

The Quarterback Trial: A Randomized Phase III Clinical Trial Comparing Reduced and Standard Radiation Therapy Doses for Locally Advanced HPV16 Positive Oropharynx Cancer

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1.0 INTRODUCTION

1.1 Study Design

This is a randomized Phase III study comparing two doses of definitive radiation therapy given with induction and concurrent chemotherapy in HPV-positive oropharynx, unknown primary or nasopharynx cancer. Eligible, consented and registered patients will receive three cycles of Docetaxel Cisplatin and 5-FU (TPF) induction chemotherapy. After 3 cycles, the patients will be assessed for clinical, radiographic and pathologic response to TPF. Patients with a clinical or radiographic CR or PR will be randomized on the second phase of this study, where patients with HPV 16 or with another strain of HPV will undergo a 2:1 randomization or 1:1 randomization, respectively, to reduced (5600 cGy) or standard (7000 cGy) dose radiotherapy with weekly Carboplatin. Patients not meeting the response criteria will be treated with standard dose CRT. Patients not completing 3 cycles TPF for reasons of toxicity, progressive disease, choice, or other medical necessity will be treated with standard dose CRT or surgery depending on their primary site and overall medical condition and followed for survival. Any adverse events occurring thereafter in these patients will not be considered related to the study and will not be tracked or reported.

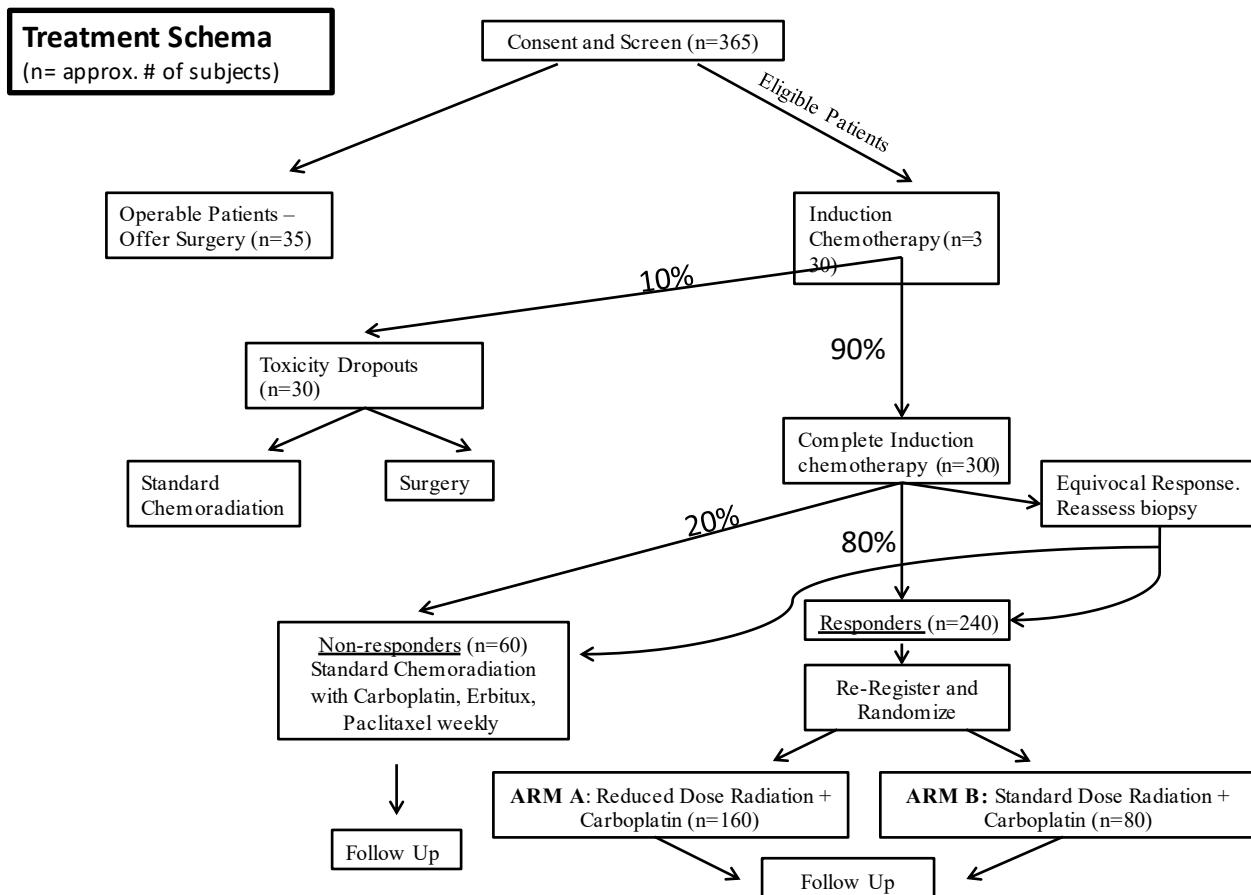
1.2 Primary Objectives

- 1.2.1 To determine the comparative rate of progression free survival (PFS) at 3 years in patients with advanced HPV related oropharynx cancer, nasopharynx cancer or unknown primary treated with reduced or standard dose CRT.
- 1.2.2 To determine the comparative rate of local-regional control (LRC) at 3 years in patients with advanced HPV related oropharynx cancer or unknown primary treated with reduced or standard dose CRT.

1.3 Secondary Objectives

- 1.3.1 To determine the comparative rate of local-regional control (LRC) over 5 years in patients with advanced HPV related oropharynx cancer or unknown primary treated with reduced or standard dose CRT.
- 1.3.2 To determine the comparative rate of progression free survival (PFS) over 5 years in patients with advanced HPV related oropharynx cancer or unknown primary treated with reduced or standard dose CRT.
- 1.3.3 To determine Overall Survival (OS) at 3 and 5 years treated with reduced or standard dose CRT.
- 1.3.4 To compare acute toxicity in patients treated with reduced or standard dose CRT.
- 1.3.5 To compare long term toxicity of patients treated with reduced or standard dose CRT at 2, 3 and 5 years.
- 1.3.6 To determine biomarkers predictive of failure with either reduced or standard dose radiotherapy.
- 1.3.7 To establish a tumor tissue, germline DNA and plasma bank for future studies of the protocol selected and treated populations.

1.4 Treatment Schema



2.0 BACKGROUND

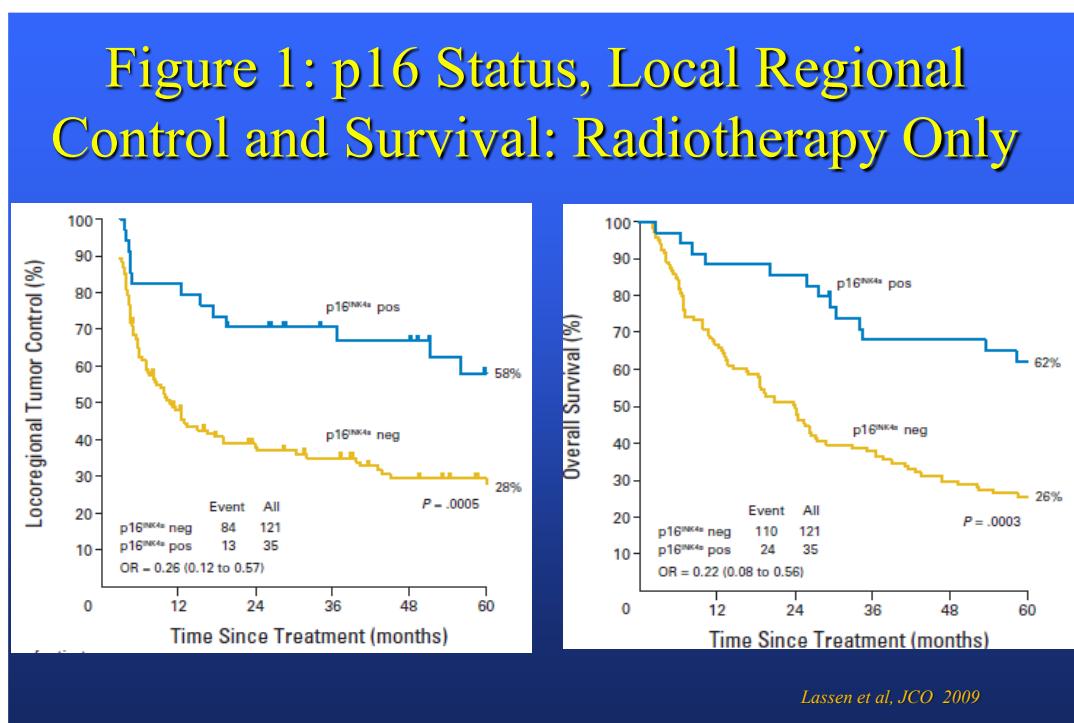
2.1 HPV-Related Oropharynx Cancer

The demographics and prognosis of locally advanced head and neck squamous cell cancer (HNC) has changed dramatically over the last two decades. Epidemiologic evidence has revealed a significant increase in the incidence of oropharynx cancer (OPC) in North America and Europe. Molecular studies of oropharyngeal tumors have revealed that this increase is due to an increase in the incidence of tumors which contain Human Papillomavirus (HPV), most specifically HPV16 and for which there is direct evidence that HPV16 is the molecular cause mechanistically driving the development and viability of the cancer cells. HPV-related oropharynx cancer (HPVOPC) now accounts for almost 60% of OPC seen in the USA and an increasing fraction of these malignancies in Europe (1-3).

Based on the existing data from clinical trials and patient material through retrospective analysis, it is now understood that there are two dominant carcinogenic and biologic pathways where oropharynx cancer develops: Environmentally related OPC (EROPC), caused by smoking and alcohol, and HPV related OPC (HPVOPC). The relative paucity of genetic changes in HPV-positive head and neck cancer is in sharp

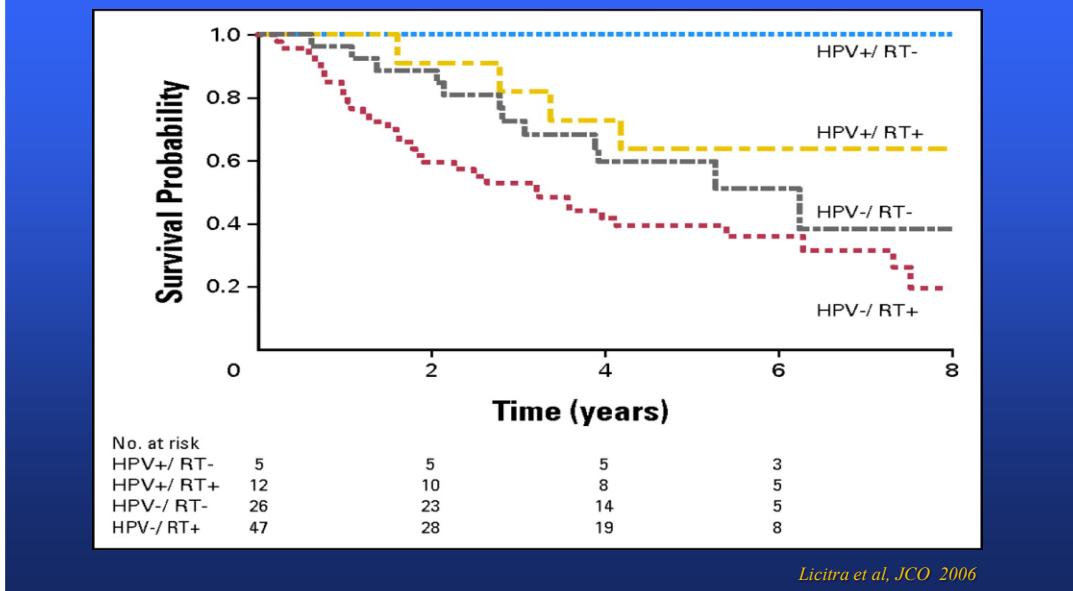
contrast to what is observed in HPV-negative head and neck cancer and is mechanistically related to the direct effects of viral proteins in inactivating regulators of key cellular processes(4-7). In the typical EROPC, mutations and deletions of p53 have very frequently been demonstrated. In contrast, HPVOPC do not contain p53 mutations. Similarly, p16 in the Rb pathway of cell growth is frequently mutated, deleted or silenced in EROPC but is often up-regulated in HPVOPC as a consequence of viral alterations in Rb function. Up regulation of p16 can be seen in up to 20% of non-HPV related cancers including other sites in the head and neck, however, p16 appears to be up-regulated in >95% of HPVOPC making it a good screening tool(8).

Studies in unselected patients suggest that patients with HPVOPC have a better prognosis than patients with HPV-negative, predominantly environmentally related OPC (EROPC) (9-11). In one retrospective study of radiotherapy as sole therapy from Denmark, p16 was used as a surrogate for HPV. In this randomized study of a radiation sensitizer, the control arm of radiotherapy only was analyzed for p16 expression. There was 62% 5-year survival among p16+ patients compared to 26% in p16 -patients. LRC was 58% vs. 28%, respectively (Figure 1). A significant fraction of p16+ tumors were not of oropharyngeal origin (12).



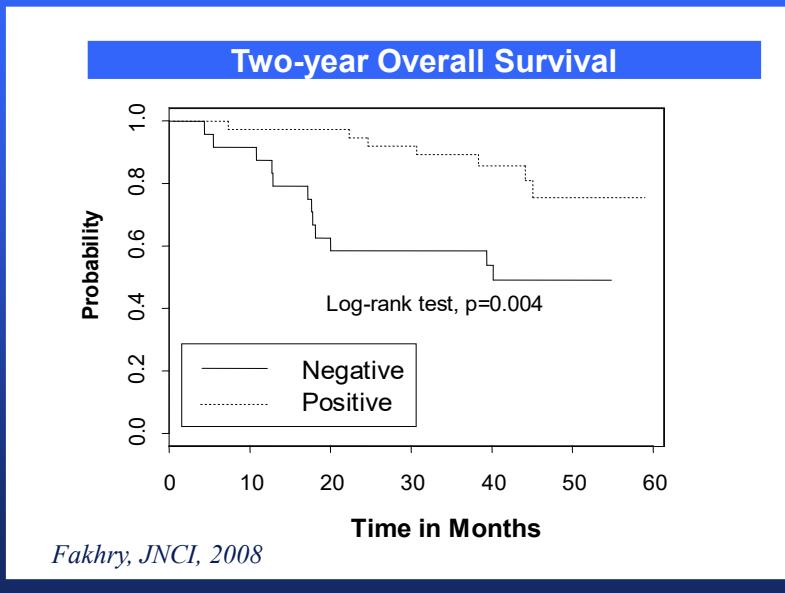
A second trial, Licitra et al retrospectively evaluated surgery in the HPV positive and negative cases. Surgery alone was effective therapy for a small group of patients. The surgery only patients were spared the long term consequences of radiation. However, selection for surgery only was not well explained(13).

Figure 2: Surgery and HPV in Oropharynx Cancer



ECOG (E) 2399, a Phase II study of operable patients treated with an aggressive Sequential Therapy (ST) regimen of induction chemotherapy followed by chemoradiotherapy for organ preservation, prospectively evaluated HPV status and reported a significant difference in survival for patients with HPVOPC compared to EROPC. Sixty two OPC cases were treated and all of the 38 of the HPVOPC cases were HPV 16 positive. Even among this small group of less than 65 patients, overall survival was significantly better for the HPVOPC. An analysis of failure in this population revealed several important features. First, LRC was much better in the HPVOPC patients. Additionally, co-morbidities and non-cancer deaths were much reduced. The impact of therapy on LRC was most striking however; 5% versus 33% Local Regional Failure (LRF) in HPVOPC vs. EROPC, respectively (14, 15).

Figure 3: Oropharynx Tumor HPV Status And Survival in ECOG 2399



The University Michigan used a single cycle of induction chemotherapy to select operable OPC patients for radiotherapy or surgery. They analyzed 42 informative cases for HPV and HPV copy number and found responses to induction chemotherapy correlated with HPV status as did disease specific survival. The relationship to copy number of HPV in the tumors was less clear although there was a suggestion that increasing copy number was associated with a better prognosis(16).

