug administration and aggressive symptomatic therapy. Patients who experience a severe hypersensitivity reaction to *nab*-paclitaxel should not be re-challenged. The use of nab-paclitaxel in patients previously exhibiting hypersensitivity to paclitaxel injection or human albumin has not been studied.

7.1.6 Other Toxicities

If toxicities are ≥ grade 3 and deemed by the treating physician to at least possibly be related to *nab*-paclitaxel, except for anemia and lymphopenia, treatment should be withheld until resolution to ≤ grade 1 or baseline if baseline was greater than grade 1, then reinstituted, if medically appropriate, at the next lower dose level.

7.1.7 Dose Reductions and Guidelines for Optional Use of Growth Factors for Hematologic Toxicity

The table below provides a guideline for implementing dose reductions and optional use of growth factor treatment for hematologic toxicity:

Use of G-CSF and Dose Reductions for Hematologic Toxicity

Adverse Event	Occurrence	Action to be Taken
ANC < 500 cells/mm^3 (nadir count) with neutropenic fever > 38° C OR Delay of next cycle due to persistent neutropenia (ANC < 1500 cells/mm^3) OR For patients whose next treatment within a cycle	First Occurrence	The same dose of *nab*-Paclitaxel is maintained and G-CSF at 5 mcg/kg/day is given the day after *nab*-Paclitaxel is given and should stop at least 48 hours prior to when *nab*-Paclitaxel is given the following week.

(Day 8 or Day 15) is omitted due to persistent neutropenia (ANC < 500 cells/mm^3) OR Neutropenia < 500 cells/mm^3 for > 1 week	Recurrence	In the event that a hematological toxicity re-occurs in the face of G-CSF, dose reduction to the next lower level will be required for subsequent cycles once ANC is ≥ 1500 cells/mm^3.
Grade 3 or 4 platelets decreased	First Occurrence	Dose reduction to next lower level; no administration of G-CSF required
	Recurrence	Dose reduction to next lower level; no administration of G-CSF required

7.2 Cisplatin Dose Modifications

7.2.1 Peripheral Neuropathy

Grade 0, 1, or 2: no dose modification.

Grade 3 or 4: Hold cisplatin until the event resolves to < grade 3.

7.2.2 Ototoxicity

If grade 1 or 2 hearing loss occurs, the risk of additional hearing loss versus the potential benefit of continuing cisplatin chemotherapy should be made. Grade 3 and 4 hearing loss is an indication to discontinue the drug.

7.2.3 Kidney Impairment

Calculated Creatinine Clearance	**Percent Dose to Give**	
≥ 60 mL/min	100%	
< 60 mL/min	0% (withhold treatment for this dose and repeat serum creatinine weekly after additional hydration), then for next chemotherapy dose:	
	If CrCl was already < 60 mL/min and is now:	**The percent dose to give is:**
	> 50 but < 60	80%
	≥ 40 but ≤ 50	50%
	< 40	0%

Please note that dose reduction percentage is calculated by taking off from the original dose and not the previous dose.

7.2.4 Thrombocytopenia

Nadir of last course	**Platelets (Day 1 of each cycle)**	
	< 100,000	≥ 100,000
between 50,000 and 100,000	Hold cisplatin	Cisplatin = 100%
< 50,000 (1st occurrence)	Hold cisplatin	Cisplatin = 80%
<50,000 (2nd occurrence)	Hold cisplatin	Cisplatin = 60%

7.3 Cetuximab Dose Modifications

Dose Levels for Cetuximab

Dose Levels	**Weekly Cetuximab Dose**
Starting dose	250 mg/m^2
Dose Level –1	200 mg/m^2
Dose Level –2	150 mg/m^2

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

Any other toxicities deemed necessary of a dose reduction per the PI, using the 80% and 60% dose reduction levels.

7.3.1 Management of Dermatologic Adverse Effects

Patients developing dermatologic toxicities while receiving cetuximab should be monitored for the development of inflammatory or infectious sequelae, and appropriate treatment of these symptoms initiated. Dose modifications of any future cetuximab infusions should be instituted in case of grade 3 acneiform rash. Treatment with topical and/or oral antibiotics (minocycline 100 mg bid) should be considered, but should not be given prophylactically; topical corticosteroids are not recommended.

If a patient experiences grade 3 acneiform rash, cetuximab treatment adjustments should be made according to the following table. In patients with mild and moderate skin toxicity, treatment should continue without dose modification.

Cetuximab Dose Modification Guidelines for Grade 3 Acneiform Rash

Occurrence	Action	Outcome	Dose Modification
First	Delay infusion 1-2 weeks	Improvement	Continue at 250 mg/m^2
		No Improvement	Discontinue cetuximab
Second	Delay infusion 1-2 weeks	Improvement	Reduce to Dose Level -1
		No Improvement	Discontinue cetuximab
Third	Delay infusion 1-2 weeks	Improvement	Reduce to Dose Level -2
		No Improvement	Discontinue cetuximab
Fourth	Discontinue cetuximab	N/A	N/A

7.3.2 Management of Gastrointestinal Adverse Effects

Antiemetic agents may be administered prior to the administration of cetuximab. Diarrhea will be treated symptomatically with antidiarrheal agents. Should GI toxicity become severe enough to require hospitalization or outpatient IV fluid replacement, all treatment should be discontinued temporarily until the patient's condition improves.

7.3.3 Management of Hypersensitivity Reactions

Grading:
Mild (grade 1) hypersensitivity reactions (HSRs) consist of urticaria, fever, or chills and are treated with symptom-directed management.

Moderate (grade 2) HSRs consist of dyspnea, angioedema, or hypotension which reverses within one to two hours of appropriate symptom-directed management and stopping the cetuximab infusion. Symptom-directed management includes nebulized b_2 agonists (albuterol 2.5 mg) for dyspnea and bronchospasm, intravenous fluid boluses (normal saline 1-2 liters) for hypotension, and the use of H1 and H2 antagonists (diphenhydramine and famotidine) and corticosteroids (hydrocortisone 100 mg).

Severe (grade 3) HSRs consist of dyspnea, angioedema, or hypotension, as the Grade 2 reactions do, but do not reverse following one to two hours of symptom directed management.

Life-threatening/disabling (grade 4) HSRs consist of airway obstruction, shock, cardiac arrest, or prolonged hypotension.

Grade 4 HSRs require the immediate interruption of cetuximab therapy and permanent discontinuation from further treatment. Appropriate medical therapy including epinephrine, corticosteroids, intravenous antihistamines, bronchodilators, and oxygen should be available for use in the treatment of such reactions. Patients should be carefully observed until the complete resolution of all signs and symptoms.

In prior clinical trials, grade 1 and grade 2 infusion reactions were managed by slowing the infusion rate of cetuximab and by continued use of antihistamine pre-medications (e.g., diphenhydramine) in subsequent doses. If the patient experiences a grade 3 infusion reaction, the infusion rate should be permanently reduced by 50%. For grade 1 or 2 reactions, additional doses of diphenhydramine or corticosteroids may be administered.

7.3.4 Management of Isolated Drug Fever

If a patient experiences isolated drug fever, subsequent pre-treatment with acetaminophen or a non-steroidal anti-inflammatory agent may be considered. If a patient experiences recurrent isolated drug fever following premedication and post-dosing with an appropriate antipyretic, the infusion rate for subsequent dosing should be 50% of previous rate.

7.3.5 Management of Pulmonary Adverse Effects

In the event of acute onset (grade ≥ 2) or worsening pulmonary symptoms which are not thought to be related to underlying cancer, cetuximab therapy should be interrupted and a prompt investigation of these symptoms should occur. Cetuximab re-treatment should not occur until these symptoms have resolved to grade 1. If interstitial lung disease is confirmed, cetuximab should be discontinued and the patient should be treated appropriately.

7.3.6 Management of Renal Adverse Effects

Hypomagnesemia has been reported with cetuximab when administered as a single agent and in combination with multiple different chemotherapeutic regimens. Patients receiving cetuximab should be monitored for hypomagnesemia. Magnesium repletion may be necessary based on clinical judgment.

8.0 CORRELATIVE STUDIES

8.1 Genomic Analysis

Our hypothesis is that the high anti-tumor efficacy of *nab*-paclitaxel in HNSCC is due to the frequent presence of Ras and PI3K (and EGFR) pathway activation in this cancer. Pre-treatment tumor biopsies will undergo mutational (and IHC) analyses of the PI3 kinase pathway and H-ras. Mutational analysis of the PI3 Kinase pathway includes PIK3CA, PIK3CG, PTEN, PIK3R1 and PIK3R5. IHC analysis of the PI3kinase pathway includes EGFR, AKT, PIK3CA, PTEN, MET and pS6 kinase. The association of these biomarkers with CR at the PTS and relapse events will be evaluated.

8.2 Immunologic Analysis

Immunodeficiency is a risk factor for HNSCC. Novel HNSCC-specific tumor antigens exist (mutCASP-8, Cyclin D, ALDH). TILs are associated with increased recurrence risk in some studies. FoxP3 expression is associated with poorer OS in oropharyngeal and hypopharyngeal HNSCC. PD-L1, an immune checkpoint inhibitory ligand, is expressed on tumor and macrophage cells in HPV-positive and HPV-negative HNSCC. B7-H1 blockade augmented adoptive T-cell immunotherapy in HNSCC[32-45].

Paclitaxel has effects on immunity with selectively reduced Tregs. It promoted cytotoxic T-cell responses, abolished tumor cell inhibition of dendritic cell differentiation and stimulated macrophages[46-49]. Our hypothesis is that *nab*-paclitaxel will deplete Tregs, decrease PD-L1, and increase TIL at the PTS. PTS tumor biopsies obtained before and after 2 cycles of *nab*-paclitaxel induction chemotherapy (Arms 1-3) will be analyzed for Tregs, TIL, and PD-L1 by IHC. IHC analysis includes TIL markers and PD-L1. CD3, CD4, CD8, Foxp3 and the monocytic marker CD116 will also be analyzed. The association of these biomarkers (before *nab*-paclitaxel and the change after 2 cycles of *nab*-paclitaxel) with CR at the PTS and relapse events will be evaluated.

Specimens shall be transported to the Washington University lab c/o Dr. Douglas Adkins, located on the 3rd floor of the McKinley Ave. building or shipped to the address listed below:

Dr. Brian Van Tine – Research lab
4515 McKinley Building, 3rd Floor
4523 Clayton Avenue
St. Louis, MO 63110

8.3 Quality of Life Assessments

Quality of Life (QOL) questionnaires will be administered to patients at baseline, prior to starting radiation, at the last week of radiation, at the 6-month follow-up visit, and at the 12-month follow-up visit. The 4-page questionnaire will assess physical, social, emotional,

and functional well-being through questions designed specifically for patients with head & neck cancer. An additional 4-question QOL survey will assess symptoms of peripheral neuropathy, a side effect often seen in patients receiving *nab*-paclitaxel.

9.0 DEFINITION OF TUMOR RESPONSE CRITERIA

9.1 Visual Categorical Outcomes

Visual categorical outcomes will be used to assess tumor response at the primary site and involved regional nodes after two cycles of induction chemotherapy and after completion of definitive radiation and concurrent cetuximab therapy. Primary site responses will be dictated in ENT note. Neck node measurements will be taken from the medical oncology physical exam measurements also dictated, but into the medical oncology note.

Visual Categorical Outcomes	
CR	Complete resolution – 100% decrease/minimal residual mucosal abnormality
PR	99-50% decrease
SD	49-0% decrease
PD	Any increase

9.2 RECIST Criteria

The RECIST 1.0 criteria will be used to assess anatomic tumor response (Appendix 2).

9.3 PET/CT Imaging

FDG-PET/CT will be utilized to assess tumor metabolic response. PET/CT imaging will be performed with a PET/CT scanner All patients will undergo FDG-PET/CT imaging at baseline (no more than 42 days prior to Cycle 1 day 1), between Cycle 2 Days 16 and 20, and at 16 weeks (+/- 2 weeks) following completion of definitive radiation therapy in accordance with the Division of Nuclear Medicine standard procedure for FDG-whole-body tumor imaging. Care should be taken to match follow-up examinations as close as possible to the baseline imaging parameters with no more than 10 minutes deviation in uptake time but must also adhere to the minimum 50 minutes of uptake time. In rare instances uptake times of greater than 70 minutes are allowed providing the overall uptake time does not go beyond the 10 minute deviation from baseline examination. Each patient will undergo all 3 FDG-PET/CT scans even if s/he has measurable disease by RECIST but not by PET criteria.

The standard whole-body examination for FDG-PET/CT imaging in patients with head and neck cancer typically includes images from the skull vertex to the upper thighs. An i.v. (typically, a 20- or 22-gauge Angiocath) or butterfly needle will be placed in an upper extremity vein for injection of FDG and i.v. hydration (up to 500 ml of 0.9% saline solution). The administered dose of FDG will be based upon subject weight and range from a minimum of 10 mCi to a maximum of 20 mCi with up to a 20% range on each side

of maximum and minimum dose allowed. FDG will be administered intravenously. In cases of poor venous access (butterfly injection of FDG), oral hydration will replace intravenous hydration. Approximately 60 (50-70) minutes after injection of FDG, imaging will be initiated.

PET/CT imaging will be according to local protocol. The following is minimum suggested imaging requirements: With the patient positioned supine in the scanner and with the patient's arms at the side of the body, the CT images used for attenuation correction and image fusion will be obtained. The CT will consist of a 5-10 second topogram a followed by a diagnostic quality CT scan without i.v. contrast for attenuation correction. Scans are reconstructed using a 5-mm slice thickness. This is followed by a series of sequential 2 to 5-minute emission scans at each bed position, beginning at the vertex of the skull and proceeding caudally to the upper thighs. Images are reconstructed with ordered subset expectation maximization (OSEM) and smoothing per scanner manufacturer recommendations

10.0 REGULATORY AND REPORTING REQUIREMENTS

The entities providing oversight of safety and compliance with the protocol require reporting as outlined below.

The Washington University Human Research Protection Office (HRPO) requires that all events meeting the definition of unanticipated problem or serious noncompliance be reported as outlined in Section 7.2.

Celgene requires that all adverse events be reported as outlined in Section 10.6.

10.1 Definitions

10.1.1 Adverse Events (AEs)

Definition: any unfavorable medical occurrence in a human subject including any abnormal sign, symptom, or disease.

Grading: the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 will be utilized for all toxicity reporting. A copy of the CTCAE version 3.0 can be downloaded from the CTEP website.

Attribution (relatedness), Expectedness, and Seriousness: the definitions for the terms listed that should be used are those provided by the Department of Health and Human Services' Office for Human Research Protections (OHRP). A copy of this guidance can be found on OHRP's website: (http://www.hhs.gov/ohrp/policy/AdvEvntGuid.html).

10.1.2 Serious Adverse Event (SAE)

Definition: any adverse drug experience occurring at any dose that results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity (i.e., a substantial disruption of a person's ability to conduct normal life functions)
- A congenital anomaly/birth defect
- Any other experience which, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above

Please refer to Section 10.7 for reporting restrictions.

10.1.3 Unexpected Adverse Experience

Definition: any adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure (or risk information, if an IB is not required or available).

10.1.4 Life-Threatening Adverse Experience

Definition: any adverse drug experience that places the subject (in the view of the investigator) at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

10.1.5 Unanticipated Problems

Definition:

- unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- related or possibly related to participation in the research (in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

10.1.6 Noncompliance

Definition: failure to follow any applicable regulation or institutional policies that govern human subjects research or failure to follow the determinations of the IRB. Noncompliance may occur due to lack of knowledge or due to deliberate choice to ignore regulations, institutional policies, or determinations of the IRB.

10.1.7 Serious Noncompliance

Definition: noncompliance that materially increases risks, that results in substantial harm to subjects or others, or that materially compromises the rights or welfare of participants.