Recently, results of retrospective analyses of survival and HPV status were reported from two International Phase III trials comparing chemoradiotherapy (CRT) regimens in locally advanced HNC. In both trials there were insufficient patient numbers to report a treatment effect; however the impact of HPV on survival, regardless of therapeutic assignment, was highly significant (8, 17). The RTOG (R) 01-29 has the most extensive data and retrospectively analyzed on 323 out of 433 OPC cases. In RTOG 01-29, patients were randomized between CRT with accelerated fractionation with cisplatin versus regular fractionation and cisplatin. The overall survival (OS) and progression free survival (PFS) at three years were 82% and 74% in HPVOPC compared to 57% and 43% for EROPC, respectively. A careful analysis of failure and death revealed a LRF rate of 14% versus 35% for HPVOPC versus EROPC and a second primary tumor rate of 6% versus 15% respectively. Non-cancer deaths also occurred in 9% and 19% respectively. All these data support a better outcome for HPVOPC, much of which is found in improved LRC, some of which is explained by less co-morbidity.

2.2 TPF and HPV Oropharynx Cancer

We retrospectively evaluated tumor HPV16 status, survival and demographics in subjects with OPC treated in TAX324, a large international randomized Phase III clinical trial. TAX 324 compared survival between ST with TPF or PF followed by chemoradiotherapy with weekly carboplatin in patients with locally advanced HNC (18, 19). The data demonstrate a significant difference in survival outcome and patterns of failure between patients with HPVOPC and EROPC and significant differences in demographic characteristics in the populations.

Demographic Differences between HPVOPC and EROPC Patients Of the 501 patients entered on TAX 324, 264 (53%) were identified as having oropharynx cancer (OPC). Of these 264 subjects, 119 had tissue prospectively collected and 111, or 42% of all OPC cases, were analyzable for HPV 16 status and constitute the study population. The demographic data and test results for group comparisons are shown in Table 1. Comparisons of the cases with analyzable tissue to those without such tissue are also shown. There are 56 (50%) patients identified as HPV positive (HPVOPC) and 55 (50%) as HPV negative (EROPC). Both HPVOPC and EROPC cases are evenly divided with regard to treatment assignment and sex. HPVOPC cases are significantly younger, 54 compared to 58 years ($P=.02$), than the EROPC cases, despite a highly selected population for a phase III trial. Performance status (PS) was also significantly different between the two populations, despite selection for good PS in patients for enrollment in this trial. Thus, 77% of HPVOPC patients were PS 0 compared to 49% of the EROPC patients ($P=.003$).

Table 1: TAX 324 Demographics By HPV Status

	HPV+ N=56 (50%)	HPV- N=55 (50%)	P-value
Treatment			
TPF	28 (50%)	26 (47%)	0.85
PF	28 (50%)	29 (53%)	
Age Yrs			
Median (Range)	54 (39-71)	58 (41-78)	0.02
Nodal Stage			
N0-N1	13 (23%)	18 (33%)	0.30
N2-N3	43 (77%)	37 (67%)	
T stage			
T1-T2	28 (50%)	11 (20%)	0.001
T3-T4	28 (50%)	44 (80%)	
PS WHO			
0	43 (77%)	27 (49%)	0.003
1	13 (23%)	28 (51%)	

Posner et al, ASCO, 2010

Outcome Differences between HPVOPC and EROPC Patients. Results for OS, PFS and site of failure for the 111 patients analyzed for HPV16 status, independent of treatment arm, are shown in Table 2. HPVOPC and EROPC surviving patients were followed for a median of 83 months and 82 months respectively. At the time of analysis 79% of HPVOPC patients were still alive, and their PFS rate was 73% compared to the 31% OS and 29% PFS, for the EROPC patients (both $P<.0001$).

OS and PFS are shown in Figure 4, respectively. The median overall survival time for the EROPC patients is 21 mo (95% CI: 13-49 mo), while median survival has not been reached in the HPVOPC group after almost 7 years median follow-up. There is an 80% reduction in mortality in HPVOPC compared to EROPC (HR=0.2, 95% CI: 0.10-0.38; $P<.0001$).

Analysis of the site of failure, as shown in Table 2, reveals a significant reduction in local-regional failure (13% vs. 42%, $p = .0006$) and slightly reduced distant failure in the HPVOPC patients compared to the EROPC patients. There was also a significant difference in total disease failures (16% vs. 49%, $p = .0002$) and a borderline improvement in deaths without recurrence ($p = .07$). These data indicate that local-regional

control is the major parameter contributing to improved survival and that PS and co-morbidities among EROPC patients account for another fraction of mortality.

Table 2: TAX 324 Analysis of Failure By HPV Status

	HPV+ N=56	HPV- n=55	P-value [#]
Median Follow Up Months (95% CI)	83 (77-93)	82(68-86)	NS
Survival Status			
Alive	44 (79%)	17 (31%)	<0.0001
Dead	12 (21%)	38 (69%)	
PFS Status			
No Progression/Death	41 (73%)	16 (29%)	<0.0001
Progression/Death	15 (27%)	39 (71%)	
Local-Regional Failure	7 (13%)	23 (42%)	0.0006
Distant Metastases	3 (5%)	6 (11%)	NS
Both	1 (2%)	2 (4%)	NS
Total Disease Failures	9 (16%)	27 (49%)	0.0002
Died Without Recurrence	5 (9%)	12 (22%)	0.07

Posner et al, ASCO, 2010

OS and PFS rate-over-time data - as a yearly analysis of events over 5 years - are shown in Table 3. These data are informative in aligning information on OS and PFS for qualitative comparisons among trials focusing on OPC. As can be seen, early PFS at 2 and 3 years predicts later survival for HPVOPC and EROPC patients when treated with Sequential Therapy. PFS is a potential indicator of the durability of survival in both populations of oropharynx cancer compared to other head and neck sites and the slope of PFS in ST trials can be used to inform long-term survival estimates in a qualitative manner for future studies.

Table 3: TAX324 Oropharynx Cancer, HPV, Survival and PFS

OS (95% CI)	HPV+	HPV-	All
1- yr	0.93 (0.82-0.97)	0.69 (0.54-0.79)	0.81 (0.72-0.87)
2- yr	0.89 (0.78-0.95)	0.48 (0.34-0.61)	0.69 (0.60-0.77)
3 -yr	0.87 (0.75-0.94)	0.41 (0.28-0.53)	0.65 (0.55-0.73)
5 -yr	0.82 (0.69-0.90)	0.35 (0.23-0.48)	0.59 (0.49-0.67)
PFS (95% CI)			
1- yr	0.85 (0.73-0.92)	0.52 (0.38-0.64)	0.69 (0.59-0.76)
2- yr	0.83 (0.70-0.91)	0.35 (0.23-0.48)	0.59 (0.49-0.68)
3 -yr	0.81 (0.68-0.90)	0.33 (0.21-0.46)	0.57 (0.48-0.66)
5 -yr	0.78 (0.64-0.87)	0.28 (0.17-0.40)	0.53 (0.43-0.62)

It is apparent from the data presented here from TAX 324 as well as other trials that survival is significantly better for HPVOPC compared to EROPC. In Table 4, comparable data on OS and PFS for TAX 324, R01-29 and OS data from the HeadStart trial are shown for a qualitative comparison(8, 17, 19).

Table 4: The Impact of HPV on Survival in Protocol Driven Large Phase III Trials

Study GeoLocation	Patients Tested	Therapeutic Regimens	HPV+/HPV- (%HPV+)	Time Interval	Survival HPV+/HPV-
01-29 USA	323/433 (75%)	CRT vs. RT	206/323 (65%)	3 year OS	82% vs. 57%
				3 Year PFS	74% vs. 43%
HeadStart International	195/465 (42%)	CRT vs. CRT	54/141 (28%)	2 Year OS	94% vs. 77%
				2 Year PFS	NA
TAX324 International	111/264 (42%)	ST vs. ST	56/55 (50%)	3 Year OS	87% vs. 41%
				3 Year PFS	81% vs. 33%
				5 Year OS	82% vs. 35%
				5 Year PFS	78% vs. 28%

Ang, NEJM, 2010; Rischin; JCO, 2010

As can be seen, survival in all three trials is similar at the 3-year analysis time point. PFS is different between R01-29 and TAX 324 in the first 3 years by as much as 7%, in favor of TAX324. Importantly, in

assessing outcomes, CRT trials may also have greater rates of late distant metastases and/or late fatal morbidity not captured in the early analysis of the CRT trial. Data from this 5-year minimum follow-up analysis indicate that the 2- and 3-year actuarial PFS rates in this Sequential Therapy plan predict 5-year actuarial overall survival in HPVOPC and, therefore, can be used to predict long-term survival in Sequential Therapy studies. The data from R01-29 has been limited to the 3-year survival data reported. Longer-term survival and PFS in R01-29 are not available yet, and thus, data on the impact of the lower 3-year PFS in HPVOPC, late toxicity and the risk for delayed distant metastases on 5-year OS in the CRT regimen are not available.

2.3 Rationale for Dose Reduction of Radiotherapy and Trial Design

In general, patients with HPVOPC are young and will live for prolonged periods. They are at high risk for long-term toxicity and mortality from therapy(20). While the long-term consequences of chemotherapy for head and neck cancer are relatively constrained, high-dose radiotherapy (RT) and chemoradiotherapy substantially impact on local tissues and organ function and result in a significant rate of late mortality and morbidity in patients(21-25). Studies are now being designed to reduce the impact of RT and CRT for patients. Identifying appropriate endpoints and study arms which will allow an early assessment of outcomes will be problematic, particularly for equivalence studies wherein survival differences are small, and where prolonged time periods and large patient numbers are necessary to accurately assess outcomes. For Sequential Therapy as given with TAX 324, 3-year PFS may be an appropriate endpoint. The same may not be possible for CRT. The best example of changing outcomes in CRT trials would be R91-11, in which a premature negative conclusion regarding the efficacy of induction therapy was published with the early analysis. Late toxicity and morbidity, a hallmark of upfront cisplatin-based CRT trials, led to equivalence between induction therapy and CRT for laryngectomy-free survival at 5 years, and more importantly a non-significant relative 10% improvement in overall survival in the PF induction arm compared to the CRT arm which included an every 3-week bolus cisplatin for 3 cycles during radiotherapy(8, 19, 22).

The survival results in HPVOPC achieved in TAX 324 strongly suggest that it might be possible to reduce long-term morbidity in HPVOPC and preserve survival perhaps by better selection and by reducing radiotherapy intensity in the context of ST for more advanced cases. We might best approach HPV-negative disease with novel therapies and more aggressive ST or CRT.

Current radiation dose reduction trials are under way in ECOG and at Dana Farber Cancer Institute (DFCI). ECOG 1308 is a Phase II trial treating patients with p16 positive resectable OPC with an aggressive regimen of induction chemotherapy using weekly Paclitaxel, cisplatin every 3 weeks, and Cetuximab weekly for 3 cycles, followed by Cetuximab plus radiotherapy to a total radiation dose of 5400 cGy for responders. Non-responders receive standard radiotherapy with Cetuximab. The DFCI is conducting a Phase II trial of TPF induction followed by radiotherapy with Carboplatin and Cetuximab to a total radiotherapy dose of 6000 cGy in HPV16 positive patients. There are currently no other trials that are active, although a randomized trial is planned at Johns Hopkins. The RTOG plans a randomized trial to compare cisplatin CRT to erbitux CRT, with full dose radiotherapy in both arms.

The data from TAX 324 suggest that it is possible to reduce the radiation dose because of the superior progression free survival and the ability to select risk based CRT. Data from the randomized Bonner trial of radiotherapy +/- Cetuximab suggest that Cetuximab might be an effective radiotherapy sensitizer for oropharynx cancer on the basis of a significant survival advantage for the Cetuximab arm in oropharyngeal cancer patients(26). In that trial, as with TAX 324, oropharynx cases fared significantly better for survival with Cetuximab compared with radiotherapy alone. Furthermore, late toxicity was not adversely affected by adding Cetuximab to radiotherapy although acute toxicity was enhanced. In the setting of a reduced dose trial there are pros and cons to cetuximab including non-cross resistance (pro) and enhanced toxicity (con).

Because of the uncertainty around the relative value of a platinum sensitizer and cetuximab there is no clear advantage and perhaps enhanced toxicity to adding erbitux.

For the Quarterback Trial TPF will be modified to reduce the 5-fluorouracil dose by 25% to reduce the rates and duration of grade 3 and 4 mucositis and eliminate febrile neutropenia. Neulasta and G-CSF will not be allowed during induction chemotherapy to enhance recovery from neutropenia due to ambiguous data regarding tumor protection in one randomized trial. Based on the plan by ECOG to test a radiation dosage of 5400 cGy and DFCI to test 6000 cGy, we feel a dose of 5600 cGy is a reasonable therapy endpoint representing an approximate 20-25% dose reduction from the standard 6900-7200 cGy of definitive radiotherapy and a proportional decrease in radiation toxicity. Both arms will receive weekly carboplatin as a radiation sensitizer. We will compare the reduced dose experimental arm to the established therapy in TAX324.

There are currently no active randomized trials of radiation dose reduction for HPVOPC. The current trials by DFCI and ECOG are non-randomized Phase II trials and will not realistically provide data that would lead to a change of practice. The RTOG trial compares standard dose radiotherapy with cisplatin or cetuximab and will not reduce long term morbidity. This trial aims to directly compare a reduced radiation dose to the standard of care in HPVOPC for non-inferiority, thus allowing for direct comparison of outcomes between the two groups.

2.4 Smoking History and Histological Requirements

Patient selection for the Quarterback Trial will include squamous cell carcinomas of head and neck classified as oropharynx, unknown primary (cervical lymph nodes) or nasopharynx primary that are both HPV16 positive by PCR and p16 positive(1, 27-29). Tissue for confirmation of HPV and p16 status will be required and analyzed at a central laboratory. Although p16 has been found to be a potential independent risk factor for prognosis, and a negative p16 is highly predictive of a negative HPV test, about 10-20% of HNC tumors are p16 positive independent of HPV presence. Because the biologic behavior of this population may be heterogeneous and is less well understood, p16+ HPV16- patients will be excluded from the second phase of the trial – randomization to radiotherapy. Similarly, 95% of HPV positive oropharynx cancer is HPV16+, and the behavior of other serotypes is unknown. Hence this study will be limited to HPV16+ cancers and HPV other strains will be analyzed separately. In addition, smoking has been shown to be a prognostic factor and prospective smoking and tobacco utilization data will be collected for this study(30). In the original analysis of RTOG 0129, a history of smoking above and below 20 pack years correlated to meaningfully different populations(8). We have therefore chosen to retain this as a stratification factor. Patients will be stratified based on smoking history of 20 pack years or greater versus less than 20 pack years. Correlative science studies will be performed and all patients entered will be asked to provide plasma and germ line DNA as well as additional slides from diagnostic biopsies.

2.5 Correlative Studies Background

It is still not well understood as to what biological factors influence the growth and response to treatment of HPVOPC tumors. Current research strongly suggests that there are multiple pathways that may account for the difference in growth and treatment response between HPVOPC and non-HPVOPC tumors. Furthermore, there are several mechanisms reported in the literature that may account for differences in survival within the HPVOPC subset of patients.

This study will collect blood and tumor samples in order to further quantify such mechanisms. It will be difficult to predict what studies will be most likely to be valuable and informative given the rapid advances in technology and knowledge that we will be refining the translational components of this study as we

proceed. At present we plan several potential research studies: we plan to analyze expression of p16, p53, cMET in tumor, and quantify HPV copy number. Serial blood samples will be collected to measure sequential plasma anti-HPV antibody titers to HPV16 proteins, cytokines and growth factors (eg HGF) and quantify of circulating tumor cells, whole blood HPV DNA, MDSC, and other immune function cells. Additionally, studies will be performed to quantify tumor EGFR copy number and Bcl-xL expression, in order to further study the relationship between these proteins and survival of HPVOPC patients. Finally, HPV related signaling pathways will be analyzed possibly using such markers as NFκB and STAT3 in tissues or a high throughput screening system. Antibodies the HPV16 early antigens are elevated in HPVOPC and may prove to be a useful biomarker for assessing risk of recurrence and response to therapy(31).

Kumar, et. al. reported that low EGFR and high p16 expression are markers of good response to treatment (32). Other studies have also shown HPV copy number to be linked to better response to treatment and improved OS(7). p16 will be measured as a marker for HPV status, as it is a cyclin-dependent kinase inhibitor which acts to inhibit pRb phosphorylation, thus blocking cell cycle progression. The inactivation of pRb by HPV leads to overexpression of p16, making it a good marker for HPV status. Additionally, high EGFR expression, low p53, as well as high Bcl-xL (an antiapoptotic protein) expression are factors that may indicate poor response to treatment and poor outcomes. This study will seek to analyze these factors, as well as proteins that are often mutated in cell signaling pathways, such as cMET, in order to further correlate these proteins with treatment response. Having a robust, protocol driven study with tissue and blood collection will be a valuable resource to establish predictive markers of response and understand the biology of HPVOPC.

3.0 PARTICIPANT SELECTION

All patients will be evaluated in the multidisciplinary head and neck cancer clinic where eligibility criteria, entry and disease parameters will be evaluated and documented. Subjects who enroll on this study must be diagnosed with squamous cell carcinoma in the oropharynx, nasopharynx, or cervical nodal unknown primary as documented in the medical record, and must not have received any prior chemotherapy, radiotherapy or surgery for their cancer. Potential participants will be screened based on their past medical history, the results of their radiological scans, blood work, as well as a number of other required studies that will determine their eligibility. To enroll on this study, tumor tissue must be available and p16 must be assessed and proven to be positive by IHC in a lab verified by the central laboratory or with slides that can be reviewed in the central laboratory (28, 29). To be randomized into a radiotherapy arm in cohort 1, HPV 16 status must be assessed and proven to be positive by PCR. If the HPV status is a HPV oncogenic type other than 16, the patient will be randomized 1:1 separately into cohort 2. If the patient is HPV negative, the patient will not be randomized into a radiotherapy arm, but instead will be transferred to standard of care treatment.

3.1 *Inclusion Criteria*

Participants must meet the following criteria to be eligible to participate in the study. Patients may enroll in the study if they are p16+ and not yet tested for HPV by PCR and if they meet the other eligibility criteria. They will enter the experimental post-Induction portion of the study if the surgical specimens or biopsies are proven to be HPV+ on PCR testing:

3.1.1 Participants must have histologically or cytologically confirmed squamous cell carcinoma of the oropharynx, unknown primary, or nasopharynx that is p16 positive as determined by IHC. Tissue from the primary site must be available for biomarker studies and for PCR testing. IHC must be

performed in a lab verified by the central laboratory or the slides must be available for review by the central laboratory (Zhang, MSSM) and PCR must be done in the central laboratory prior to randomization. See section 13.3 for exception regarding urgency of therapy. HPV16 PCR must be performed and results available for randomization after induction.

- 3.1.2 Stage 3 or 4 disease without evidence of distant metastases.
- 3.1.3 At least one clinically evaluable or uni- or bi-dimensionally measurable lesion by RECIST 1.1 criteria.
- 3.1.4 Age \geq 18 years.
- 3.1.5 No previous surgery, radiation therapy or chemotherapy for SSCHN (other than biopsy or tonsillectomy) is allowed at time of study entry.
- 3.1.6 ECOG performance status of 0 or 1.
- 3.1.7 No active alcohol addiction (as assessed by medical caregiver and defined as at least 6 months without activity).
 -
- 3.1.8 Participants must have adequate bone marrow, hepatic and renal functions as defined below:
 - Hematology:
 - Neutrophil count $\geq 1.5 \times 10^9/l$.
 - Platelet count $\geq 100 \times 10^9/l$.
 - Hemoglobin $\geq 10 \text{ g/dL}$.
 - Renal function: $\geq 60 \text{ mL/min}$ (actual or calculated by the Cockcroft-Gault method) as follows:
$$\text{CrCl (mL/min)} = \frac{(140-\text{age}) (\text{weight kg})}{72 \times \text{serum creatinine (mg/dL)}}$$
N.B. For females, use 85% of calculated CrCl value.
Or a Creatinine \leq the upper limits of normal
- Women of childbearing potential must have a negative pregnancy test within 7 days of starting treatment.
- Hepatic:
 - Total Bilirubin \leq institutional upper level of normal (ULN)
 - AST or ALT and Alkaline Phosphatase must be within the range allowing for eligibility, as in the table below:

AST, ALT AND ALKALINE PHOSPHATASE ELIGIBILITY

ALK PHOS:	AST or ALT:			
	\leq ULN	$>1x$ but $\leq 1.5x$	$>1.5x$ but $\leq 5x$	$>5x$ ULN
\leq ULN	Eligible	Eligible	Eligible	Ineligible
$>1x$ but $\leq 2.5x$	Eligible	Eligible	Ineligible	Ineligible
$>2.5x$ but $\leq 5x$	Eligible	Ineligible	Ineligible	Ineligible
$>5x$ ULN	Ineligible	Ineligible	Ineligible	Ineligible

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

3.1.10 Patients with Gilbert's Disease and absent hepatic pathology by history and clinical assessment maybe treated on study with bilirubins $>$ the ULN for the institution if other liver function studies are within the normal range

3.2 Exclusion Criteria

Participants who exhibit any of the following conditions at screening will not be eligible for admission into the study.

3.2.1 Pregnant or breast feeding women, or women and men of childbearing potential not willing to use adequate contraception while on treatment and for at least 3 months thereafter.

3.2.2 Previous or current malignancies at other sites, with the exception of adequately treated in situ carcinoma of the cervix, basal or squamous cell carcinoma of the skin, thyroid cancer, or other cancer curatively treated by surgery and with no current evidence of disease for at least 5 years.

3.2.3 Symptomatic peripheral neuropathy \geq grade 2 by NCI Common Terminology Criteria (NCI-CTC) version 4.

3.2.4 Symptomatic altered hearing $>$ grade 2 by NCI-CTCv4 criteria.

3.2.5 Other serious illnesses or medical conditions including but not limited to:

- Unstable cardiac disease despite treatment, myocardial infarction within 6 months prior to study entry
- History of significant neurologic or psychiatric disorders including dementia or seizures
- Active clinically significant uncontrolled infection
- Active peptic ulcer disease defined as unhealed or clinically active
- Hypercalcemia
- Active drug addiction including alcohol, cocaine or intravenous drug use defined as occurring within the 6 months preceding diagnosis
- Chronic Obstructive Pulmonary Disease, defined as being associated with a hospitalization for pneumonia or respiratory decompensation within 12 months of diagnosis. This does not include obstruction from tumor

- Autoimmune disease requiring therapy, prior organ transplant, or HIV infection
- Interstitial lung disease
- Hepatitis C by history

3.2.6 Patients that have experienced an involuntary weight loss of more than 25% of their body weight in the 2 months preceding study entry.

3.2.7 Concurrent treatment with any other anticancer therapy.

3.2.8 Participation in an investigational therapeutic drug trial within 30 days of study entry.

3.2.9 Active smoking within the past 20 years with a cumulative Pack Year history of > 20 Pack Years or active smoking (Defined as \geq 1 cigarette per day) within the last 5 years.

3.3 Inclusion of Women, Minorities and Other Underrepresented Populations

The inclusion and exclusion criteria do not affect enrollment of women, minorities, or other underrepresented populations.

4.0 REGISTRATION PROCEDURES

After the patient signs the informed consent the patient will be registered for screening and once the investigator has verified that the patient meets all inclusion/exclusion criteria, the patient will be registered for and started on therapy. Patients who only have p16 testing and lack HPV PCR may proceed to induction however they will not be assigned to an experimental group until HPV PCR is completed and the results are available. The verification of patient's eligibility will be performed centrally after the receipt of the patient registration form. It is mandatory not to exceed 14 days between the date of registration for therapy and the start of the study treatment. p16 testing in a lab verified by the central lab or slides must be available to be reviewed by the central laboratory must be confirmed prior to registration for therapy, unless there is an urgency of therapy. External sites can utilize their own Pathology Department for p16 testing if they submit their standard operating procedures (SOP) for p16 testing to the central lab prior to their first enrollment, along with slides and pathological material for 10 test cases for verification (see SOP). In any case, all events occurring after the registration must be recorded in the case report form and will be taken into account in the analysis, whether the patient received the study treatment or not. Patient must receive a treatment to be included in the intent to treat analysis.

4.1 General Guidelines

Institutions will register eligible participants with the Mount Sinai Cancer Clinical Trials Office. Registration must occur prior to the initiation of therapy. Any participant not registered to the protocol before treatment begins will be considered ineligible and registration will be denied.

A member of the study team will confirm eligibility criteria and complete the protocol-specific eligibility checklist. A registration form will be faxed to the CRC prior to the start of therapy.

Following registration, participants may begin protocol treatment. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a participant does not receive protocol therapy following registration, the participant's protocol status must be changed. Notify the registrar of participant status changes as soon as possible.

4.2 Registration Process

The registration procedures are as follows:

1. Obtain written informed consent from the participant prior to the performance of any study related procedures or assessments and register consent.
2. Complete the protocol-specific eligibility checklist using the eligibility assessment documented in the participant's medical/research record. **To be eligible for registration to the therapeutic study, the participant must meet each inclusion and exclusion criteria listed on the eligibility checklist including p16, however HPV PCR results need not be necessary.**
3. Patients will be re-registered for post-induction treatment assignment as per the protocol design and will require final HPV PCR for this. Pathologic and radiologic criteria as outlined in the protocol will determine the post-induction arm assignment.

Reminder: Confirm eligibility for ancillary studies at the same time as eligibility for the treatment study. Registration to both treatment and ancillary studies will not be completed if eligibility requirements are not met for all studies.

5.0 TREATMENT PLAN

Treatment should generally be administered on an outpatient basis. Expected toxicities and potential risks as well as dose modifications for Docetaxel, Cisplatin, 5-Fluorouracil, and Carboplatin are described in Section 6 (Expected Toxicities and Dosing Delays/Dose Modifications). Patients will initially be treated with cisplatin during TPF induction therapy, as not carboplatin. Carboplatin will only be substituted for cisplatin during TPF if toxicity precludes continuing with cisplatin as described below. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy. All therapy and clinical studies are Standard of Care for SCCHN and require no special handling.

In the first phase of the study, three cycles of TPF induction chemotherapy will be delivered. TPF chemotherapy will be given every 21 days starting on days 1, 22 and 43 (\pm 2 days). All patients, if possible, will have a port-a-cath placed prior to initiating chemotherapy so that chemotherapy may be given efficiently and completely. Patients who refuse a port or have an infection that necessitates removing the port should be treated in the inpatient setting or with a PICC line. Following the first phase of treatment with induction chemotherapy, patients will be re-assessed for response to treatment. Those who do not respond to treatment will not be randomized to the second phase of treatment. Rather, they will be treated with more intensive chemoradiotherapy in a non-responder treatment arm (treatment and follow up data will still be collected on these patients.) Those who respond with a CR or PR (see section 5.4.4 for PR specific criteria) will be continue on the second phase of the trial, which will include randomization to standard or reduced radiation dose chemoradiotherapy. Concurrent chemoradiotherapy with weekly Carboplatin for the experimental and standard arms respectively should start 4-6 weeks after day 1, cycle 3 of induction chemotherapy for all patients, regardless of their phase two treatment arm.

Induction Chemotherapy Treatment Plan Overview*				
Agent	Pre-medications; Precautions	Dose	Route	Schedule
Docetaxel	Refer to Section 5.2.1	75 mg/m ²	Intravenous infusion over 60 minutes, mixed in 250 mL normal saline	Day 1, every 21 days (\pm 2 days)
Cisplatin	Refer to Section 5.2.2	100 mg/m ²	Intravenous infusion over 60 minutes to 3 hours, mixed in 1000 mL of normal saline	Day 1, every 21 days (\pm 2 days)
5-FU	Refer to Section 5.2.4	750 mg/m ² /day	24-hour continuous infusion over 4 days	Days 1, 2, 3 and 4 of Cycles 1, 2 and 3, every 21 days (\pm 2 days)
Carboplatin <i>(as a substitute for cisplatin in response to cisplatin toxicity)</i>	Refer to Section 5.2.3	AUC 6, calculated by the Calvert formula	IV over approximately 30 to 45 minutes, mixed in normal saline or D5W per pharmacy standards	Day 1, every 21 days (\pm 2 days)
Chemoradiotherapy Treatment Plan Overview*				
Carboplatin	Refer to Section 5.4.3	AUC 1.5, calculated by the Calvert formula	IV over approximately 30 minutes, mixed in 250ml normal saline or D5W	Weekly on Monday or Tuesday anytime, or Wednesday prior to radiation
*Please refer to section 5.2 Induction Chemotherapy Agent Administration and 5.4 Chemotherapy Agent Administration for additional agent administration specifications.				

5.1 *Induction Chemotherapy Pre-treatment Criteria*

5.1.1 Cycle 1, Day 1: All eligibility criteria must be met

5.1.2 Subsequent Cycles:

ANC \geq 1500 mm³
 Platelets \geq 100,000 mm³
 Bilirubin \leq institutional ULN

5.2 *Recommendations for Induction Chemotherapy Agent Administration*

5.2.1 Docetaxel

Dose: 75 mg/m²

Route: Intravenous infusion over 60 minutes, mixed in 250 mL normal saline

Schedule: Day 1, every 21 days (\pm 2 days)

Recommended premedication for docetaxel is as follows: dexamethasone 8 mg by mouth twice daily for 6 doses, starting the evening before chemotherapy, plus 10 mg PO or IV 30 to 60 minutes before docetaxel (or solumedrol 80 mg IV bolus), ranitidine 50 mg IV bolus (or equivalent). After premeds, Docetaxel 75 mg/m² will be mixed in 250 ml of normal saline and infused over 1 hour.

5.2.2 Cisplatin

Dose: 100 mg/m²

Route: Intravenous infusion over 60 minutes to 3 hours, mixed in 1000 ml of normal saline

Schedule: Day 1, every 21 days (\pm 2 days)

Day 1

One liter of normal saline solution containing KCl (20 mEq/L) and MgSO₄ (2g/L) will be infused as prehydration for cisplatin prior to beginning cisplatin infusion. An oral equivalent dose of KCl may replace the KCl contained in the saline solution.

The antiemetic regimen may be chosen by the treating physician. In general, the antiemetics should include a 5-HT₃ antagonist (i.e. Ondansetron 8-24 mg IV or orally) and fosaprepitant. Additional antiemetics may include, but are not limited to, lorazepam and metoclopramide.

Furosemide 10 mg IV bolus will be given as premedication for cisplatin, then cisplatin 100 mg/m² in 1000 ml of normal saline will be given over 60 minutes to 3 hours. Mannitol 12.5 g will be mixed in the bag with cisplatin, or given immediately after completion of cisplatin. If mannitol is given after cisplatin, mannitol may be mixed in one liter of post-cisplatin IV fluids, and the cisplatin may then be mixed with 250 ml of normal saline. One liter of normal saline solution containing KCL (20 mEq/L) and MgSO₄ (2g/L) will be infused as post-hydration for cisplatin. An oral equivalent dose of KCl may replace the KCl contained in the saline solution.

5.2.3 Carboplatin (*as a substitute for cisplatin*)

Dose: AUC 6, calculated by the Calvert formula

Route: IV over approximately 30 to 45 minutes, mixed in normal saline or D5W

Schedule: Day 1, every 21 days (\pm 2 days)

5.2.4 5- Fluorouracil

Dose: 750 mg/m²/day

Route: 24-hour continuous infusion over 4 days

Schedule: Days 1, 2, 3 and 4 of Cycles 1, 2 and 3 (every 21 days) (\pm 2 days)

5-FU continuous infusion is for each of days 1-4 and should be delivered as one total infusion.

5.2.5 Days 2-5

Day 2 Patients receiving cisplatin should receive a minimum of 2 liters of normal saline with or without MgSO₄ and KCL on Day 2, either in a local clinical area, at home or in their main clinic treatment facility, with anti-emetic therapy as necessary.

Days 2, 3, 4, 5

Patients should be able to tolerate a minimum oral fluid intake (≥ 2 L oral intake/day) day 3 and after. If inadequate oral intake of fluids is observed, the patient should return to a treatment facility for additional IV hydration, or receive home hydration as clinically indicated. If the patient is unable to return to the treatment facility, they will be instructed to visit a local medical facility for IV hydration. With a disconnection on Day 5 consider giving at least an additional liter of NS with or without MgSO₄ and KCL and antiemetic therapy.

Patients will be given ciprofloxacin, levoquin or a suitable substitute immediately after the termination of the 5-FU infusion on day 5, and no later than day 6 through day 15 of each cycle for prophylaxis.

5.3 *Chemoradiotherapy Pre-Treatment Criteria*

5.3.1 All eligibility criteria must be met

5.3.2 Subsequent cycles:

ANC ≥ 1500 mm³
Platelets $\geq 100,000$ mm³

5.4 *Recommendations for Chemoradiotherapy Agent Administration*

5.4.1 Carboplatin

Dose: AUC 1.5, calculated by the Calvert formula

Route: IV over approximately 30 minutes, mixed in 250ml normal saline or D5W

Schedule: Weekly on Monday or Tuesday any time, or Wednesday prior to radiation

Carboplatin will be given at a low dose of AUC 1.5 per TAX 324 study (Posner et al NEJM 2007).