10.1.8 Protocol Exceptions

Definition: A planned deviation from the approved protocol that are under the research team's control. Exceptions apply only to a single participant or a singular situation.

Local IRB pre-approval of all protocol exceptions must be obtained prior to the event. For secondary sites, the Washington University PI will issue approval of the exception, but it must also be submitted to the local IRB with documentation of approval forwarded to Washington University. Washington University IRB approval is not required for protocol exceptions occurring at secondary sites.

10.2 Reporting to the Human Research Protection Office (HRPO) at Washington University

The PI is required to promptly notify the IRB of the following events:

- Any unanticipated problems involving risks to participants or others which occur at WU, any BJH or SLCH institution, or that impacts participants or the conduct of the study.
- Noncompliance with federal regulations or the requirements or determinations of the IRB.
- Receipt of new information that may impact the willingness of participants to participate or continue participation in the research study.

These events must be reported to the IRB within **10 working days** of the occurrence of the event or notification to the PI of the event. The death of a research participant that qualifies as a reportable event should be reported within **1 working day** of the occurrence of the event or notification to the PI of the event.

The Investigator must keep copies of all AE information, including correspondence with Celgene and the IRB/EC, on file.

10.3 Reporting to the Quality Assurance and Safety Monitoring Committee (QASMC) at Washington University

The PI is required to notify the QASMC of any unanticipated problem occurring at WU or any BJH or SLCH institution that has been reported to and acknowledged by HRPO as reportable. (Unanticipated problems reported to HRPO and withdrawn during the review process need not be reported to QASMC.)

QASMC must be notified within 10 days of receipt of IRB acknowledgment via email to a QASMC auditor.

10.4 Reporting Requirements for Secondary Sites

The research team at each secondary site is required to promptly notify the Washington University PI and research coordinator of all reportable events (as described in Section 10.6) within **1 working day** of the occurrence of the event or notification of the secondary site's PI of the event. This notification may take place via email if there is not yet enough information for a formal written report (using either an FDA MedWatch form if required or an institutional SAE reporting form if not). A formal written report must be sent to the Washington University PI and research coordinator within **10 working days** of the occurrence of the event or notification of the secondary site's PI of the event. The death of a research participant that qualifies as a reportable event should be reported within **1 working day** of the occurrence of the event or notification of the secondary site's PI of the event.

The research team at a secondary site is responsible for following its site's guidelines for reporting applicable events to its site's IRB according to its own institutional guidelines. The research team at Washington University is responsible for reporting all applicable events to the FDA.

10.5 Reporting to Secondary Sites

The Washington University PI (or designee) will notify the research team at each secondary site of all reportable events that have occurred at other sites within **10 working days** of the occurrence of the event or notification of the PI of the event. This includes events that take place both at Washington University and at other secondary sites, if applicable.

10.6 Reporting to Celgene

An adverse event is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a subject during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the subject's health, including laboratory test values (as specified by the criteria below), regardless of etiology. Any worsening (i.e., any clinically significant adverse change in the frequency or intensity of a pre- existing condition) should be considered an AE.

An overdose, accidental or intentional, whether or not it is associated with an AE, or abuse, withdrawal, sensitivity or toxicity to an investigational product should be reported as an AE. If an overdose is associated with an AE, the overdose and adverse event should be reported as separate terms.

All patients will be monitored for AEs during the study. Assessments may include monitoring of any or all of the following parameters: the subject's clinical symptoms, laboratory, pathological, radiological or surgical findings, physical examination findings, or other appropriate tests and procedures.

All AEs will be recorded by the Investigator from the time the subject signs informed consent to 30 days after the last dose of IP. All SAEs must be reported to Celgene Drug Safety within 24 hours of the Investigator's knowledge of the event by facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form using the contact information below:

Celgene Corporation
Global Drug Safety and Risk Management
Connell Corporate Park
300 Connell Dr., Suite 6000
Berkeley Heights, N.J. 07922
Fax: 908-673-9115
Email: drugsafety@celgene.com

10.6.1 Seriousness

A serious adverse event (SAE) is any AE occurring at any dose that:

- Results in death;
- Is life-threatening (i.e., in the opinion of the investigator, the subject is at immediate risk of death from the AE);
- Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization is defined as an inpatient admission regardless of length of stay)
- Results in persistent or significant disability/incapacity (a substantial disruption of the subject's ability to conduct normal life functions);
- Is a congenital anomaly/birth defect;
- Constitutes an important medical event.

Important medical events are defined as those occurrences that may not be immediately life threatening or result in death, hospitalization, or disability, but may jeopardize the subject or require medical or surgical intervention to prevent one of the other outcomes listed above. Medical and scientific judgment should be exercised in deciding whether such an AE should be considered serious.

Events **not considered** to be SAEs are hospitalizations for:

- A standard procedure for protocol therapy administration. However, hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as an SAE.
- Routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
- The administration of blood or platelet transfusion as routine treatment of studied indication. However, hospitalization or prolonged hospitalization for a complication of such transfusion remains a reportable SAE.
- A procedure for protocol/disease-related investigations (e.g., surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling). However, hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable SAE.
- Hospitalization or prolongation of hospitalization for technical, practical, or social reasons, in absence of an AE.
- A procedure that is planned (i.e., planned prior to start of treatment on study). Hospitalization or prolonged hospitalization for a complication remains a reportable SAE.
- An elective treatment of a pre-existing condition unrelated to the studied indication.
- Emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above.

10.6.2 Severity / Intensity

For both AEs and SAEs, the Investigator must assess the severity / intensity of the event.

The term "severe" is often used to describe the intensity of a specific event (as in mild, moderate or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This criterion is *not* the same as "serious" which is based on subject/event *outcome* or *action* criteria associated with events that pose a threat to a subject's life or functioning.

Seriousness, not severity, serves as a guide for defining regulatory obligations.

10.6.3 Causality

The Investigator must determine the relationship between the administration of IP and/or gemcitabine and the occurrence of an AE/SAE as Not Suspected or Suspected as defined below:

- Not suspected: The temporal relationship of the adverse event to IP administration makes **a causal relationship unlikely or remote**, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.

- Suspected: The temporal relationship of the adverse event to IP administration makes **a causal relationship possible**, and other medications, therapeutic interventions, or underlying conditions do not provide a sufficient explanation for the observed event.

If an event is assessed as suspected of being related to a comparator, ancillary or additional IP that has not been manufactured or provided by Celgene, please provide the name of the manufacturer when reporting the event.

10.6.4 Duration

For both AEs and SAEs, the Investigator will provide a record of the start and stop dates of the event.

10.6.5 Action Taken

The Investigator will report the action taken with IP as a result of an AE or SAE, as applicable (eg., discontinuation or reduction of IP, as appropriate) and report if concomitant and/or additional treatments were given for the event.

10.6.6 Outcome

All SAEs that have not resolved upon discontinuation of the subject's participation in the study must be followed until recovered, recovered with sequelae, not recovered (death due to another cause) or death (due to the SAE).

10.6.7 Abnormal Laboratory Values

An abnormal laboratory value is considered to be an AE if the abnormality:

- Results in discontinuation from the study;
- Require treatment, modification/interruption of IP dose, or any other therapeutic intervention, or
- Is judged to be of significant clinical importance.

Regardless of severity grade, only laboratory abnormalities that fulfill a seriousness criterion need to be documented as a serious adverse event.

10.6.8 Pregnancies

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on IP, or within 30 days of the subject's last dose of IP, are considered immediately reportable events. IP is to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Celgene Drug Safety

immediately by facsimile, or other appropriate method, using the Pregnancy Initial Report Form, or approved equivalent form.

The Investigator will follow the female subject until completion of the pregnancy, and must notify Celgene Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form, or approved equivalent form.

If the outcome of the pregnancy was abnormal (e.g., spontaneous or therapeutic abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to Celgene Drug Safety immediately by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the in utero exposure to the IP should also be reported to Celgene Drug Safety immediately by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

10.6.9 Male Subjects

If a female partner of a male subject taking investigational product becomes pregnant, the male subject taking IP should notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately.