Prehydration: Prehydration IV fluids are not required, but once patients develop treatment-induced mucositis that affects their comfort when eating and drinking, at least 500 mL of normal saline prehydration is recommended weekly. Additional IV fluids may be given anytime at the discretion of the treating physician.

5.4.2 Other Modality(ies) or Procedures:

A PEG will not be placed prior to chemoradiotherapy for patients.

6.0 ASSESSMENT OF RESPONSE AND ASSIGNMENT OF RADIATION ARM

6.1 Patients will all have a clinical examination, a PET/CT and a high resolution contrast enhanced (when possible) neck CT or MRI prior to initiating induction therapy and will have these repeated shortly on week 9, 10 or after completing their 3rd cycle of induction. After repeat scans following induction, all patients determined to have a CR, and eligible patients with a PR (as outlined below), who continue to meet eligibility criteria will then be randomized in a 2:1 ratio to the experimental reduced dose or to the control standard dose radiation therapy. Patients with no response, or with progressive disease will receive CRT. We recommend standard radiation dosing plus carboplatin (AUC 1.5), Paclitaxel (40 mg/M2) and Erbitux (with loading when feasible) weekly for these patients.

The following guidelines have been developed specifically to identify subjects with a Partial Response:

Partial Response: If patients do not have a CR to induction, the partial response will need to be further assessed to determine subsequent radiation dosing. Clinical response of nodal disease is important and informs the overall response assessment. Clinical response will be recorded. Slightly different criteria will be applied to the primary or nodal site.

Primary Site: The patient can be considered for randomization and potential reduced radiation dosing if the primary site demonstrates significantly decreased FDG avidity, such that the pattern and/or intensity is more suggestive of, or at least consistent with, physiologic or inflammatory uptake, as opposed to oncologic uptake. Altered anatomy at the site of the primary after treatment can be present, as the initial tumor mass may have destroyed normal tissue, distorted normal contours and eliminated normal tissue planes. However, if the primary site has a residual PET positive mass lesion an EUA should be strongly recommended and even if biopsy is negative, careful consideration with agreement by the multi-disciplinary team as to whether there is a partial response should occur and be documented before assignment to randomization.

Nodal Disease: If a lymph node was PET avid at presentation and has no, or only minimal uptake after induction and the residual node is < 2 cm in maximal diameter, randomization for potential reduced dosing is acceptable. If the residual disease is greater than 2 cm and there is considerable PET avidity consistent with tumor present in the lymph node rather than inflammation and post-radiation nodal dissection is not feasible, randomization should not occur. For Nodes > 2 cm which are not PET avid the degree of shrinkage must be considered and the possibility of post-radiotherapy neck dissection raised prior to randomization. Special cases need to be considered as well:

Cystic Lymph Nodes: These are frequently seen in HPV positive tumors and have distinct behavior from solid nodal metastases. They may not take up FDG at presentation due to the large component of fluid present and they may not demonstrate a size decrease, although ultimately they are almost uniformly shown to negative post-treatment. Thus, these lymph nodes will not have the same size criteria applied to them as for solid nodes and can be randomized for potential reduced doses if there has been a decrease in PET avidity even if there has not been a change in their size.

In order for the patient to be considered for randomization, both the primary and the nodal site need to have had a response as outlined above. There must be agreement between the surgical, medical and radiation oncologists as to the extent of final response prior to moving to the next phase. If either the primary or nodes do not achieve an adequate response, standard radiation doses must be used. We recommend standard radiation dosing plus carboplatin (AUC 1.5), Paclitaxel (40 mg/M2) and Erbitux (with loading when

feasible) 250 mg/M² weekly during radiotherapy for these patients. Patient receiving this treatment will be followed as a separate cohort.

6.2 Randomization

Randomization will be accomplished through eRAP by the clinical research coordinator and the registration center. Eligibility and HPV status will be reviewed and confirmed by the team. Once the patient has passed the eligibility criteria and the eligibility checklist has been sent to central registration, central registration will query the eRAP randomization module and obtain a radiation assignment. This will be communicated by email and fax to the site Clinical Research Coordinator and by email to the site radiation oncologist of record, the treating medical oncologist and the site principal investigator (see Section 20.4 for randomization process).

7.0 RECOMMENDATIONS FOR DELIVERY OF RADIATION (XRT)

7.1 All patients will receive daily radiation treatment with intensity-modulated radiotherapy (IMRT). Treatment will be given 5 days per week and will not routinely be delivered on Saturday, Sunday or major holidays unless a treatment is missed during the week due to technical and/or medical reasons. No more than 5 treatments should be given per week. Radiotherapy will be administered according to the guidelines below:

7.2 Technical Factors

Photon beams of ≥ 4 MV are required. Intensity Modulated Radiotherapy (IMRT) is required for all cases. IMRT via dynamically moving leaves, step-and-shoot with a multileaf collimator, Rapid Arc, binary multileaf collimator and tomotherapy are allowed. Three-dimensional conformal radiotherapy (3D-CRT) and proton therapy are not allowed.

Immobilization, Simulation, and Localization

A thermoplastic head mask (or similar immobilization device) is required for IMRT. Bite blocks, dental rolls and other set-up techniques may be used at the discretion of the treating radiation oncologist. A treatment planning CT scan is mandatory for defining target volumes. IV contrast is not required for the treatment planning CT as long as a pre-induction CT, MRI and/or PET/CT scan with contrast is available and is fused to the treatment planning CT. CT scan thickness should be ≤ 0.3 cm. The treatment planning CT scan should be acquired with the patient in the same position and using the same immobilization device as for treatment. Volumes for all structures must be contoured on each relevant CT slice.

Treatment Planning/Target Volumes

Gross Tumor Volume (GTV)

GTV consists of gross tumor at the primary site and gross nodal disease. The volumes will be defined based on imaging studies (CT, MRI, and/or PET/CT) in conjunction with information from clinical examination. All of the information utilized for target volume delineation must be obtained prior to the initiation of induction chemotherapy. Therefore, it is essential that all patients need to be seen by a radiation oncologist prior to enrollment on the trial.

As this is an induction trial, in many cases, definition of the “GTV” is not a straightforward exercise, since it may have decreased in size or not be visible after IC and prior to initiating

radiation. The goal is to reconstruct the pre-IC GTV volume on the post induction, pre-radiation, planning CT scans. This can be done using the pre-treatment imaging as a guide or preferably using image fusion, at the discretion of the treating physician. It is critical that the volume defined for radiation treatment is the initial volume of disease and not only the residual found after IC.

Clinical Target Volume (CTV) – Standard Dose Arm

The clinical target volume (CTV) is generated to account for microscopic disease. The CTVs should not include bone (unless involved) or air. There will be two CTVs for the Standard Dose Arm. CTV70 will include the primary tumor and involved nodal GTVs with a 0.5 cm margin to account for microscopic extension. The second CTV will be the bilateral elective neck, and there are two options for treating this region:

- CTV56 can be delineated if the radiation oncologist prefers to utilize a simultaneous integrated boost (SIB) IMRT technique which allows for one treatment plan. This region would receive 1.6 Gy per fraction x 35 fractions while the CTV70 received 2.0 Gy per fraction x 35 fractions.
- CTV50 can be delineated if the radiation oncologist prefers to utilize a sequential boost technique which allows the elective neck to receive a higher dose per fraction. The CTV50 will receive 2 Gy per fraction x 25 fractions concurrently with the CTV70. At 50 Gy (25 fractions), a second plan would provide a 20 Gy boost to the CTV70 region only (2 Gy x 10 fractions).

Clinical Target Volume (CTV) – Reduced Dose Arm

There will be two CTVs for the Reduced Dose Arm. The CTVs should not include bone (unless involved) or air. CTV56 will include the primary tumor and involved nodal GTVs with a 0.5 cm margin to account for microscopic extension. CTV50.4 will include the bilateral elective neck. The CTV56 and CTV50.4 will be treated with an SIB technique where the CTV56 will receive 2 Gy per fraction x 28 fractions and the CTV50.4 will receive 1.8 Gy per fraction x 28 fractions.

Planning Target Volume (PTV)

PTV incorporates a margin that accounts for daily set up variation. The PTV should be a 0.3-0.5 cm expansion of all CTVs depending on the treating physician's comfort level. Modification of PTV is allowed at the discretion of the treating radiation oncologist for sparing of normal tissues, or if it is needed to facilitate the planning process, e.g. if the PTV overlaps a critical structure that must be spared. Each CTV will have an individual PTV designed for set-up uncertainty. No PTV expansion will be done for the GTV, as these will be included within the volume of their respective CTV.

Avoidance Structures

The following normal tissue structures will be defined. The dose constraints are listed for each structure.

- A. Spinal cord: Maximum dose <45 Gy
- B. Expanded spinal cord (5 mm expansion around spinal cord): Maximum dose <50 Gy
- C. Brainstem: Maximum dose <54 Gy
- D. Parotid glands: Mean dose <26 Gy. If this is not possible due to adjacent disease, then the volume of one parotid gland receiving 30 Gy or more (V30) should be <50%.
- E. Larynx: Mean dose <45 Gy
- F. Mandible: Maximum dose <70 Gy

G. Oral cavity: Mean dose <40 Gy

For cases in which treatment volumes approach the base of skull, the following avoidance structures will be added:

- A. Inner ear: Mean dose <30 Gy
- B. Optic nerves: Maximum dose <50 Gy
- C. Optic chiasm: Maximum dose <50 Gy
- D. Expanded optic nerve and chiasm (2 mm expansion around these structures): Maximum dose <54 Gy
- E. Retina: Maximum dose <45 Gy
- F. Brain: Maximum dose <60 Gy

Target Dose Prescriptions

To accommodate for tissue heterogeneity, density corrections are required, and will be applied to all plans, unless contraindicated, for example, by significant amounts of scatter on the planning CT scan. Patients whose tumors that respond to induction chemotherapy as outlined above will be randomized to either standard dose (70 Gy) or reduced dose (56 Gy) as follows:

Standard Radiation Dosing

- Option 1 via Simultaneous Integrated Boost
 - (a) **PTV70** will be treated to a total dose of 70 Gy in 2.0 Gy/fraction x 35 fractions.
 - (b) **PTV56** will be treated to a total dose of 56 Gy in 1.6 Gy/fraction x 35 fractions.
- Option 2 via Sequential Boost
 - (a) **PTV70** will be treated to a total dose of 70 Gy in 2.0 Gy/fraction x 35 fractions.
 - (b) **PTV50** will be treated to a total dose of 50 Gy in 2.0 Gy/fraction x 25 fractions.

Reduced Radiation Dosing (via Simultaneous Integrated Boost)

- (a) **PTV56** will be treated to a total dose of 56 Gy in 2.0 Gy/fraction x 28 fractions.
- (b) **PTV50.4** will be treated to a total dose of 50.4 Gy in 1.8 Gy /fraction x 28 fractions.

PTV coverage

All plans must be normalized such that 95% of the PTV is covered with the prescription dose. No more than 10% of the PTV may receive > 105 % of the prescription dose. No more than 1cc of the PTV may receive >110% of the prescription dose. No more than 1% of the PTV may receive < 93% of the prescription dose. No more than 1cc of tissue outside the PTV may receive > 110% of the prescription dose.

Note: in any case with a conflict/overlap between target and normal tissue, target dose considerations will take priority, with the exception of the spinal cord limits.

Treatment Breaks

There are no planned treatment breaks on this study; any breaks in planned radiotherapy are strongly discouraged. Radiotherapy interruptions will be permitted for unavoidable mechanical malfunction or serious illness requiring hospitalization, such as sepsis, delirium, severe respiratory compromise or hemodynamic instability, at the discretion of the Principal Investigator. Treatment breaks should be as short as possible. The reason for any interruption in treatment must be documented in the treatment chart.

7.3 Quality Assurance

Initial: Prior to the first radiation treatment, the standard quality assurance procedures will be followed. The monitor units required to deliver the prescribed dose shall be calculated. The monitor units generated by the IMRT planning system must be independently checked prior to the patient's first treatment. Measurements in a quality assurance phantom will be done for each patient that will be treated. An ion chamber measurement, to assess absolute dose, in addition to a film or matrix measurement will be taken during the QA period.

On the first day of treatment each patient will have electronic portal images taken that localize the isocenter placement, which will be approved by a radiation oncologist prior to delivery of the first treatment, per standard practice.

Weekly: Verification portal images will be taken at least twice per week and approved by a radiation oncologist prior to continuation of treatment per standard practice. During treatment, patients may lose a significant amount of weight and the RT plan may need to be adjusted. It is at the discretion of the treating radiation oncologist to re-simulate and re-plan a patient's radiation treatment due to significant weight loss, though this is not mandatory. If the patient is re-planned, the PTV coverage and dose constraints for normal tissues, as specified above, need to be met for the combined plan.

Isodose Distribution

All plans will have complete documentation in the patient's chart, including representative CT slices with treatment isodoses. A DVH with all PTV and CTV structures and all normal tissue structures will be generated for each patient and documented in the patient's radiotherapy chart.

Quality Assurance

Each treatment plan will be reviewed by at least one non-treating radiation oncologist prior to therapy to assure that the appropriate fields and doses will be delivered. The Radiation oncologist will review the plan according to the checklist provided in Appendix x, which will be included in the record.

8.0 SURGICAL INTERVENTIONS

8.1 *Determination of Stage*

Clinical stage will be based on clinical exam, and office based endoscopic evaluation with flexible endoscopy of the upper aerodigestive tract as well as radiographic evaluation with CT and/or MRI in conjunction with CT/PET. Formal operative endoscopy with biopsy under general anesthesia will be performed as indicated when diagnostic or staging dilemma occurs. When the primary tumor is identifiable, a preoperative tissue biopsy will be taken and used for histopathological analysis and assignment of HPV status. Biopsies performed outside the institution will be internally reviewed by pathology department according to protocol guidelines and repeat biopsies will be obtained if there is inadequate tissue for analysis. In the case of unknown primary tumors, a needle biopsy of the metastatic lymph node will be performed for these purposes. Final staging will be performed according to standard AJCC TNM criteria.

8.2 *Examination and EUA/biopsy for Post Induction Response Assessment*

The treating team (Medical Oncology, Radiation Oncology and Surgical Oncology) will determine whether an EUA is required after three cycles of chemotherapy to adequately assess response primary site and possible post-radiation neck dissection. Study subjects may undergo a repeat endoscopy and biopsy to determine response, if in question. Both a superficial and a deep biopsy, if possible, will be obtained from the primary site to determine tumor status. In partial response patients, biopsies will be directed at the visible/palpable mucosal abnormality or submucosal mass. In patients with clear evidence of persistent disease at the primary site (By clinical exam and office fiberoptics), a repeat biopsy is not mandatory and is at the discretion of the treating team. Patients with an unknown primary carcinoma should not undergo an examination under anesthesia (EUA) after induction chemotherapy unless it is clinically indicated and only after discussion with overall PI. Patients who have had tonsillectomy prior to treatment will not undergo EUA or biopsy post induction chemotherapy.

8.3 Post-radiation Neck Dissection

At the completion of the radiation residual cervical disease will be assessed clinically and with CT/PET at 12-16 weeks after therapy (33). Patients with residual cervical metastases >2cm, or any size in conjunction with PET positivity (SUV >3.0) will be treated with planned neck dissection and pathologic evaluation of the residual lymph node. PET negative nodes <2cm will be observed and repeat PET/CT will be obtained in 6 months after completion of therapy to determine complete resolution of disease unless, in the opinion of the radiologist there is indication of persistent cancer. PET negative cystic nodes will be followed and a repeat scan performed at 6 months. All patients undergoing salvage neck dissection will also undergo EUA and, if indicated, biopsy of the primary site at the time of the neck dissection.

9.0 GENERAL CONCOMITANT MEDICATION AND SUPPORTIVE CARE GUIDELINES

Recommended premedication for docetaxel is as follows: dexamethasone 8 mg by mouth twice daily for 3 days, starting the night before chemotherapy. Patients will automatically receive prophylactic antibiotic therapy.

9.1 Hydration

Patients receiving cisplatin should receive a minimum of 2 liters of normal saline with or without MgSO₄ on Day 2, either in a local clinical area, at home or in their main clinic treatment facility, with anti-emetic therapy as necessary.

Patients should be able to tolerate a minimum oral fluid intake (≥ 2 L oral intake/day) day 3 of TPF and after. If inadequate oral intake of fluids is observed, the patient should return to a treatment facility for additional IV hydration, or receive home hydration as clinically indicated. If the patient is unable to return to the treatment facility, they will be instructed to visit a local medical facility for IV hydration.