10.6.10 Reporting of Serious Adverse Events

All SAEs must be reported to Celgene Drug Safety within 24 hours of the Investigator's knowledge of the event by facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form. This instruction pertains to initial SAE reports as well as any follow-up reports.

The Investigator is required to ensure that the data on these forms is accurate and consistent.

This requirement applies to all SAEs (regardless of relationship to IP) that occur during the study (from the time the patient signs informed consent to 30 days after the last dose of IP), and those made known to the Investigator at anytime thereafter that are suspected of being related to IP. SAEs occurring prior to treatment will be captured.

The SAE report should provide a detailed description of the SAE and include summaries of hospital records and other relevant documents. If a patient died and

an autopsy has been performed, copies of the autopsy report and death certificate are to be sent to Celgene Drug Safety as soon as these become available. Any follow-up data will be detailed in a subsequent SAE Report Form, or approved equivalent form, and sent to Celgene Drug Safety.

Where required by local legislation, the Investigator is responsible for informing the IRB/EC of the SAE and providing them with all relevant initial and follow-up information about the event. The Investigator must keep copies of all SAE information on file including correspondence with Celgene and the IRB/EC.

10.6.11 Expedited Reporting of Adverse Events

For the purpose of regulatory reporting, Celgene Drug Safety will determine the expectedness of events suspected of being related to nab-paclitaxel based on the Investigator Brochure.

Celgene or its authorized representative shall notify the Investigator of the following information:

- Any AE suspected of being related to the use of IP in this study or in other studies that is both serious and unexpected (ie., SUSAR);
- Any finding from tests in laboratory animals that suggests a significant risk for human patients including reports of mutagenicity, teratogenicity, or carcinogenicity.

The Investigator shall notify his/her IRB/EC promptly of these new serious and unexpected AE(s) or significant risks to patients. The Investigator is also responsible to report all SAEs to the FDA within 24 hours.

10.7 Timeframe for Reporting Required Events

Adverse events will be tracked for 30 days following the last day of study treatment. For the purposes of this protocol, adverse events that meet the definition of serious (as per Sections 10.1.2 and 10.6.1) but occur outside of the induction period will not be considered SAEs unless determined to be at least possibly related to nab-Paclitaxel. The induction period starts at time of informed consent and continues through 30 days after the last dose of nab-paclitaxel.

For Arm 3, the event of disease relapse will be specifically tracked from Day 1 of radiation through 6 months post-completion of radiation. Also refer to Section 11.3, Paragraph 2.

11.0 STATISTICAL CONSIDERATIONS

11.1 Study Design

This is a non-randomized phase II trial with three parallel treatment arms whose primary objective is to determine the CR rate by clinical exam at the primary tumor site to an IC regimen of Arm 1 weekly *nab*-Paclitaxel with P (AP) given for two cycles (over 6 weeks), Arm 2: weekly *nab*-Paclitaxel (A) given for two cycles (over 6 weeks), and Arm 3 (HPV-related OPSCC): AP given for two cycles (over 6 weeks) in patients with locally advanced non-metastatic HNSCC.

Arms 1 and 2: Each treatment group will be compared with a historical control from the APF study. There will be no comparison between the AP and A treatment groups.

The primary endpoint for each arm (AP or A) is that the PTS CR rate will be non-inferior to the PTS CR rate observed with APF (77%). A CR rate ≥ 58%, or no more than 19% less than the historically observed 77%, will be considered noninferior.

In each treatment group patient recruitment will be stratified by HPV status (positive/negative) in order to ensure that the proportion of positive and negative patients is approximately equal in the two treatment groups. The expected CR rate is 77% in both HPV positive and negative patients.

For the following secondary objectives, the analysis of primary tumor site response to the IC regimen will also be stratified based on T stage (T2 vs. T3 vs. T4) and will be reported as frequencies (with 95% confidence intervals) in each T stage category. For purposes of testing hypotheses, stratification will be included as an adjustment variable in:

- Documenting the clinical partial response (PR) rate at the primary tumor site and the clinical CR and PR rates at the involved regional nodes following two cycles of AP or A;
- Documenting the anatomic tumor response as assessed by CT scan using RECIST criteria following two cycles of AP or A;
- Documenting and quantifying Ki-67 expression by IHC and histologic tumor response in primary tumor tissue obtained at baseline and following two cycles of AP or A and correlate these results with clinical primary tumor site response to AP or A;
- Documenting and grading AE's with AP or A, and comparing to those observed with APF;
- Determining median or year-by-year overall survival (OS), disease-free survival (DFS), and progression-free survival (PFS) in these patients; and,
- Documenting the measures of Quality of Life (QoL) before, during, and at one year after completion of treatment in both treatment groups.

ARM 3: This arm will be compared with Arm 1 (data as of October, 2017).

The primary endpoint is to determine the median percent weight loss in patients with HPV-positive OPSCC who are treated with AP. De-escalated CRT will reduce the median percent weight loss by 50% compared to CRT. Mucosal toxicity during CRT resulted in a median weight loss of 13.1% (range: 5% - 23.2%) in Arm 1 (null hypothesis). We hypothesize that the de-escalated CRT regimen in Arm 3 will result in a 50% reduction in the median weight loss (alternative hypothesis).

A secondary endpoint for Arm 3: The PTS CR rate will be non-inferior to the PTS CR rate observed with APF (77%). A CR rate ≥ 58%, or no more than 19% less than the historically observed 77%, will be considered noninferior.

For the following secondary objectives (except AEs and QOLs), the analysis of primary tumor site response to the IC regimen will also be stratified based on T stage (T1/2 vs. T3 vs. T4) and will be reported as frequencies (with 95% confidence intervals) in each T stage category. For purposes of testing hypotheses, stratification will be included as an adjustment variable in:

- Documenting the clinical partial response (PR) rate at the primary tumor site and the clinical CR and PR rates at the involved regional nodes following two cycles of IC;
- Documenting the anatomic tumor response as assessed by CT scan using RECIST criteria following two cycles of IC;
- Documenting and quantifying Ki-67 expression by IHC and histologic tumor response in primary tumor tissue obtained at baseline and following two cycles of IC and correlate these results with clinical tumor response at the primary tumor site;
- Documenting and grading AE's and comparing to those observed with Arm 1;
- Determining median or year-by-year overall survival (OS), disease-free survival (DFS), and progression-free survival (PFS) in these patients; and,
- Documenting the measures of Quality of Life (QoL) before, during, and at one year after completion of treatment.

In addition, the study will compare arm 3 to arm 1 (the AP arm) as follows:

- Response rate, OS, DFS, and PFS.
- Rate of grade 3-4 AEs during CRT.
- The median absolute and percent weight loss during CRT.

11.2 Analysis Plan and Study Power

Arms 1 and 2: Two one-sample tests for noninferiority, stratified by HPV status, will be used to determine whether the CR with AP or A is no more than 19% less than the CR rate with APF. Given an expected rate of CR with APF is 77%, a 19% difference (58% vs 77%) is considered to be clinically equivalent. With a noninferiority margin of 19%, a sample of 40 patients will provide each treatment group with power = 0.80 power at a

significance level of 0.05 to conclude that the CR rate with AP or A is not inferior to that with APF.

Proportions of patients with clinical PR at the primary tumor site, clinical CR and PR rates at the involved regional nodes, anatomic and metabolic tumor responses, and AEs by type, grade and patient will be calculated with 95% confidence intervals. The proportion of patients with grade 3-4 AEs is 40% in the APF study. It is expected to be at least 25% lower with AP (40% decreased to 30%) and at least 50% lower with A (40% decreased to 20%).

Arm 3: The primary hypothesis for Arm 3 is: de-escalated CRT will reduce the median percent weight loss by 50% compared to CRT. **Mucosal toxicity during CRT resulted in a median weight loss of 13.1% (range: 5% - 23.2%) in Arm 1 (null hypothesis). We hypothesize that the de-escalated CRT regimen in Arm 3 will result in a 50% reduction in the median weight loss (alternative hypothesis). If weight loss is 50% of the historical amount (that is, about 6.5% vs. historical 13.1%), the standard deviation of percent weight loss is about the same as the mean (that is, ± 13%), then a sample of 30 patients will provide power=.84 at a .05 significance level to detect this difference.** Nonparametric Kruskal-Wallis test, a Friedman nonparametric one-way ANOVA or paired permutation test will be used to compare median weight loss during CRT in arm 3 vs. arm 1. Median weight loss will be calculated in the treatment arm with bootstrapped confidence intervals.