10.0 DURATION OF THERAPY

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. In the absence of treatment delays due to adverse events, induction chemotherapy will continue for 3 cycles followed by 6 or 7 weeks of chemoradiation or until one of the following criteria applies:

- Patient withdraws consent
- Patient is removed early from protocol therapy at PI's discretion

- Patient is found ineligible
- Patient completion of protocol requirements
- Unacceptable toxicity
- Pregnancy
- Adverse Event
- Progressive disease/ relapse
- Lost to follow-up
- Non-Compliance with therapy and protocol procedures
- Death
- Other

10.1 Duration of Follow Up

Participants will be followed with a physical examination every 1-2 months during the first year of follow up, every 2-3 months in the second year and every 3-4 months in the third year. Thereafter participants will be followed biannually. Routine PET/CT scans should be performed at 12, 24, and 36 months after therapy has been completed in the absence of prior progression and then according to local practice. Participants will be followed for minimum of 5 years after completion of study treatment or until death, whichever occurs first through standard of care treatment after therapy as prescribed by the Investigator which can include clinic visits or other follow-up by other means. Participants removed from study for unacceptable adverse events will also be followed until resolution or stabilization of the adverse event.

10.2 Criteria for Removal from Study

Participants will be removed from study when any of the criteria listed in Section 10.0 applies. The reason for study removal and the date the participant was removed must be documented in the study-specific case report form (CRF). Alternative care options will be discussed with the participant.

In the event of unusual or life-threatening complications, participating investigators must immediately notify the Principal Investigator, Marshall Posner, MD at 212-659-5461.

11.0 EXPECTED TOXICITIES AND DOSING DELAYS/DOSE MODIFICATIONS

Dose delays and modifications will be made using the following recommendations. Toxicity assessments will be done using the CTEP Active Version v.4 of the NCI Common Terminology Criteria for Adverse Events (CTCAE) which is identified and located on the CTEP website at:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm as incorporated into the eRAP Case Report Forms.

If possible, symptoms should be managed symptomatically. In the case of toxicity, appropriate medical treatment should be used (including anti-emetics, anti-diarrheals, etc.).

All Severe or unexpected adverse events and selected adverse events (non-severe) experienced by participants will be collected from the time of the first dose of study treatment, through the study and until the final study visit. Participants continuing to experience toxicity at the off study visit may be contacted for additional assessments until the toxicity has resolved or is deemed irreversible.

11.1 Anticipated Toxicities

A list of the adverse events and potential risks associated with the agents administered in this study appear below and will determine whether dose delays and modifications will be made or whether the event requires expedited reporting **in addition** to routine reporting.

11.1.1 Adverse Event Lists(s) for Docetaxel

When used as single agent, the prominent dose-limiting effects of Docetaxel are neutropenia, anaphylactoid type reactions, fluid retention, digestive tract toxicities (nausea, vomiting, oral mucositis, and diarrhea) and reversible paresthesias.

11.1.2 Adverse Event List(s) for Cisplatin

The major dose limiting toxicities observed with Cisplatin single agent are nausea and vomiting, peripheral neuropathy, nephrotoxicity and ototoxicity.

11.1.3 Adverse Event List(s) for 5-Fluorouracil

The major dose limiting toxicities observed with 5-fluorouracil single agent are mucositis, myelosuppression and diarrhea.

11.1.4 Adverse Event List(s) for Carboplatin

The major dose limiting toxicities observed with Carboplatin single agent are myelosuppression and renal toxicity.

11.2 Dose Modifications/Delays

11.2.1 Docetaxel

Neutropenia and/or Its Complications

Fever should be graded using the NCI-CTC v.4 grading system. The reported temperature should be the oral or equivalent temperature. In case of grade 2 fever [temperature $\geq 38.1^{\circ}\text{C}$ (100.6°F)] concomitant with grade 4 neutropenia ($\text{ANC} < 0.5 \times 10^9/\text{L}$), the following approach is recommended:

- Hospital admission except where outpatient care may be indicated
- Pre-antibiotic evaluation
- Complete Blood Count with differential and blood culture should be performed
- Start of an empirical antibiotic therapy

In case of febrile neutropenia [grade 2 fever (temp. $\geq 38.1^{\circ}\text{C}$)] with grade 4 neutropenia ($\text{ANC} < 0.5 \times 10^9/\text{L}$)] requiring I.V. antibiotics, the blood counts must be done every 2 days until recovery of $\text{ANC} \geq 0.5 \times 10^9/\text{L}$. This must be documented on the Case Report Form for Febrile Neutropenia.

Action Taken for Febrile Neutropenia or Documented Neutropenic Infection: Adverse event	Action to be taken for subsequent cycles
<ul style="list-style-type: none"> • Febrile neutropenia • Documented infection 	<ol style="list-style-type: none"> 1. The first episode of febrile neutropenia or documented grade 3 /4 neutropenia with documented infection will result in a reduction of docetaxel to 60 mg/m². 2. If there is a second episode, the patient will remain on study and additionally, the cisplatin dose will be reduced to 75 mg/m²

Action Taken Following Results of Neutrophil Counts On Day 21: ANC (x10 ⁹ /L)	Action to be taken
≥ 1.5	– Treat on time and at full dose
< 1.5	<ol style="list-style-type: none"> 1. Delay 1-7 days and repeat complete blood count on every other day on days 21- 28 2. If ANC ≥ 1.5 x 10⁹/L, then proceed with full dose chemotherapy 3. If ANC < 1.5 x 10⁹/L on Day 28, then consider GM-CSF for 7 days <ul style="list-style-type: none"> • On day 35, perform complete blood count with differential • Proceed with full dose chemotherapy if ANC ≥ 1.5 4. If there is no recovery by day 35, (ANC < 1.5 x 10⁹/L), the patient will go off drug therapy

Stomatitis

- If stomatitis is present on day 1 of any cycle, treatment should be withheld until stomatitis has resolved.

Thrombocytopenia

- Grade 4 thrombocytopenia requires a dose reduction of docetaxel from 75 to 60 mg/m². The drug will be held to resolution for up to 2 weeks and must resolve to ≥100,000.

Cutaneous Reactions

- **Grade 0, 1 and 2:** No change
- **Grade 3:** Delay until ≤ grade 1 and retreat with a dose reduction of Docetaxel from 75 to

60 mg/m². If no recovery to \leq grade 1 within 2 weeks delay, patient will go off protocol therapy

- The patient will go off all drug therapy Grade 4:
- changes will not motivate dose-modification Nail

Nausea and/or Vomiting

- Propylactic antiemetic regimen with 5-HT3 antagonists and aprepitant should be administered from the first cycle. In addition, the corticosteroids used during 3 days for the prophylaxis of fluid retention should also reduce the incidence and severity of emesis.
- Patients with nausea and vomiting despite these measures may be treated with another antiemetic regimen (i.e. high dose metoclopramide) as appropriate.

Bilirubin and Impaired Liver Function

- In the event that bilirubin levels are above institutional ULN on Day 1 of cycles 2 and/or 3, the cycle will be delayed by a maximum of 2 weeks. If no recovery, the patient should be taken off chemotherapy.
- In the event that AST and/or ALT and/or alkaline phosphatase levels are abnormal in the absence of progressive disease, on Day 1 of cycles 2 and/or 3 the following dose modifications will apply:

Dose Modifications for Abnormal Liver Function (Docetaxel)

ALK PHOS:	AST or ALT:			
	\leq ULN	$>1x$ but $\leq 1.5x$	$>1.5x$ but $\leq 5x$	$>5x$ ULN
\leq ULN	75 mg/m ²	75 mg/m ²	75 mg/m ²	Hold*
$>1x$ but $\leq 2.5x$	75 mg/m ²	75 mg/m ²	65 mg/m ² **	Hold*
$>2.5x$ but $\leq 5x$	75 mg/m ²	60 mg/m ² **	Hold*	Hold*
$>5x$ ULN	Hold*	Hold*	Hold*	Hold*

*Hold until recovered, maximum 2 weeks, then re-treat at a reduced dose. “Recovered” is defined as meeting the study baseline eligibility criteria.

Bilirubin: Docetaxel should not be administered to patients with serum total bilirubin >ULN. If serum total bilirubin is > institutional ULN on treatment day, hold Docetaxel until serum total bilirubin is ≤ institutional ULN (maximum 2 weeks), then re-treat at a reduced dose.

**Reduced doses of Docetaxel will be at 60mg/m². After Docetaxel is dose is reduced, there will be no re-escalation. There will be only one dose reduction.

Guidelines for the Management of Other Docetaxel-Specific Toxicities (No Dose Modification Required)

Anaphylactoid Type Reactions, Hypersensitivity Reactions

- During the 1st and the 2nd infusions, a careful evaluation of general sense of well being and whenever possible blood pressure and heart rate monitoring will be performed for at least the first 10 minutes, so that immediate intervention would occur in response to symptoms of an untoward reaction. The frequency of monitoring blood pressure and heart rate is per nursing standard.
- Facilities, care provider and equipment for resuscitation have to be immediately available: antihistamine, steroids, and epinephrine.
- In case anaphylactoid or hypersensitivity reaction occurs, the following will apply:

Management of Hypersensitivity Reactions

Mild symptoms:	<ul style="list-style-type: none">• Localized cutaneous reaction, such as pruritus, flushing, rash. <ul style="list-style-type: none">▪ Decrease the rate of infusion until recovery of symptoms, stay at bedside. The time allowed is per the physician's assessment at bedside.▪ Then, complete Docetaxel infusion at the initial planned rate.▪ At subsequent cycles use the same pre medication guidelines. Section 5.2.1
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<u>Moderate</u> symptoms:	<ul style="list-style-type: none"> Any symptom not listed above (mild symptoms) or below (severe symptoms), such as generalized pruritus, flushing, rash, dyspnea, hypotension with systolic blood pressure > 80 mmHg Stop Docetaxel infusion. Give i.v. antihistamine and i.v. corticosteroids** After recovery of symptoms; depending on the physician's assessment of the patient, Docetaxel infusion should be resumed at a slower rate, then increased incrementally to the initial planned rate, (<i>e.g. infuse at an 8 hour rate for 5 minutes, then at a 4-h rate for 5 minutes, then at a 2-h rate for 5 minutes, then finally, resume at the initial planned rate.</i>) The time allowed to hold the drug is per the physician's assessment at bedside. For the next cycle of treatment the rate of infusion should be decreased initially and then increased back to initial planned rate, (<i>e.g. infuse at an 8 hour rate for 5 minutes, then at a 4-h rate for 5 minutes, then at a 2-h rate for 5 minutes, and finally, administer at the initial planned rate.</i>) For all subsequent cycles, antihistamines* and steroids** will be given intra-venous one hour before infusion in addition to the premedication planned. Section 5.2.1
<u>Severe</u> symptoms:	<p>Such as bronchospasm, generalized urticaria, hypotension with systolic blood pressure ≤ 80 mmHg, angioedema</p> <ul style="list-style-type: none"> Stop Docetaxel infusion. Give i.v. antihistamine and steroids**. Add epinephrine*** or bronchodilators and/or i.v. fluids, if indicated. Once all signs and/or symptoms of hypersensitivity reaction disappear, Docetaxel may be reinfused the same treatment guidelines outlined under moderate symptoms. At the subsequent cycles, Dexamethasone will be given at 20 mg orally the evening before chemotherapy, the morning of chemotherapy and one hour before Docetaxel infusion. Additionally diphenhydramine (or equivalent) will be given at 50 mg intra-venous 1 hour before Docetaxel infusion. If a severe reaction recurs, patient will go off protocol chemotherapy.
NCI-CTC Grade 4 reaction	<ul style="list-style-type: none"> Patient will go off therapy.

* antihistamines:

dexchlorpheniramine	(*) i.v. 5-10 mg
or clemastine	(*) i.v. 2 mg
or diphenhydramine	(*) i.v. 25-50 mg
or promethazine	(*) i.m. 50-100 mg

** corticosteroids: dexamethasone or equivalent (*) i.v. 5-10 mg of dexamethasone

*** epinephrine: administered at a 1:1000 dilution (0.01 mg per kilogram with a maximum dose of 0.5 mg subcutaneously repeated every 20 minutes as necessary).

Fluid Retention

- There are no dose reductions for fluid retention.
- Patients developing new onset edema, progression of existing edema, or another sign of fluid retention (e.g. 2 pound weight gain) are to be treated with oral diuretics. Regimens found to be effective in the management of fluid retention due to Docetaxel are listed below.
- Triamterene/hydrochlorothiazide one capsule orally once daily up to three times daily.
- Furosemide 40 mg orally daily if edema progresses despite Triamterene/hydrochlorothiazide therapy. Potassium supplementation should be given as needed.
- If after a two-week trial, furosemide 40 mg once orally per day is ineffective, the patient may be treated with furosemide 20 mg orally per day plus metolazone 2.5 mg orally per day with potassium supplementation as needed.
- Further therapy should be customized depending upon the clinical situation. The clinical tolerance of the patient, the overall tumor response and the medical judgment of the investigator will determine if it is in the patient's best interest to continue or discontinue treatment.

11.2.2 Cisplatin

Peripheral Neuropathy

- A neurological examination must be performed at least before entry into the study and then once every cycle and when the patient goes off chemotherapy. In case of symptoms or signs experienced by the patient, more frequent examinations should be performed and dose modification will be as follows:
 - Grade 0, 1: No change
 - Grade ≥ 2 : Carboplatin at an AUC of 6 may be substituted for Cisplatin during induction TPF
 -

Ototoxicity

- Cisplatin is known to cause high frequency hearing loss. 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 however this decision can be made with the patient and after a formal hearing tests.
- **In cases of grade 3 or 4 toxicity, or risk decision made for grade 1 or 2 hearing loss, Carboplatin (at dosage of AUC 6) may be used to replace Cisplatin in the remaining Induction chemotherapy cycles. The dose of Carboplatin AUC 6 will be calculated based on the Calvert formula.**

Thrombocytopenia

Dose Modification for Thrombocytopenia

Nadir of last course $\leq 100,000$	Dose of Cisplatin Platelets (day 1 of each cycle)	
	$<100,000$	$\geq 100,000$
$\geq 50,000$	Hold	Cisplatin = 100%
$< 50,000$ (1 st occurrence)	Hold	Cisplatin = 80%
$<50,000$ (2 nd occurrence)	Hold	Cisplatin = 60%

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

Dose Modification of Cisplatin in Kidney Impairment

Calculated Creatinine Clearance (mL/min)	Percent Dose to Give	
≥ 60	100%	
< 60	0% (withhold treatment for a maximum of 1 weeks and repeat serum creatinine weekly after additional hydration), then	
	If CCI was < 60 mL/min and is now:	** The percent dose to give is:
	> 50 but < 60	80%
	≥ 40 but ≤ 50	Carboplatin should be substituted at an AUC of 6
	< 40	Carboplatin should be substituted at an AUC of 6

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

If creatinine clearance recovers, and in the opinion of the treating physician the patient can tolerate it, cisplatin should be reinstated and the dose of Cisplatin for the last cycle should be re-escalated to 100 mg/M² dose level.

Carboplatin Dose Adjustments (as substitute for Cisplatin in induction Chemotherapy)

Formula to calculate Creatinine Clearance:

$$\text{CrCl (mL/min)} = \frac{(140-\text{age}) (\text{weight kg})}{72 \times \text{serum creatinine (mg/dL)}}$$

N.B. For females, use 85% of calculated CrCl value.

Ototoxicity, Nausea and Vomiting

Cisplatin is the preferred therapy for TPF and chemoradiotherapy, Carboplatin may be substituted for Cisplatin if a patient develops grade 3 ototoxicity, or an unacceptable Cisplatin associated nausea and vomiting, after receiving 1 or 2 doses of Cisplatin.

Dose alteration for toxicity is to be based on single worst toxicity. Once Carboplatin dose is reduced, there will be no re-escalation.

Hematologic Toxicity

Absolute Neutrophil Count (Reduce doses only for febrile neutropenia or if ANC is $< 500/\text{mm}^3$ for ≥ 5 days. ANC must be $\geq 1,500/\text{mm}^3$ and platelet count must be $\geq 100,000/\text{mm}^3$ on day 1 of each cycle).

Dose Modification for Hematologic Toxicity

Absolute Neutrophil Count (ANC)		
Nadir of last course	Dose of Carboplatin ANC (day 1 of each cycle)	
	< 1500	≥ 1500
Febrile neutropenia (regardless of duration)	Hold	Carboplatin = AUC 4
< 500 for < 5 days	Hold	Carboplatin = AUC 6
< 500 for ≥ 5 days	Hold	Carboplatin = AUC 4

Platelets

Nadir of last course	Dose of Carboplatin Platelets (day 1 of each cycle)	
$\leq 100,000$	$< 100,000$	$\geq 100,000$
$\geq 50,000$	Hold	Carboplatin = AUC 5
$< 50,000$	Hold	Carboplatin = AUC 4

- In the event that dose adjustments are needed for both Absolute Neutrophil Count (*ANC*) and platelets, patients are to receive the lower dose.

- Treatment should be delayed for up to 2 weeks until ANC is $\geq 1500/\text{mm}^3$ and the platelet count is $\geq 100,000/\text{mm}^3$. However, if the counts have not recovered in 2 weeks, the patient should go off chemotherapy.
- Dose reductions for reduced ANC are NOT based on a single nadir count. The ANC must remain < 500 for ≥ 5 days before a dose reduction is made. If the results of the scheduled weekly Complete Blood Count documents an ANC of < 500 , repeat counts are to be obtained every other day until the ANC recovers to a level of > 500 .
- If chemotherapy must be withheld due to hematologic toxicity, Complete Blood Count and platelet counts should be obtained weekly until the counts reach the lower limits for treatment as outlined.
- No dose reduction will be made for anemia.

Neurotoxicity

- In the event of neurotoxicity (\geq grade 3), Carboplatin therapy is discontinued.

Nephrotoxicity

If, despite adequate rehydration, serum creatinine increases to Formula to calculate Creatinine Clearance using real weight:

$$\text{CrCl (mL/min)} = \frac{(140-\text{age}) (\text{weight kg})}{72 \times \text{serum creatinine (mg/dL)}}$$

N.B. for females, use 85% of calculated CrCl value.

- - Grade 0, 1: No change
 - Grade ≥ 2 : Carboplatin at an AUC of 6 may be substituted for Cisplatin

11.2.3 5- Fluorouracil

Mucositis

- In case of grade 3 mucositis lasting more than 96 hours , 5-fluorouracil dose will be reduced by 10%. A mouth rinse, such as Magic Mouthwash (Maalox, Benadryl, and Lidocaine) should always be allowed.
- In case of grade 3 mucositis lasting more than 96 hours as a second occurrence or grade 4 mucositis, the patient will have 5-fluorouracil reduced a total of 20% from baseline and will continue on docetaxel and cisplatin.
- Other dose adjustments to 5-fluorouracil may be made at the discretion of the local PI based on a given patient's clinical profile to preserve patient safety. The rationale for such decisions are to be clearly documented in the relevant clinic note.

-

Diarrhea

- For the first episode of grade 3 diarrhea lasting 3 or more days, reduce dose of 5-FU by 10%. For the second episode of grade 3 diarrhea lasting 3 or more days, we will reduce the dose of docetaxel by an additional 10 %. For the first episode of grade 4 diarrhea, we will reduce both 5-FU and Docetaxel by 10%. For the second episode of grade 4 diarrhea, we will discontinue cisplatin, 5-FU and Docetaxel and move to standard chemoradiotherapy. Anti-diarrheals and other supportive measures, such as IV fluids, should be used, as deemed clinically indicated. Octreotide is recommended for severe diarrhea. If the patient has a significant diarrhea occurrence again (> 3 loose stools/24 hr), the patient should be treated prophylactically in the subsequent cycles with 2 tablets of loperamide or atropine atropine/diphenoxylate in addition to 1 or 2 tablets after each loose stool. The maximum daily dose of loperamide is 16mg and diphenoxylate is 20mg/day.

Skin

- In case of rash or moist desquamation of grade 3 lasting > 7 days, the dose of 5-fluorouracil will be reduced by 10 % in the subsequent cycle. For second occurrence of grade 3 toxicity or grade 4 skin toxicity, 5-Fu will be discontinued.

Other Guidelines:

- Doses will be modified in cases of severe hematological and/or non- hematological toxicities. Dose adjustments are to be made according to the NCI-CTC criteria showing the greatest degree of toxicity. Toxicities will be graded using the NCI-CTC criteria version 4.0.
- Cutaneous toxicity can be caused by Docetaxel or 5-fluorouracil. Palmar and plantar rash and scrotal or vulvar dermatitis are examples of 5-fluorouracil toxicity, but plantar and palmar rash has also been reported with Docetaxel. Rash with Docetaxel may occur on arms, face and thorax and can be associated with pruritus. The investigator should consider the agent causing the rash and modify the appropriate agent accordingly.
- After dose reduction for toxicity, 5-FU will not be re-escalated.
- For \geq grade 3 toxicities, chemotherapy should be held for a maximum of two weeks from the planned date of reinfusion until resolution to \leq grade 1.

If a patient experiences several toxicities and there are conflicting recommendations, you must follow the most conservative dose adjustment recommended (dose reduction appropriate to the most serious toxicity).

Note that the doses, which have been reduced for toxicity, must not be re-escalated (except for nephrotoxicity of Cisplatin).

In case of dose delay >2 weeks, the patient will go off all protocol therapy and will be immediately referred to the radiation oncologist or surgical oncologist for treatment depending on each situation. However he/she will remain on study and be evaluated and followed for survival accordingly.

11.2.4 Carboplatin (AUC 1.5)

The carboplatin dose for weekly concurrent chemoradiotherapy is an AUC of 1.5. Thereafter, the AUC will be changed only in case of hematological toxicity.

See the tables below for approach to myelosuppression.

Table: Carboplatin dose modification based on ANC

ANC ($\times 10^9/L$) within 24 hrs of therapy	Action to be taken
≥ 1.5	Treat at current dose
$\geq 1.0, < 1.5$ < 1.0	Treat at AUC of 1.0 Hold treatment, and resume therapy at AUC of 1.0 at the next weekly therapy planned when ANC ≥ 1.0 . If neutropenia requiring further chemotherapy break occurs, carboplatin will be discontinued for the remainder of the therapy.

**For febrile neutropenia, instructions for ANC <1.0 will be followed. In addition, prophylactic antibiotics and growth factor support may be administered as clinically indicated.

Table: Carboplatin dose modification based on platelet count

Platelet count within 24 hrs of therapy	Action to be taken
$\geq 100,000$	Treat at current dose
$< 100,000$	Hold treatment, and resume therapy at AUC of 1.0 at the next weekly therapy planned when platelets $\geq 100,000$. If thrombocytopenia requiring further chemotherapy break occurs, carboplatin will be discontinued for the remainder of the therapy.

- Renal toxicity: Serum creatinine will be measured weekly within 24 hours of carboplatin dosing. If the serum creatinine has not changed more than 25% relative to the serum creatinine at baseline, the creatinine clearance and carboplatin dose need not to be recalculated. If there is a rise or fall greater than 25% relative to baseline serum creatinine values, then the creatinine clearance and carboplatin dose must be recalculated.

12 DRUG FORMULATION AND ADMINISTRATION

Drug formulation and administration are in accordance with commercially available product guidelines for all agents listed in Section 5.0.

13 CORRELATIVE/SPECIAL STUDIES

13.1 Probable Laboratory Correlative Studies

This clinical trial aims to investigate a reduction in radiation intensity in patients with HPVOC. The goals of these exploratory translational studies are to understand the tumor biology, immunology, and epidemiology; and to develop predictive biomarkers to be examined in a larger prospectively randomized trial. Tissue and unstained slides will be stored in the tissue biorepository. Plasma, sera, Whole blood DNA, and cells will be stored in the Posner Laboratory.

The following projects may be carried out with specimens from study participants with collaborators:

1. Tumor tissue will be evaluated for the biomarkers (this is a preliminary list which may change and expand as new technology and biomarkers become available): HPV copy number, c-Met expression, BCL-x, EGFr copy number, EGFr expression and EGFr phosphorylation. (Zhang Laboratory)
2. CTC assessment: The number of circulating tumor cells may be evaluated as a possible prognostic indicator. (Investigator TBD)
3. Cytokine profiling of the patients plasma will be assessed with baseline samples obtained prior to therapy (Sikora Lab).
4. Circulating immune cells will be assessed including MDSC, T regulatory and T cell subsets. (Sikora and Posner lab)
5. The immunologic function and specificity of patient's T lymphocyte responses to HPV epitopes will be studied and targeted epitopes identified (Posner Lab).
6. Serologic responses to HPV proteins will be investigated in patients over time in response to therapy. (Anderson Lab)
7. Tissue microarrays and IHC will be used to establish differences between primary tumors with and without distant spread Zhang, Anderson, and Posner Labs.
8. Whole blood DNA will be collected for future analysis (Zhang lab).

13.2 Specific Study Plans

The following studies are given a brief description of current plans, which may change as technology will change and samples will not be accessed until the study is complete unless approved by the tissue committee for pilot analyses.

1) T Cell specificity and Function in HPV Oropharynx Cancer

It is possible that preserved or improved immune responses in HPVOC patients may protect against distant metastases, second primaries or recurrence or may mediate some portion of the responsiveness. We have identified immunogenic HLA-A2-restricted peptides derived from HPV16E6 and E7(34). Here, we will evaluate pre and post therapy T cell function towards HPV peptides by ELISPOT in vitro and correlate responses with stage, clinical response and tumor control. We hypothesize that cured patients will have a more robust response after therapy has completed and we may identify preferred peptide epitopes associated with improved survival and/or response.

2) Serologic assessments

We have developed a novel multiplex antibody assay using the Luminex system that allows us to establish the titers of complex and seemingly heterogeneous antibody responses to the full genome of HPV16. Using this system we will monitor the antibody response of the HPVOC prior to, and 6 months after therapy has completed and then at 6

month intervals for 2 years to determine if response are maintained, can predict tumor control, and can establish patterns that might be useful in predicting the development of cancers.

3) Tissue microarrays

There will be distinct differences between primary tumors and metastatic, nodal and persistent disease in patients. We will use TMA to evaluate biomarkers and tumor differences that can be used to predict metastatic behavior and response. While tumor control is frequently a process related to tumor volume, those cells that can metastasize may have a distinct signature that can point to a pathway that can be exploited for better anti-tumor therapy, could be identified in small numbers of tumor cells, might be present in CTC, etc. This is exploratory study data set.

13.3 *Blood and Tissue Collection and Preparation*

Blood will be collected to measure plasma and serum factors such as antibodies, cytokines, DNA, etc and cells for immune studies and germ line DNA. The target amount to be collected from each subject will be less than 200 mls of whole blood (46 ml at baseline; 36 ml at 12, 24 and 36 months post-CRT; 6 ml at post-induction and 3, 6, 9 and 18 months post-CRT). Blood will be collected in 10ml green top tubes (only at MSSM), 6ml red top tubes and 10 ml EDTA Tubes (EDTA only collected at baseline). Processing and labeling of the blood will be done according to the “Blood Handling” section outlined below. Lag time between collection and the start of processing will be as brief as possible, preferably not overnight and this time will be recorded for each sample. Components will be stored from these tubes including plasma and buffy coat. If collected and handled properly, each of the tubes should yield approximately 3mls of plasma, buffy coat and PBMCs. Plasma will be maintained as 1ml aliquots and frozen and stored at -80°C and buffy coat will be stored from green tubes, at local institutional temperature guidelines. A portion of each of these samples will be stored at the biospecimen repository, and a portion maintained at this facility, until exhausted. Samples will be labeled a code linked to the patient case report form. All patients will have tumor testing for HPV16 and p16 in a central laboratory as part of their screening. Slides and microarrays from tumor tissues will be labeled similarly as blood samples above.

Blood Handling

Blood collection will be performed before surgery (if necessary) and in the absence of any systemic anesthesia. Blood will be obtained at each visit, according to the table below:

	V1	V2	V3	V4	V5	V6	V7	V8	V9
	Baseline	Post Induction pre XRT	3 Mo Post CRT	6 Mo Post CRT	9 Mo Post CRT	12 Mo Post CRT	18 Mo Post CRT	24 Mo Post CRT	36 Mo Post CRT
Window Period	n/a	n/a	± 1 month	± 1 month	± 1 month	± 1 month	± 2 months	± 2 months	± 2 months
*Green Top	30 ml	n/a	n/a	n/a	n/a	30 ml	n/a	30 ml	30 ml
Red Top	6 ml	6 ml	6 ml	6 ml	6 ml	6 ml	6 ml	6 ml	6 ml
EDTA lavender	10 ml	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
KEY:									
*Green Top: 10 ml tube; collected ONLY at MSSM									
Red Top: 6 ml tube; to be processed, frozen at each site and batch shipment on dry ice									
EDTA: 10 ml tube to be shipped at ambient temperature by next day priority mail									
n/a: not applicable									

Viable lymphocytes will be processed from green top tubes using standard ficoll-hypaque density gradient separation. Buffy coat layers will be stored as viable cells in DMSO-containing media at -80C to -170C.

Blood for plasma will be spun within 5 hours of collection. Blood tubes will be spun at 3000 x g for 10' at 4°C and the plasma and buffy coat removed by pipetting. Plasma will be stored in 1ml aliquots. All samples will be stored at -80°C. White blood cell fraction will be stored in a single tube at local institutional temperature guidelines and kept locally.

Blood for whole blood DNA extraction will be delivered to the Zhang Laboratory for processing.

Tissue Collection

All patients will have their tumors tested for HPV and p16 in the central laboratory of David Zhang, MD or by a laboratory verified by the central lab, respectively. p16 test slides from other outside laboratories must be available for review and may be reviewed post registration if there is an urgency of therapy. If the external site is relying on the central lab to conduct p16 testing, paraffin embedded and formalin fixed blocks from the original and subsequent biopsy specimens will be sent

to Dr. Zhang's laboratory and will be cut in his laboratory for PCR testing and IHC. If the external site is conducting p16 testing using its own Pathology Department, the site must submit their standard operating procedures to the central lab before their first enrollment, along with the slides and archived pathological material for 10 test cases for verification purposes. p16 testing can only be done at the external site if the central lab has cleared it. In the event that there is an urgency to initiate therapy, and there is a delay in receiving requested pathological material from an outside laboratory, results from p16 testing done at the outside laboratory can be used for screening the study candidate. However, the Overall PI must be informed of this exception and subsequently provided with a copy of the p16 testing repeated at the laboratory verified by the central lab. If there is a discrepancy in the results of the outside laboratory and the laboratory verified by the central lab, the Overall PI will advise on how to address and document the difference. HPV testing must be done by the central lab of David Zhang. The primary untreated tumor will be tested for p16 prior to the start of induction chemotherapy and for HPV 16 prior to the start of chemoradiotherapy.

The p16 slides will be sent for review by the central lab. Additional slides, from 5-20, and tissue microarrays will be cut from the blocks and stored in Dr. Michael Donovan's Biorepository before they are returned to the site. Any additional biopsies from the primary tumor or a recurrence will be obtained and handled in the same fashion.

Specimen Management Committee

A Specimen Management team will decide priority and allocation of samples not included in the original plan. The team will consist of the Overall study PI, and the Site PIs and Chairmen of the Pathology, Radiation Oncology, ENT, and Medical Oncology for the study and for the teams at each site, and Dr. Karen Anderson. Proposals will be reviewed and upon a majority agreement, samples will be allocated for each study. A quorum for decisions would include at least one member from each site and one of the Study chairmen of Radiation Oncology, ENT. Pathology, and Medical Oncology.

14 STUDY CALENDAR (History, Exam and Lab)

	Pre-Study*	Induction Chemotherapy	Chemo/RT	Reassessment ¹ (Week 8-10)	Post-Study Follow-up
Informed Consent	To be obtained before enrollment				
Tissue - HPV Status and p16 by Central Laboratory	P16 done prior to Induction; HPV16 prior to CRT				
Medical History	Within 10 days before registration	Every 3 weeks (Day 1 of each cycle before treatment)	Weekly		1-2 months and 3-4 months post-CRT
Smoking History	Within 10 days before registration				
Concurrent meds	At Screening	Every 3 weeks (Day 1 of each cycle before treatment)	Weekly		
Physical Exam²	Within 10 days before registration	Every 3 weeks (Day 1 of each cycle before treatment)	Weekly	X	1-2 months in first year, 2-3 months in second year, 3-4 months in third year and every 6 months through year 5.
Hematology³	Within 10 days before registration	Day 1 of each dose (before treatment) and during Week 2 of cycle	Weekly		1-2 months and 3-4 months post-CRT
Urinalysis	Within 10 days before registration				
Serum chemistry⁴	Within 10 days before registration	Day 1 and 5 of each treatment cycle (Day 1 of each dose before treatment)	Weekly		1-2 months and 3-4 months post-CRT

*Many of these tests and procedures are likely to be part of regular cancer care. If some of these tests or procedures were done recently, they may or may not have to be repeated.