All Arms: Nonparametric Wilcoxon tests will be used to compare Ki-67 expression by ICH categories. Two clustered logistic regression (GEE) models also may be used to quantify the odds of histologic tumor response over time by clinical primary tumor response. AE rates during CRT will be described as binomial proportions with exact 95% confidence intervals in arm 3 versus arm 1. One sided tests for difference of binomial proportions may be used to test for differences in AE rates with a false discovery rate adjustment for multiple testing if >5 tests are carried out. Kaplan-Meier models will be used to estimate median OS, DFS, and PFS (if the median is reached) and to estimate 1 and 2 year rates of OS, DFS, and PFS with 95% confidence intervals. Kaplan-Meier models will be used to compare OS, DFS and PFS in arm 3 vs. arm 1.

All Arms: Summary and subscale scores from the FACT-N&N and the FACT-GOG-NTX-4 will be plotted at baseline, completion of treatment, and one year after end of treatment. Ordinal logistic regression will be used to estimate the association of demographic, clinical, and response covariates with QOL at each time point. Generalized estimating equations (GEE) may be used to estimate the association of the same covariates with change in QOL over time. These plots and models are exploratory and descriptive.

11.3 Adverse Primary Outcome Monitoring

The rate of unfavorable PTS response, SD + PD, will be monitored using a continuous toxicity monitoring rule. The observed SD + PD rate in the APF study was 7%, and the maximum allowable rate is considered to be 20%. Enrollment will be suspended for review

due to excess unfavorable response if the number of patients with unfavorable responses reaches 2 in the first 5, or 3 in the first 11, or 4 in the first 19, or 5 in the first 27, or 6 in the first 37, or if the 7th is observed before the 40th patient has completed the trial. Forty patients will be accrued to each arm of the study.

In Arm 3, unfavorable response will be monitored as the number of relapses, also using continuous toxicity monitoring criteria. The expected relapse rate is 10%, and the maximum acceptable rate is 25%. A modified Pocock boundary with boundary shape parameter=0.2 specifies that the study will be suspended for review if it observes 3 relapses among the first 7 patients, or 4 among the first 14 patients, or 5 among the first 21 patients, or 6 among the first 29 patients, or if the 7th relapse is observed before the 30th patient has completed the study. These criteria have probability=.80 of correct early stopping if the true relapse rate is 25% and probability=.10 of incorrect early stopping if the true relapse rate is 10%.

12.0 DATA SUBMISSION SCHEDULE

Case Report Form	Submission Schedule
Original Consent Form	Prior to registration
Registration Form Eligibility Form Baseline Form	Prior to starting treatment
AP or A Induction Form	Every cycle
Definitive Therapy Form	At completion of definitive therapy
AE Tracking Form	Continuous
Follow Up Form	Per protocol
CT Measurement Form	Baseline, end of Cycle 2, 8 week follow-up, 16 week follow-up 12 month follow-up, 20 month follow-up, 28 month follow-up, 36 month follow-up

Any queries generated by Washington University must be responded to within 28 days of receipt by the participating site. The Washington University research team will conduct a regular review of data status at all secondary sites, with appropriate corrective action to be requested as needed.

13.0 DATA AND SAFETY MONITORING

In compliance with the Washington University Institutional Data and Safety Monitoring Plan, an independent Data and Safety Monitoring Committee (DSMC) will be specifically convened for this trial to review toxicity data at least every 6 months following the activation of the first secondary site. A DSMC will consist of no fewer than 3 members including 2 clinical investigators and a biostatistician. Like investigators, DSMC members are subject to the Washington University School of Medicine policies regarding standards of conduct. Individuals invited to serve on the DSMC will disclose any potential conflicts of interest to the trial principal investigator and/or appropriate university officials, in accordance with institution policies. Potential conflicts that develop during a trial or a member's tenure on a DSMC must also be disclosed.

The DSM report will be prepared by the study statistician with assistance from the study team, will be reviewed by the DSMC, and will be submitted to the Quality Assurance and Safety Monitoring Committee (QASMC). This report will include:

- HRPO protocol number, protocol title, Principal Investigator name, data coordinator name, regulatory coordinator name, and statistician
- Date of initial HRPO approval, date of most recent consent HRPO approval/revision, date of HRPO expiration, date of most recent QA audit, study status, and phase of study
- History of study including summary of substantive amendments; summary of accrual suspensions including start/stop dates and reason; and summary of protocol exceptions, error, or breach of confidentiality including start/stop dates and reason
- Study-wide target accrual and study-wide actual accrual including numbers from participating sites
- Protocol activation date at each participating site
- Average rate of accrual observed in year 1, year 2, and subsequent years at each participating site
- Expected accrual end date and accrual by site
- Objectives of protocol with supporting data and list the number of participants who have met each objective
- Measures of efficacy
- Early stopping rules with supporting data and list the number of participants who have met the early stopping rules
- Summary of toxicities at all participating sites
- Abstract submissions/publications
- Summary of any recent literature that may affect the safety or ethics of the study

Until such a time as the first secondary site activates this protocol, a semi-annual DSM report to be prepared by the study team will be submitted to the QASM Committee beginning 6 months after study activation at Washington University.
The study principal investigator and Research Patient Coordinator will monitor for serious toxicities on an ongoing basis. Once the principal investigator or Research Patient Coordinator becomes aware of an adverse event, the AE will be reported to the HRPO and QASMC according to institutional guidelines.

14.0 AUDITING

Since Washington University is the coordinating center, each site will be audited annually by Siteman Cancer Center personnel (QASMC) unless the outside institution has an auditing mechanism in place and can provide a report. The outside sites will be asked to send copies of all audit materials, including source documentation. The audit notification will be sent to the Washington University Research Patient Coordinator, who will obtain the audit materials from the participating institution.

Notification of an upcoming audit will be sent to the research team one month ahead of the audit. Once accrual numbers are confirmed, and approximately 30 days prior to the audit, a list of the cases selected for review (up to 10 for each site) will be sent to the research team. However, if during the audit the need arises to review cases not initially selected, the research team will be asked to provide the additional charts within two working days.

Additional details regarding the Auditing Policies and procedures can be found at http://www.siteman.wustl.edu/uploadedFiles/Research_Programs/Clinical_Research_Resources/Protocol_Review_and_Monitoring_Committee/QASMCQualityAssurance.pdf

15.0 MULTICENTER REGULATORY REQUIREMENTS

Washington University requires that each participating site sends its informed consent document to be reviewed and approved by the Washington University Principal Investigator (or designee) prior to IRB/IEC submission.

Each participating institution must have the following documents on file at Washington University prior to first subject enrollment:

- Documentation of IRB approval of the study in the form of a letter or other official document from the participating institution's IRB. This documentation must show which version of the protocol was approved by the IRB.
- Documentation of IRB approval of an informed consent form. The consent must include a statement that data will be shared with Washington University, including the Quality Assurance and Safety Monitoring Committee (QASMC), the DSMC (if applicable), and the Washington University study team.
- Documentation of FWA, a signed financial disclosure form, signed FDA Form 1572, and signed and dated CVs of all participating investigators.
- Documentation of training in protection of human subjects by all participating investigators.
- Protocol signature page signed and dated by the investigator at each participating site.

The Principal Investigator is responsible for disseminating to the participating sites all study updates, amendments, reportable adverse events, etc. There will be one current version of the protocol document at any given time and each participating institution will utilize that document. Protocol/consent modifications and IB updates will be forwarded electronically to the secondary sites within 2 weeks of obtaining Washington University IRB approval with acknowledgement of

receipt requested. Secondary sites are to submit protocol/consent/IB modifications to their local IRBs within 4 weeks of receipt, and confirmation of submission must be forwarded to the appropriate contact person on the Washington University study team at the time of submission. Upon the secondary sites obtaining local IRB approval, documentation of such shall be sent to the Washington University study team within 2 weeks of receipt of approval.

Documentation of participating sites' IRB approval of annual continuing reviews, protocol amendments or revisions, all SAE reports, and all protocol violations/deviations/exceptions must be kept on file at Washington University.

The investigator or a designee from each institution must participate in a regular conference call to update and inform regarding the progress of the trial.

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17.0 STUDY CALENDARS

17.1 Study Calendar 1: ARM 1 or ARM 3: Induction Chemotherapy with AP

	Base-line[7]	Cycle 1					Cycle 2						Cycle 3					Definitive Chemotherapy/ Radiation
		D1	D2	D3	D8	D15	D1	D2	D3	D8	D15	Between D16 and D20[3]	D1	D2	D3	D8	D15	
nab-Paclitaxel administration[4]		X			X	X	X			X	X		X			X	X	
Cisplatin administration[2]		X					X						X					**See separate study calendar below.**
Informed consent	X																	
PE w/palpation	X	X			X	X	X					X	X					
CBC	X	X			X	X	X			X	X		X			X	X	
CMP + magnesium	X	X					X						X					
CT - Neck	X											X						
FDG-PET/CT	X											X[8]						
Laryngoscopy w/biopsy[1]	X											X						
PT/PTT, EKG	X																	
Pregnancy test[5]	X																	
FACT-H&N, FACT/GOG-NTX-4	X																	
Pulmonary Function Tests[6]	X																	
Rad Tx Planning													X					

Window for all assessments +/2 days unless otherwise noted.

1. Primary Tumor Site biopsy specimens (punch, incisional or core needle) will be obtained at baseline and at completion of Cycle 2 for Ki-67 expression and routine surgical pathology. If a biopsy is not feasible for financial reasons or safety concerns, at the Primary Investigator's discretion one or both of the biopsies may be forgone. However, the laryngoscopies are needed to continue on the study. Assessment of primary tumor site will be done by laryngoscopy performed in the office or in the operating room.
2. Hydration: 1L IVF NS (recommended: 10 meq KCL/L + 8 meq MgSO4/L) over one hour before and after cisplatin on Day 1. 2L IVF NS over 2 hours on Days 2 & 3.
3. If CR or PR at primary tumor site and without radiographic or FDG evidence of disease progression, proceed with Cycle 3. If PD or SD, proceed to surgery followed by reduced CRT or definitive full dose chemoradiation.
4. Recommended premedication is granisetron 1 mg prior to each administration.
5. In women of childbearing potential only.
6. Spirometry, lung volumes, DLCO
7. Window for baseline assessment is 28 days, with the exception of PET scan, which is 42 days.
8. Only done when possible per insurance coverage.

17.2 Study Calendar 2: ARM 2: Induction Chemotherapy with A

	Base-line[5]	Cycle 1			Cycle 2				Cycle 3					Definitive Chemotherapy/ Radiation
		D1	D8	D15	D1	D8	D15	Between D16 and D20[2]	D1	D2	D3	D8	D15	
nab-Paclitaxel administration[6]		X	X	X	X	X	X		X			X	X	
Cetuximab administration														**See Study Calendar 4**
Informed consent	X													
PE w/palpation	X	X	X	X	X			X	X					
CBC	X	X	X	X	X	X	X		X			X	X	
CMP + magnesium	X	X			X				X					
CT - Neck	X							X						
FDG-PET/CT	X							X[7]						
Laryngoscopy w/biopsy[1]	X							X						
PT/PTT, EKG	X													
Pregnancy test[3]	X													
FACT-H&N, FACT/GOG-NTX-4	X													
Pulmonary Function Tests[4]	X													
Rad Tx Planning									X					

Window for all assessments +/2 days unless otherwise noted.

1. Primary Tumor Site biopsy specimens (punch, incisional or core needle) will be obtained at baseline and at completion of Cycle 2 for Ki-67 expression and routine surgical pathology. If a biopsy is not feasible for financial reasons or safety concerns, at the Primary Investigator's discretion one or both of the biopsies may be forgone. However, the laryngoscopies are needed to continue on the study. Assessment of primary tumor site will be done by laryngoscopy performed in the office or in the operating room.
2. If CR or PR at primary tumor site and without radiographic or FDG evidence of disease progression, proceed with Cycle 3. If PD or SD, proceed to surgery or definitive chemoradiation.
3. In women of childbearing potential only.
4. Spirometry, lung volumes, DLCO
5. Window for baseline assessment is 28 days, with the exception of PET scan, which is 42 days.
6. Recommended premedication is granisetron 1 mg prior to each administration
7. Only done when possible per insurance coverage.

17.3 Study Calendar 3: Definitive Radiation and Concurrent Chemotherapy – Cisplatin (In conjunction with Arm 1)

To begin 1 to 35 days after the end of Cycle 2 (if SD/PD and no surgery) or 3.

	Definitive Chemoradiation (weeks)								**Short-term Follow-up (weeks)**		**Long-term Follow-up (months from completion of definitive therapy) (± 6 week window until 60, then ± 3 month window)**													
	0	**1 (D1)**	**2**	**3**	**4 (D22)**	**5**	**6**	**7 (D43)**	**8 wks ± 2 wks**	**16 ± 2 wks**	**9**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**42**	**48**	**54**	**60**	**72**	**Annually (+/- 3 months)**
Cisplatin[3]		X			X			X																
IMRT[4]		X----------X																						
PE w/palpation		X			X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CBC		X			X			X	X															
CMP + magnesium		X			X			X	X															
CT – Neck and Chest									X[5]			X		X		X		X						
FDG-PET/CT										X[6]														
Laryngoscopy[1]										X	X	X	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]
FACT-H&N, FACT/GOG-NTX-4	X							X		X		X												

Window for all assessments +/2 days unless otherwise noted.

1. Assessment of primary tumor site will be done by laryngoscopy performed in the office or in the operating room [ENT follow-up, including laryngoscopy procedures, will be conducted as standard of care after 12 months of follow-up so will occur at some, but not all, long-term follow-up visits]
2. Hydration: 1L IVF NS (recommended: 10 meq KCL/L + 8 meq MgSO4/L) over one hour before and after cisplatin on Day 1. 2L IVF NS over one hour on Days 2 and 3.
3. Hold if grade 4 mucositis or skin. Dose reduce if creatinine clearance < 60 and/or grade 3 mucositis/grade 3 skin.
4. Delivered once per day M-F (See Section 5.10).
5. CT neck only.
6. If PET/CT cannot be performed, a CT of Neck and Chest should be done in place of the PET/CT.

17.4 Study Calendar 4: Definitive Radiation and Concurrent Chemotherapy – Cetuximab (Arms 1 {selected patients} and 2 only)

To begin 1 to 35 days after the end of Cycle 2 (if SD/PD and no surgery) or 3.

	Definitive Chemoradiation (weeks)								**Short-term Follow-up (weeks)**		**Long-term Follow-up (months from completion of definitive therapy) (± 6 week window until 60, then ± 3 month window)**													
	0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8 wks ± 2 wks**	**16 ± 2 wks**	**9**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**42**	**48**	**54**	**60**	**72**	**Annually (+/- 3 months)**
Cetuximab[2, 4]	X	X	X	X	X	X	X	X																
IMRT[3]		X----------X																						
PE w/palpation	X				X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CBC	X				X			X	X															
CMP + magnesium	X				X			X	X															
CT – Neck and Chest									X[5]			X		X		X		X						
FDG-PET/CT										X[6]														
Laryngoscopy[1]										X	X	X	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]
FACT-H&N, FACT/GOG-NTX-4	X							X		X		X												

Window for all assessments +/2 days unless otherwise noted.

1. Assessment of primary tumor site will be done by laryngoscopy performed in the office or in the operating room. [ENT follow-up, including laryngoscopy procedures, will be conducted as standard of care after 12 months of follow-up so will occur at some, but not all, long-term follow-up visits]
2. Premedications: diphenhydramine 50mg, solucortef 100mg IVPB, and albuterol inhalation (2.5 mg/inhaler)
3. Delivered once per day M-F (See Section 5.10)
4. Loading dose of 400 mg/m^2 at time point 0 followed by maintenance dose of 250 mg/m^2.
5. CT neck only.