¹ Evaluations after chemotherapy

² Ht, Wt, Performance status, neurologic examination, vital signs (heart/blood pressure/temperature). Height is only required at baseline.

³ CBC with differential: WBC, neutrophils and platelets count, hemoglobin

⁴ Alkaline phosphatase, AST (SGOT), ALT (SGPT), bilirubin, creatinine clearance, electrolytes, calcium, protein, albumin, magnesium, urinalysis (dipstick)

MDADI-HN (Dysphagia Assessment Questionnaire)	Within 10 days before registration			X	3, 6, 12, 24, 60 and 120 months
Electrocardiogram	Within 28 days before registration				
Adverse Event evaluation		Every 3 weeks (Day 1 of each cycle before treatment)	Weekly		At every study visit until resolved or stable
B-HC (for WOCP)	Within 7 days before registration				

STUDY CALENDAR (Tumor Assessment)

Tumor Assessment					
	Pre-Study	Induction Chemotherapy	Chemo/RT	Reassessment (Week 8-10)	Post-Study Follow-up
Physical tumor Examination	Within 10 days registration	Prior to every cycle		X	
TNM Staging	Within 10 days before registration				
Nasopharyngoscopy/ Laryngoscopy		At end of Cycle 2, if clinically indicated; Mandatory at end of cycle 3 (if no EUA)		X	
Examination under anesthesia (EUA)	Within 8 weeks before registration if possible. (Does not need to be repeated if time period exceeds 8 weeks)	May be done if investigator deems it necessary			
PET/CT and CT/MRI of the neck (base of skull clavicles)	A PET/CT and CT/MRI of the neck; or only a PET/CT (Within 28 days before registration)	At Week 9, 10, or completion of Cycle 3		A PET CT and High resolution CT scan or MRI should be performed at 12-16 weeks to assess complete response	12, 24 and 36 months (only PET/CT)

CORRELATIVE STUDIES CALENDAR (See Section 16.0 for QOL)					
	Pre-Study	Induction Chemotherapy	Chemo/RT	Reassessment (Week 8-10)	Post-Study Follow-up
Tissue Microarray	X				
CTC's (cell Save tube)	X				
T Cell Specificity and Function	X			X	3, 12, and 24, 36 months
Whole Bood DNA					
4-5 large green top tubes, 1 EDTA					
Serologic Assessments (1 Green Top)	X			X	3, 6, 9, 12, 18, and 24, 36 months
Swallowing Function					6, 12, 24, and 36 months

SCREENING/PRE-STUDY/BASELINE – Prior to start of Induction Chemotherapy

Note: All standard of care procedures done prior to consent during the window period are valid.

- Signed informed consent form
- Eligibility (Inclusion/Exclusion) Checklist
- Medical history (within 10 days before registration)
- TNM staging (within 10 days before registration)
- Smoking history and questionnaire (within 10 days before registration)
- Questionnaires (within 10 days before registration):
 - EORTC QLQ-C30
 - EORTC QLQ H&N35
 - MDASI-HN
 - MDADI-HN (Dysphagia)
 - Xersotomia
- Physical examination, including height, weight, and vital signs (within 10 days before registration),
- Neurological examination (within 10 days before registration)
- ECOG Performance Status (within 10 days before registration)
- Electrocardiogram (ECG) (within 28 days before registration)
- Tumor assessment
- Adverse Events
- Concomitant medications

- Examination under anesthesia (EUA) and biopsy (within 8 weeks before registration, if possible; does not need to be repeated if time period exceeds 8 weeks)
- HPV and p16 tests by central lab or by a lab verified by the central lab, respectively – Pathological material is required for both tests. However, only p16 results are required for entry into the study. HPV 16 results are not required until randomization.
- Urinalysis (dipstick)
- Blood tests – Hematology, Chemistry, and Research labs (within 10 days before registration)
- Pregnancy test, if applicable (within 7 days before registration)
- PET/CT and CT/MRI of the neck; or PET/CT alone (within 28 days before registration)

INDUCTION CHEMOTHERAPY (PHASE I) – Day 1 of Each Cycle (\pm 2 days)

- Medical history
- Physical examination, including weight, and vital signs
- Neurological examination
- Physical tumor examination
- ECOG Performance Status
- Blood tests - Hematology Chemistry. Hematology will also be performed during week 2. Chemistry will also be performed on Day 5 of each cycle.
- Examination under Anesthesia (EUA) – done at the discretion of the Investigator
- Nasopharyngoscopy/Laryngoscopy at end of Cycle 2 (at discretion of Investigator) - if there was no EUA done.
- Concomitant medications
- Adverse events
- Questionnaires – does not need to be repeated if done during Screening
 - EORTC QLQ-C30
 - EORTC QLQ H&N35
 - MDASI-HN
 - MDADI-HN (Dysphagia)
 - Xerostomia
- Induction Chemotherapy (~ 7-hr infusion)

POST-INDUCTION (REASSESSMENT EVALUATION) – After 3 cycles but prior to CRT

- Randomization Eligibility (Inclusion/Exclusion) Checklist
- Blood tests – Only research labs
- HPV16 results by central lab
- PET/CT and CT/MRI of the neck (end of Cycle 3)
- EUA (at Investigator's discretion)
- Nasopharyngoscopy/Laryngoscopy (if no EUA was done)
- Repeat endoscopy and biopsy (if clinically indicated)

CHEMORADIATION THERAPY (CRT) (PHASE 2) – Weekly

- Medical History
- Physical examination, including weight, and vital signs

- Neurological examination
- ECOG Performance Status
- Concomitant medications
- Blood Tests - Hematology Chemistry
- Questionnaires (Bi-weekly on even weeks):
 - EORTC QLQ-C30
 - EORTC QLQ H&N35
 - MDASI-HN
 - MDADI-HN (Dysphagia) – done weekly
 - Xerostomia – done weekly
- Adverse events
- Chemotherapy (once per week)
- Radiotherapy (5 times per week)

POST-CHEMORADIATION (REASSESSMENT EVALUATION) - 8-10 weeks post-CRT

- Physical examination, including weight, and vital signs
- Neurological examination
- Physical tumor examination
- ECOG Performance Status
- Nasopharyngoscopy, if clinically indicated.
- PET/CT and CT/MRI of the neck – done at 12-16 weeks.

FOLLOW-UP PERIOD:

Visits will occur 1-2 months for first year, every 2-3 months for second year and then yearly for 5 years after completion of study treatment. Refer to grid above for the specific time points.

- Medical History
- Physical examination, including weight, and vital signs
- Neurological examination
- ECOG Performance Status
- Blood Tests – Hematology, Chemistry, TSH (Q 6 months as SOC), and Research
- PET/CT
- Questionnaires:
 - EORTC QLQ-C30
 - EORTC QLQ H&N35
 - MDASI-HN
 - MDADI-HN (Dysphagia)
 - Xerostomia
- Adverse events
- Record of relapse progression, new treatments, and new primary
- Survival status

15.0 MEASUREMENT OF EFFECT

15.1 Antitumor Effect–Solid Tumors

Response will be reported after three cycles of induction for primary site and for neck disease (day 21-35). Clinical assessment, pathological assessment (primary site biopsy) and radiographic assessment will be used to report response to treatment.

Radiologic Response Assessment

Radiographic response will be assessed by objective response defined by Response Evaluation Criteria in Solid tumors (RECIST 1.1). **However, the response criteria to determine eligibility for reduced radiation will be followed according to guidelines outlined in section 5.0.**

Sites of malignant disease must be documented at baseline evaluation and recorded in the source documents and in the patient's Case Report Form. Tumor assessments will be performed according to RECIST 1.1 criteria (<http://www3.cancer.gov/dip/RECIST.htm>). Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria.

15.1.1 Definitions

Evaluable for toxicity. All participants who receive at least one dose of study treatment will be evaluable for toxicity from the time of their first treatment.

Evaluable for objective response. Only those participants who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These participants will have their response classified according to the definitions stated below. (Note: Participants who exhibit objective disease progression or die prior to the end of cycle 1 will also be considered evaluable.)

Evaluable for Primary Outcome: Only patients who are randomized and have received one dose of radiation and chemotherapy will be eligible for assessment of the primary outcome (LCR, PFS). All patients who have started chemotherapy will be analyzed on an ITT for LCR, PFS, and survival.

15.1.2 Disease Parameters

Measurable disease. Measurable disease is the presence of at least one (1) lesion that can be accurately measured in at least one dimension with longest diameter ≥ 20 millimeters (mm) using conventional techniques (CT, MR1, x-ray) or ≥ 10 mm with spiral CT scan. Measurable lesions must be at least 2 times the slice thickness in mm. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Target lesions. All measurable lesions up to a maximum of 5 lesions per organ and 10 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as the reference by which to characterize the objective tumor response.

15.1.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation, using a ruler, calipers, or digital measurement tool. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the anti-tumor effect of a treatment.

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

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

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

FDG PET and PET/CT. The acquisition of FDG PET and FDG PET/CT scans should follow the NCI Guidelines for using FDG PET as an indicator of therapeutic response. Patients should avoid strenuous exercise and be on a low carbohydrate diet for 24 hours prior to the scan. Patients should fast for 4 hours or longer prior to the FDG injection and should have a serum glucose of less than 200 mg/dL at the time of FDG injection. A 10-20 mCi dose of FDG should be injected for typical adult patients. For longitudinal studies with multiple scans, particular attention should be paid to ensure consistent patient preparation and acquisition parameters between the follow-up scan and the baseline scan. When designing a study where PET scans are going to be utilized as one of the modalities to evaluate efficacy, it is important to consult with physicians in nuclear medicine in designing the appropriate criteria to be utilized.

Endoscopy, Laparoscopy. The utilization of these techniques for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in reference centers. However, such techniques may 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 subject to be considered in complete clinical response. Specific additional criteria for standardized usage of prostate-specific antigen (PSA) and CA-125 response in support of clinical trials are being developed.

Cytology, Histology. These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

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

15.1.4 Response Criteria

15.1.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions.

Partial Response (PR): At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD.

Progressive Disease (PD): At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions (new lesions must be $>$ slice thickness).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.

Unknown (UN): Assessment of target lesions cannot be made due to insufficient or unevaluable data. In this case, a concise explanation must be given.

Note: If tumor response data is missing, an overall assessment cannot be done. However, if there is missing or unevaluable data for non-target lesions, but data is available for all target lesions, the overall response for that time point will be assigned based on the sum LD of all target lesions. Additionally, the assessment of CR cannot be made if there is missing or unevaluable data for non-target lesions. In this case, the overall assessment would be PR.

15.1.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level.

Note: If tumor markers are initially above the upper normal limit, they must normalize for a subject to be considered in complete clinical response.

Incomplete Response/Stable Disease (SD): Persistence of one or more non-target lesions and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions* (new lesions must be $>$ slice thickness) and/or unequivocal progression of existing non-target lesions.

Unknown (UN): Assessment of non-target lesions cannot be made due to insufficient or unevaluable data. In this case, a concise explanation must be given.

Note: Although a clear progression of "non-target" lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed at a later time by review of the Principal Investigator (or Protocol Chair). Additionally, the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment is mandatory to differentiate between stable or progressive disease.

15.1.4.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The participant's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Patients with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response for when Confirmation is Required:
CR	CR	No	CR	≥ 4 wks confirmation
CR	Non-CR/Non-PD	No	PR	≥ 4 wks confirmation
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/Not evaluated	No	PR	
SD	Non-CR/Non-PD/Not evaluated	No	SD	Documented at least once ≥ 4 wks from baseline
PD	Any	Yes or No	PD	No prior SD, PR or CR
Any	PD*	Yes or No	PD	
Any	Any	Yes	PD	
<p>* In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.</p> <p><u>Note:</u> Participants with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "<i>symptomatic deterioration</i>". Every effort should be made to document the objective progression even after discontinuation of treatment.</p>				

For Patients with Non-Measurable Disease (i.e., Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD
Not all evaluated	No	Not evaluated

Uequivocal PD	Yes or No	PD
Any	Yes	PD
Non-CR/non-PD is preferred over stable disease for non-target disease since SD is increasingly used an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.		

15.1.5 Duration of Response

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

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

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.

15.1.6 Progression-Free Survival

Progression-Free Survival (PFS) is defined as the duration of time from start of treatment to time of objective disease progression or death.

15.2 Other Response Parameters

Pathologic Response Assessment

An exam under anesthesia (EUA) is sometimes needed to confirm pathological response of the primary site after completion of chemotherapy (cycle 3, day 21-35) in responders (complete response and partial response). In addition, follow-up endoscopic examination of any concerned sites other than the primary should also be performed, but repeat routine multiple endoscopies, *per se*, are not mandatory. The treating team (Medical oncology, Radiation oncology and Surgical Oncologist) will determine whether an EUA is required after three cycles of chemotherapy to adequately assess response. Both a superficial and a deep biopsy, if possible, can be taken from a primary site area known to have been biopsy-positive previously, preferably by the same surgeon. If uncertain, 2 to 3 biopsies from the most accessible geometrical center of the primary site region should be performed. In partial response patients, biopsies will be directed at the visible/palpable mucosal abnormality or submucosal mass. In patients with clear evidence of persistent disease at the primary site (By clinical exam and office fiberoptics), a repeat biopsy is not mandatory and is at the discretion of the treating team. Patients with an unknown primary carcinoma should not undergo an examination under anesthesia (EUA) after induction chemotherapy unless it is clinically indicated and only after discussion with overall PI. Patients who have had tonsillectomy prior to treatment do not need to have an EUA with biopsy.

Clinical Response Assessment

This is typically and routinely done in the clinic with the use of direct visualization, fiber optic examination and manual palpation.

16.0 ASSESSMENT OF QUALITY OF LIFE AND PATIENT REPORTED SYMPTOMS

Head and neck cancer often arises in cosmetically or functionally important areas. Thus, the ability to eat, speak, and breathe easily, as well as the patient's overall sense of comfort are frequently affected by these patients. In addition to these disease-specific symptoms, patients with head and neck cancer may also experience symptoms related to surgery (e.g. disfigurement) or to radiation therapy (e.g., dysphagia, xerostomia, and mucositis). These may lead to feeling of general overall sickness and can potentially result in social isolation. Patient-reported symptoms tend to be more severe than those recorded by physicians, patient reported outcome instruments are increasingly being used to measure symptom burden, functionality and quality of life. It can provide more comprehensive and improved toxicity data. Quality of life (QOL) assessment is a multi-dimensional construct that involves an individual's subjective assessment of the impact of an illness or treatment on his/her physical, psychological, social, and somatic functioning and general well-being. The European Organization for Research and Treatment of Cancer Core measure (EORTC QLQ-C30) is a well validated cancer-specific QOL scale that is used as a generic measurement for patients with cancer that in head and neck patients is used in conjunction with the site specific measurement tool EORTC QLQ H&N35. The M.D. Anderson Symptom Inventory-Head and Neck (MDASI-HN) module is a validated instrument that provides a brief measure of the symptom distress experienced by the head and neck cancer patients as a result of their disease and/or treatment. This symptom burden instrument was closely associated with the severity of radiation-induced mucositis. The MDA Xerostomia and MDADI-HN (dysphagia) questionnaires are radiotherapy/head and neck cancer directed questions which have a robust, validated assessment the specific concerns of swallowing and salivary function in head and neck cancer treated patients.

In this study, patients will complete the EORTC QLQ-C30, EORTC QLQ H&N35, MDASI-HN, the MDADI-HN (dysphagia) and xerostomia questionnaires prior to therapy and then at 3, 6, 12, 24, 60 and 120 months thereafter or in conjunction with the visits in the Follow-Up Period. During the concomitant chemo-radiation phase of treatment, all of the above questionnaires will be assessed bi-weekly. As shown in the statistical plan we will use these assessments in conjunction with adverse events assessments to compare the experiment and control arms of this study.