If PET/CT cannot be performed, a CT of Neck and Chest should be done in place of the PET/CT.

17.5 Study Calendar 5: Definitive Radiation and Concurrent Chemotherapy – Cisplatin (In conjunction with Arm 3)

To begin 1 to 35 days after the end of Cycle 3 (if CR/PR at PTS) or 2 (if SD/PD and surgery).

	Definitive Chemoradiation (weeks)						**Short-term Follow-up (weeks)**			**Long-term Follow-up (months from completion of RT) (± 6 week window until 60, then ± 3 month window)**												
	0	**1 (D1)**	**2**	**3**	**4 (D22)**	**5**	**2 ± 1 wk**	**8 ± 2 wks**	**16 ± 2 wks**	**9 mo**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**42**	**48**	**54**	**60**	**Annual +/-3 months**
Cisplatin* **or**		X																				
Cetuximab[7]	X	X	X	X	X	X																
IMRT[3]		X----------X																				
PE w/palpation[8]	X	X			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight[8]	X	X			X		X															
CBC		X			X		X	X														
CMP + magnesium		X			X		X[4]	X[4]														
CT – Neck and Chest								X[5]			X		X		X		X					
FDG-PET/CT									X[6]													
Laryngoscopy[1]									X	X	X	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]
FACT-H&N, FACT/GOG-NTX-4	X						X		X		X											

Window for all assessments +/2 days unless otherwise noted.

***Patients to receive Cisplatin. Criteria to receive cisplatin: creatinine clearance > 60, ECOG 0-2, no active serious infections. Patients who do NOT meet these criteria will receive Cetuximab.**

1. Assessment of primary tumor site will be done by laryngoscopy performed in the office or in the operating room [ENT follow-up, including laryngoscopy procedures, will be conducted as standard of care after 12 months of follow-up, so will occur at some, but not all, long-term follow-up visits]
2. Hydration: 1L IVF NS (recommended: 10 meq KCL/L + 8 meq MgSO4/L) over one hour before and after cisplatin on Day 1. 2L IVF NS over one hour on Days 2 and 3.
3. Delivered once per day M-F (See Section 5.10). for approximately 4 weeks.
4. BMP not CMP at this timepoint
5. CT neck only.
6. If PET/CT cannot be performed, a CT of Neck and Chest should be done in place of the PET/CT.
7. Loading dose of 400 mg/m^2 at time point 0 followed by maintenance dose of 250 mg/m^2, Premedications: diphenhydramine 50mg, solucortef 100mg IVPB, and albuterol inhalation (2.5 mg/inhaler)
8. Cisplatin patients have PE on Week 1 and no Weight collection on Week 0. Cetuximab patients have Weight collection and PE on Week 0 and no PE on Week 1.

APPENDIX 1: ECOG Performance Status

ECOG PERFORMANCE STATUS*	
Grade	**ECOG**
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

* As published in Am. J. Clin. Oncol:

Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

APPENDIX 2: Criteria for Response, Progression, and Relapse

At baseline, tumor lesions will be characterized as either measurable or non-measurable.

Measurable:
Lesions that can be accurately measured in at least one dimension (longest diameter to be recorded) as > 20 mm (2.0 cm) with conventional techniques or as > 10 mm (1.0 cm) with spiral CT scan. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

Non-Measurable:
All other lesions, including small lesions [longest diameter < 20 mm (2.0 cm) with conventional techniques or < 10 mm (1.0 cm) with spiral CT scan] and truly non-measurable lesions. Lesions considered to be truly non-measurable include the following: bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, abdominal masses that are not confirmed and followed by imaging techniques, and cystic lesions. Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. The conditions under which such lesions should be considered must be defined in the protocol when appropriate.

Target Lesions:
All measurable lesions up to a maximum of 10 lesions representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repetitive measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference to further characterize the objective tumor response of the measurable dimension of the disease.

Complete Response (CR):
Disappearance of all target lesions. Where response is the primary endpoint, changes in tumor measurements must be confirmed by repeat studies performed no less than 4 weeks after the criteria for response are first met. Longer intervals as determined by the Principal Investigator may also be appropriate.

Partial Response (PR):
At least a 30% decrease in the sum of the longest diameter (LD) of target lesions taking as reference the baseline sum LD. Where response is the primary endpoint, changes in tumor measurements must be confirmed by repeat studies performed no less than 4 weeks after the criteria for response are first met. Longer intervals as determined by the Principal Investigator may also be appropriate.

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

Stable Disease (SD):
Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as references the smallest sum LD since the treatment started. Patients having a documented response with no reconfirmation of the response will be listed with stable disease.

Non-target Lesions:
All other lesions (or sites of disease) not included in the "target disease" definition should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as "present" or "absent."

Complete Response (CR):
Disappearance of all non-target lesions and normalization of tumor marker level. If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-complete response (non-CR)/Non-progression (non-PD):
Persistence of one or more non-target lesion and/or maintenance of tumor marker level above the upper limits of normal.

Progression (PD):
Appearance of one or more new lesions. Unequivocal progression of existing non-target lesions. Although a clear progression of non-target lesions is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed later on by the review panel (or Principal Investigator).

Cytology and Histology:
If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

These techniques can be used to differentiate between PR and CR in rare cases (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain).

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

Evaluation of Best Overall Response:
The best overall response should be recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Note: In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before confirming the complete response status.

First Documentation of Response:
The time between initiation of therapy and first documentation of PR or CR.

Confirmation of Response:
To be assigned a status of complete or partial response, changes in tumor measurements must be confirmed by repeat assessments performed no less than four weeks after the criteria for response are first met.

Duration of Response:
Duration of overall response – the period measured from the time that measurement criteria are met for complete or partial response (whichever status is recorded first) until the first date that recurrent or progressive disease is objectively documented, taking as reference the smallest measurements recorded since treatment started.

Duration of Overall Complete Response:
The period measured from the time measurement criteria are met for complete response until the first date that recurrent disease is objectively documented.

Duration of Stable Disease:
A measurement from registration until the criteria for disease progression is met, taking as reference the smallest measurements recorded since registration. To be assigned a status of stable disease, measurements must have met the stable disease criteria at least once after study entry at a minimum interval (in general, not less than eight weeks).

Survival:
Survival will be measured from the date of entry on study.

Time to Progression:
This interval will be measured from the date of entry on the study to the appearance of new metastatic lesions or objective tumor progression.

Methods of Measurement:
Imaging based evaluation is preferred to evaluation by clinical examination. The same imaging modality must be used throughout the study to measure disease.

Guidelines for Evaluation of Measurable Disease:
Clinical Lesions will only be considered measurable when they are superficial (e.g., skin nodules, palpable lymph nodes). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is recommended.

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

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

Ultrasound:
Ultrasound (US) should not be used to measure tumor lesions that are clinically not easily accessible when the primary endpoint of the study is objective response evaluation. It is a possible alternative to clinical measurements of superficial palpable nodes, subcutaneous lesions, and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

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

Tumor Markers:
Tumor Markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Confirmation Measurement/Duration of Response:
Confirmation to be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat studies that should be performed no less than 4 weeks after the criteria for response are first met. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of not less than 6 weeks.

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

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

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

APPENDIX 3: Institutional Guidelines for IMRT

A. Normal structure and treatment volume contours will be delineated using the following guidelines:

The dosimetrist will contour the following structures with name allocation exactly as written:

1. "Skin"
2. "Spinal cord"
3. "Brainstem"
4. "Brain"
5. "R eye"
6. "L eye"
7. "R Optic nerve"
8. "L Optic nerve"
9. "Optic chiasm"
10. "R Lens"
11. "L Lens"
12. "Mandible"
13. "PTV 7000" (0.5 cm universal expansion on "CTV 7000" as described below; also referred to as PTV1)
14. "PTV 6300" (0.5 cm universal expansion on "CTV 6300" as described below; also referred to as PTV2)
15. "PTV 5800" (0.5 cm universal expansion on "CTV 5600" as described below; also referred to as PTV3)

B. The physician will assist with and approve the above contours and delineate contours for the following structures with name allocation exactly as written (See guidelines below):

1. "Oral cavity"
2. "R Parotid"
3. "L Parotid"
4. "Larynx"
5. "Partial esoph"
6. "GTV-n"
7. "GTV-p"
8. "CTV 7000" (also referred to as CTV1)
9. "CTV 6300" (also referred to as CTV2)
10. "CTV 5600" (also referred to as CTV3)

C. The following guidelines will be used for delineation of efficient, systematic and reproducible target volumes and normal structures:

1. Delineation of the "Oral cavity"
    a. At the superior extent, contours will begin at the first evidence of the hard palate below the nasal airway and anterior to the nasopharynx including the soft palate.
    b. Contours will be drawn along the medial and posterior surface of the teeth and alveolar bone and will include portions of the tongue.

c. Contours will extend posteriorly to the uvula and inferiorly to the first axial slice with evidence of submandibular glands.

2. Delineation of the "R Parotid" and "L Parotid"
    a. Parotid glands will be contoured as per convention including both superficial and deep lobes.
3. Delineation of the "Larynx"
    a. At the superior extent, contours will begin just below the hyoid bone and will circumscribe the laryngopharynx and thyroid cartilage.
    b. Contours will extend inferiorly to include the inferior cornua of the thyroid cartilage as well as the superior cricoid cartilage
4. Delineation of the "Partial esoph"
    a. At the superior extent, contours will begin at the level of the complete ring of cricoid cartilage and will encircle the adjacent, posterior esophagus.
    b. Contours will extend inferiorly to the level of the sternum, following the esophagus as it enters the thorax.
5. Delineation of "GTV-n"*
    a. Contours will encircle the gross nodal tumor volume by CT criteria, i.e. lymph node > 1 cm.
6. Delineation of "GTV-p"*
    a. Contours will encircle the gross tumor volume as seen on CT scan.
7. Delineation of "CTV 7000"*
    a. Contours will become the high dose clinical treatment volume.
    b. Contours will include gross disease (GTV-n and GTV-t) with an appropriate margin of normal tissue at risk for subclinical extension as per standard of care.
    c. Also referred to as CTV1
8. Delineation of "CTV 6300"*
    a. Contours will become the intermediate dose clinical treatment volume where applicable at the discretion of the treating physician.
    b. Contours will include the adjacent 2 cm superior and/or inferior to the regions of gross disease as per standard of care.
    c Also referred to as CTV2
9. Delineation of "CTV 5600"*
    a. Contours will become the low dose clinical treatment volume.
    b. Contours will include the ipsilateral and contralateral cervical lymph node regions at risk for subclinical spread of disease as per standard of care.
    c. Also referred to as CTV3

* These contours will be specifically reviewed by one physician (WLT) to ensure consistency.

TUMOR SITE	Stage	CTV1	CTV2	CTV3
Definitive Dose (Gy)		7000/200	6300/180	5600/160
OROPHARYNX				
Tonsil	T1-2 N0	GTVp	-	IN (IIb-IV, IRPLN)
	T3-4 N0	GTVp	-	IN (IIb-IV) + BRPLN + CN (IIb-IV)
	Any T N1-3, except 2C	GTVp + GTVn	Adj levels	IN (II-V) + BRPLN + CN (IIb-IV)
	Any T N2C	GTVp + GTVn	Adj levels	IN + CN (II-V, BRPLN)
BOT/Soft Palate	Any T N0	GTVp	-	IN (IIb-IV) + BRPLN + CN (IIb-IV)
	Any T N1-3, except 2C	GTVp + GTVn	Adj levels	IN (II-V) + BRPLN + CN (IIb-IV)
	Any T N2c	GTVp + GTVn	Adj levels	IN + CN (II-V, BRPLN)
LARYNX				
Glottic	T1-2 N0	GTVp	-	-
	T3-4 N0	GTVp	-	IN (IIb-IV) + BRPLN + CN (IIb-IV)
	Any T N1-3, except N2c	GTVp + GTVn	Adj levels	IN (II-V) + BRPLN + CN (IIb-IV)
	Any T N2c	GTVp + GTVn	Adj levels	IN + CN (II-V, BRPLN)
Supraglottic	Any T N0	GTVp	-	IN (IIb-IV) + BRPLN + CN (IIb-IV)
	Any T N1-3, except N2c	GTVp + GTVn	Adj levels	IN (II-V) + BRPLN + CN (IIb-IV)
	Any T N2c	GTVp + GTVn	Adj levels	IN + CN (II-V, RPLN)
HYPOPHARYNX				
	Any T N0	GTVp	-	IN (IIb-IV) + BRPLN + CN (IIb-IV)
	Any T N1-3, except N2C	GTVp + GTVn	Adj levels	IN (II-V) + BRPLN + CN (IIb-IV)
	Any T N2c	GTVp + GTVn	Adj levels	IN + CN (II-V, BRPLN)
ORAL CAVITY				
Buccal	Any T N0	GTVp	-	IN (IIb-IV, IRPLN)
	Any T N1-3, except N2C	GTVp + GTVn	Adj levels	IN (IIb-IV) + BRPLN
	Any T N2c	GTVp + GTVn	Adj levels	IN + CN (II-V, BRPLN)
RMT, Oral Tongue, FOM	Any T N0	GTVp		IN (Ia-IV) + BRPLN + CN (Ia-IV)
	Any T N1-3, except N2C	GTVp + GTVn	Adj levels	IN (Ia-V) + BRPLN + CN (Ia-IV)
	Any T N2c	GTVp + GTVn	Adj levels	IN + CN (Ia-V, BRPLN)

Notes:
Include ipsilateral level Ib if level II is involved; include ipsilateral level Ia if level Ib is involved
CTV 2 is adjacent levels with minimum 2 cm in cranial-caudad direction
N2C disease: CTV1 is GTVp + GTVn; CTV2 is adjacent levels (min 2 cm); CTV 3 is IN + CN (II-V, BRPLN)
In cases where no CTV2 is defined, CTV3 on this form will be labeled as CTV2 for planning

APPENDIX 4: Comorbidity Index

http://oto.wustl.edu/comorbiditycalculator.html

If a patient has Grade 2 events in more than one system, their overall score will be Grade 3

APPENDIX 5: FACT/GOG-NTX-4 (Version 4)

Below is a list of statements that other people with your illness have said are important**. Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.**

		Not at all	A little bit	Some-what	Quite a bit	Very much
NTX 1	I have numbness or tingling in my hands	0	1	2	3	4
NTX 2	I have numbness or tingling in my feet	0	1	2	3	4
NTX 3	I feel discomfort in my hands	0	1	2	3	4
NTX 4	I feel discomfort in my feet	0	1	2	3	4

APPENDIX 6: FACT-H&N (Version 4)

Below is a list of statements that other people with your illness have said are important**. Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.**

	<u>PHYSICAL WELL-BEING</u>	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	<u>SOCIAL/FAMILY WELL-BEING</u>	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4

GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4

GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	ADDITIONAL CONCERNS	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
H&N1	I am able to eat the foods that I like	0	1	2	3	4
H&N2	My mouth is dry	0	1	2	3	4
H&N3	I have trouble breathing	0	1	2	3	4
H&N4	My voice has its usual quality and strength	0	1	2	3	4
H&N5	I am able to eat as much food as I want	0	1	2	3	4
H&N6	I am unhappy with how my face and neck look	0	1	2	3	4
H&N7	I can swallow naturally and easily	0	1	2	3	4
H&N8	I smoke cigarettes or other tobacco products	0	1	2	3	4
H&N9	I drink alcohol (e.g. beer, wine, etc.)	0	1	2	3	4
H&N 10	I am able to communicate with others	0	1	2	3	4
H&N 11	I can eat solid foods	0	1	2	3	4
H&N 12	I have pain in my mouth, throat or neck	0	1	2	3	4