	Pre-Study	Induction Chemotherapy	Chemo/RT	Post-Study Follow-up
Informed Consent	To be obtained before enrollment			
EORTC QLQ-C30, EORTC QLQ H&N35	Within 10 days before registration, Or on C1D1 before treatment	Every 3 weeks (Day 1 of cycles 2 & 3 before treatment)	Weeks 2,4,6,8	3, 6, 12, 24, 60 and 120 months, or in conjunction with Folllow-up Period
MDASI-HN	Within 10 days before registration, Or on C1D1 before treatment	Every 3 weeks (Day 1 of cycles 2 & 3 before treatment)	Weeks 2,4,6,8	3, 6, 12, 24, 60 and 120 months, or in conjunction with Folllow-up Period

MDADI-HN (Dysphagia Assessment Questionnaire)	Within 10 days before registration, Or on C1D1 before treatment	Every 3 weeks (Day 1 of cycles 2 & 3 before treatment)	Weekly	3, 6, 12, 24, 60 and 120 months, or in conjunction with Follow- up Period
Xerostomia	Within 10 days before registration, Or on C1D1 before treatment	Every 3 weeks (Day 1 of cycles 2 & 3 before treatment)	Weekly	3, 6, 12, 24, 60 and 120 months, or in conjunction with Follow- up Period
Adverse Event evaluation		Every 3 weeks (Day 1 of each cycle before treatment)	Weekly	At every study visit until resolved or stable

17.0 ADVERSE EVENT REPORTING REQUIREMENTS

17.1 *Definitions*

17.1.1 Adverse Event (AE)

An adverse event (AE) is any undesirable sign, symptom or medical condition or experience that develops or worsens in severity after starting the first dose of study treatment or any procedure specified in the protocol, even if the event is not considered to be related to the study.

Abnormal laboratory values or diagnostic test results constitute adverse events only if they induce clinical signs or symptoms or require treatment or further diagnostic tests.

17.1.2 Serious Adverse Event (SAE)

A serious adverse event (SAE) is any adverse event, occurring at any dose and regardless of causality that:

- Results in death.
- Is life-threatening. Life-threatening means that the person was at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form.
- Requires or prolongs inpatient hospitalization (i.e., the event required at least a 24-hour hospitalization or prolonged a hospitalization beyond the expected length of stay). Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry are not considered SAEs if the illness or disease existed before the person was enrolled in the trial, provided that it did not deteriorate in an unexpected manner during the trial (e.g., surgery performed earlier than planned).
- Results in persistent or significant disability/incapacity. Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.
- Is a congenital anomaly or birth defect; or
- Is an important medical event when, based upon appropriate medical judgment, it may jeopardize the participant and require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive

treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Events **not** considered to be serious adverse events are hospitalizations for:

- Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures.
- Elective or pre-planned treatment for a pre-existing condition that did not worsen.
- Emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission.
- Respite care.

17.1.3 Expectedness

Adverse events can be 'Expected' or 'Unexpected.'

17.1.3.1 Expected adverse event

Expected adverse events are those that have been previously identified as resulting from administration of the agent. For the purposes of this study, an adverse event is considered expected when it appears in the current adverse event list, the Investigator's Brochure, the package insert or is included in the informed consent document as a potential risk.

Refer to Section 6.1 for a listing of expected adverse events associated with the study agent(s).

17.1.3.2 Unexpected adverse event

For the purposes of this study, an adverse event is considered unexpected when it varies in nature, intensity or frequency from information provided in the current adverse event list, the Investigator's Brochure, the package insert or when it is not included in the informed consent document as a potential risk.

17.1.4 Attribution

Attribution is the relationship between an adverse event or serious adverse event and the study treatment. Attribution will be assigned as follows:

- Definite – The AE is clearly related to the study treatment.
- Probable – The AE is likely related to the study treatment.
- Possible – The AE may be related to the study treatment.
- Unlikely – The AE is doubtfully related to the study treatment.
- Unrelated – The AE is clearly NOT related to the study treatment.

17.2 *Procedures for AE and SAE Recording and Reporting*

Reporting: Participating investigators will assess the occurrence of AEs and SAEs at all participant evaluation time points during the study.

All AEs and SAEs whether reported by the participant, discovered during questioning, directly observed, or detected by physical examination, laboratory test or other means, will be recorded in the participant's medical record and on the appropriate study-specific case report forms.

The descriptions and grading scales found in the CTEP Active Version of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized for AE reporting. The CTEP Active Version of the CTCAE is identified and located on the CTEP website at:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

All appropriate treatment areas should have access to a copy of the CTEP Active Version of CTCAE.

17.3 Reporting Requirements

Each participating investigator is required to abide by the reporting requirements set by the MSSM. The study must be conducted in compliance with FDA regulations, local safety reporting requirements, and reporting requirements of the principal investigator.

Each investigator will be responsible to report SAEs that occur at that institution to their respective IRB. It is the responsibility of each participating investigator to report serious adverse events to the study sponsor and/or others as described below.

17.4 Reporting to the Study Center

17.4.1 Serious Adverse Event Reporting

All serious adverse events that occur after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment must be reported to the MSSM Overall Principal Investigator on the local institutional SAE form for the local IRB and electronically on the eRAP CRF. This includes events meeting the criteria outlined in Section 11.1.2, as well as the following:

- Grade 2 (moderate) and Grade 3 (severe) events that are unexpected and at least possibly related/associated with the intervention.
- All Grade 4 (life-threatening or disabling) events that are unexpected or not specifically listed in the protocol as not requiring reporting.
- All Grade 5 (fatal) events while the participant is enrolled and actively participating in the trial OR when the event occurs within 30 days of the last study intervention.

Note: If the participant is in long term follow up, report the death at the time of continuing review.

Participating investigators must report each serious adverse event to the MSSM Overall Principal Investigator within 24 hours of learning of the occurrence by Fax and email. In the event that the participating investigator does not become aware of the serious adverse event immediately (e.g., participant sought treatment elsewhere), the participating investigator is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the adverse event. Report serious adverse events by telephone, email or facsimile to:

Within the following 24-48 hours, the participating investigator must provide follow-up information on the serious adverse event. Follow-up information should describe whether the event has resolved or continues, if and how the event was treated, and whether the participant will continue or discontinue study participation.

17.4.2 Non-Serious Adverse Event Reporting

Non-serious adverse events will be reported to the MSSM Overall Principal Investigator where required on the toxicity Case Report Forms.

17.5 Reporting to the Institutional Review Board (IRB)

Investigative sites within MSSM will report all serious adverse events directly to the MSSM Office for Human Research Studies

Other investigative sites should report serious adverse events to their respective IRB according to the local IRB's policies and procedures in reporting adverse events. A copy of the submitted institutional SAE form should be forwarded to:

Marshall Posner, MD 212-659-5461 marshall.posner@mssm.edu

The MSSM Principal Investigator will submit SAE reports from outside institutions to the MSSM Office for Human Research Studies according to MSSM IRB policies and procedures in reporting adverse events.

17.6 Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any subject safety reports or sentinel events that require reporting according to institutional policy.

17.7 Monitoring of Adverse Events and Period of Observation

All adverse events, both serious and non-serious, and deaths that are encountered from initiation of study intervention, throughout the study, and within 30 days of the last study intervention should be followed to their resolution, or until the participating investigator assesses them as stable, or the participating investigator determines the event to be irreversible, or the participant is lost to follow-up. The presence and resolution of AEs and SAEs (with dates) should be documented on the appropriate case report form as required and recorded in the participant's medical record to facilitate source data verification.

For some SAEs, the study sponsor or designee may follow-up by telephone, fax, and/or monitoring visit to obtain additional case details deemed necessary to appropriately evaluate the SAE report (e.g., hospital discharge summary, consultant report, or autopsy report).

Participants should be instructed to report any serious post-study event(s) that might reasonably be related to participation in this study. Participating investigators should notify the MSSM Overall Principal Investigator and their respective IRB of any unanticipated death or adverse event occurring after a participant has discontinued or terminated study participation that may reasonably be related to the study.

18 DATA AND SAFETY MONITORING

18.1 Data Reporting

18.1.1 Method

The Study team and the CCTO will collect, manage, and monitor data for this study.

18.1.2 Data Submission

The schedule for completion and submission of case report forms (paper or electronic) to the QACT is as follows:

Form/eCRF	Estimated Submission Timeline
Eligibility Checklist	Complete prior to registration with MSSM
On Study Form	Within 14 days of registration
Baseline Assessment Form	Within 14 days of registration
Treatment Form	Within 10 days of the last day of the cycle
Adverse Event Report Form	Within 10 days of the last day of the cycle
Response Assessment Form	Within 10 days of the completion of the cycle required for response evaluation
Off Treatment/Off Study Form	Within 14 days of completing treatment or being taken off study for any reason
Follow up/Survival Form	Within 14 days of the protocol defined follow up visit date or call

18.2 Independent Data Safety Monitoring Committee

Because this is a Phase III trial and Independent Data Safety Monitoring Committee (IDMC) will be required to review and monitor toxicity, accrual data from this trial and interim results on this trial. The committee will be composed of clinical specialists and a statistician with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Principal Investigator and study team and regular reports made to the TCI Data and Safety Monitoring Committee (DSMC).

The IDMC will meet semi-annually and/or more often if required to review toxicity and accrual data. Information to be provided to the committee may include: up-to-date participant accrual; all grade 3 or higher unexpected adverse events that have been reported; summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

This trial will seek to screen and consent 365 subjects, with the anticipation that 330 of these subjects will undergo TPF induction chemotherapy, and 300 will successfully complete induction therapy. Of those that

complete induction, it is anticipated that 80% (or approximately 240 subjects) will have a sufficient response to treatment as to allow for randomization in the second phase of the trial. Blinded data on LRC and PFS will be reported to the DSMC after 120 patients have been followed for 12 months after completion of all therapy and/or 200 patients have been entered.

The IDMC will include one oncologist from MSSM, unrelated to the study staff, and one each: a medical oncologist, radiation oncologist and surgical oncologist from outside institutions. An independent MSSM statistician shall be a member. The chairman of the DSMB will prepare minutes and report to the TCI DSMC. The study report will remain blinded for efficacy results unless there is sufficient reason for the IDMC to consider halting the trial, based on toxicity or an efficacy signal suggesting one of the arms is underperforming significantly. The results may then be unblinded so that a full decision can be made using all the data. It is anticipated that the control arm may have more acute toxicity than the experimental arm and thus unblinding will be necessary if acute toxicity is significantly different. This decision cannot be made with less than 120 patients randomized and followed for 12 month after completion of all therapy.

18.3 Non-MSSM Site Monitoring

Involvement in this study as a participating investigator implies acceptance of potential audits or inspections, including source data verification, by representatives designated by the MSSM Overall Principal Investigator (or Protocol Chair) or MSSM. The purpose of these audits or inspections is to examine study-related activities and documents to determine whether these activities were conducted and data were recorded, analyzed, and accurately reported in accordance with the protocol, institutional policy, Good Clinical Practice (GCP), and any applicable regulatory requirements.

All data will be monitored for timeliness of submission, completeness, and adherence to protocol requirements. Monitoring will begin at the time of participant registration and will continue during protocol performance and completion.

19 REGULATORY CONSIDERATIONS

19.1 Protocol Review and Amendments

This protocol, the proposed informed consent and all forms of participant information related to the study (e.g., advertisements used to recruit participants) and any other necessary documents must be submitted, reviewed and approved by a properly constituted IRB governing each study location.

Any changes made to the protocol must be submitted as amendments and must be approved by the IRB prior to implementation. Any changes in study conduct must be reported to the IRB. The MSSM Overall Principal Investigator (or Protocol Chair) will disseminate protocol amendment information to all participating investigators.

All decisions of the IRB concerning the conduct of the study must be made in writing.

19.2 Informed Consent

All participants must be provided a consent form describing this study and providing sufficient information for participants to make an informed decision about their participation in this study. The formal consent of a participant, using the IRB approved consent form, must be obtained before the participant is involved in any study-related procedure. The consent form must be signed and dated by the participant or the participant's legally authorized representative, and by the person obtaining the consent. The participant must be given

a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

19.3 Ethics and Good Clinical Practice (GCP)

This study is to be conducted according to the following considerations, which represent good and sound research practice:

- E6 Good Clinical Practice: Consolidated Guidance
www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM129515.pdf
- US Code of Federal Regulations (CFR) governing clinical study conduct and ethical principles that have their origin in the Declaration of Helsinki
 - Title 21 Part 11 – Electronic Records; Electronic Signatures
www.access.gpo.gov/nara/cfr/waisidx_02/21cfr11_02.html
 - Title 21 Part 50 – Protection of Human Subjects
www.access.gpo.gov/nara/cfr/waisidx_02/21cfr50_02.html
 - Title 21 Part 54 – Financial Disclosure by Clinical Investigators
www.access.gpo.gov/nara/cfr/waisidx_02/21cfr54_02.html
 - Title 21 Part 56 – Institutional Review Boards
www.access.gpo.gov/nara/cfr/waisidx_02/21cfr56_02.html
 - Title 21 Part 312 – Investigational New Drug Application
www.access.gpo.gov/nara/cfr/waisidx_02/21cfr312_02.html
- State laws
- MSSM research policies and procedures

It is understood that deviations from the protocol should be avoided, except when necessary to eliminate an immediate hazard to a research participant. In such case, the deviation must be reported to the IRB according to the local reporting policy.

19.4 Study Documentation

The investigator must prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each research participant. This information enables the study to be fully documented and the study data to be subsequently verified.

Original source documents supporting entries in the case report forms include but are not limited to hospital records, clinical charts, laboratory and pharmacy records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays.

19.5 Records Retention

All study-related documents must be retained for the maximum period required by applicable federal regulations and guidelines or institutional policies.

19.6 Multi-center Guidelines

See Multi-Center SOP in Appendix

20 STATISTICAL CONSIDERATIONS

20.1 Study Design/Endpoints

This is an open label, randomized phase III study of TPF chemotherapy followed by chemoradiotherapy. The primary endpoints are PFS and the rate of local-regional control at 3 years in patients with advanced HPV 16 and p16+ related head and neck cancer, treated with standard and reduced dose radiation. The secondary objectives include Overall Survival, toxicity of reduced radiation dose, long term toxicity of reduced radiation dose, as well as establishing biomarkers predictive of treatment outcomes and collection of tumor tissue, germline DNA and a plasma bank for future studies. The study hypothesis is that LRC and PFS at 3 years for reduced dose CRT are non-inferior to standard dose CRT.

20.2 Sample Size/Accrual Rate

We plan to screen 365 patients and recruit a total 240 HPV16+ patients to the experimental chemoradiotherapy phase of this study, which will randomize 2:1 between the experimental and standard arms, respectively. HR non-HPV16 patients will be sampled as an exploratory analysis and randomized 1:1. The plan to recruit a total of 365 patients in order to eventually randomize 240 HPV16+ responding patients between these two arms, will account for drop outs, HPV16 negative and non-HPV16/HRHPV+ PCR subjects and induction non-responders. We expect approximately 35 patients to be surgically curable, and of the remaining 330, approximately 10% or 30 to stop therapy due to toxicity. Of the remaining 300, 20% may have a poor response or be HPV16 negative and will get aggressive CRT or be randomized separately because of predicted poor survival or non-HPV16 status. The experimental and control groups will be comprised of the remaining 240 patients to be randomized 2:1 to low or standard radiotherapy. Additional patients will be screened and treated until a full 240 are randomized and receive their first radiation therapy. Patients screened and undergoing treatment with induction or assessment at the time that the first 240 have been randomized will also be randomized, leading to an indeterminate final number that will be greater than 240.

This minimal sample size of 240 will provide power of 74% and 78.5% to detect a differences of 10% between the two therapy groups in the PFS or LRC rates, respectively, at 3-years following treatment using a one-sided Type I error rate of 10%. (Bergstrahl, 1984). These calculations are based on a 3.5-year accrual period with 3 more years of follow-up. The current PFS for 3 years, based on TPF is 81% and on RTOG 0129 is 74%, hence the predicted PFS for the control arm should be 77% (average of two aggressive therapies with standard XRT) for the purposes of calculation. Based on PFS and LRC recurrences in TPF representing approximately 80% of PFS failure, the LRC rate should be 82% for the purposes of sample size determination. Power is calculated based on the log-rank test at 3-years post-therapy in all patients.

Table X. Sample size and power for 1-sided Type I error rate of 10%

Outcome	Power	Rate in Std Therapy	Margin of Non-Inferiority	Sample Size Std Therapy	Sample Size Exp Therapy
PFS	74%	77%	10%	80	160
LRC	78.5%	82%	10%	80	160

20.3 Stratification Factors

We will stratify the randomization in cohort 1 for smoking > 20 pack years and N stage N3 versus other.

20.4 Randomization Process

Randomization will be performed by Central Registration within the MSSM CCTO using an eRAP based random assignment process. Randomization will take place once the patient has completed the eligibility review for randomization and will be communicated to the site study personnel as outlined in section 6.2.

Lists of random treatment assignments will be generated by the Biostatistics Core working together with informatics personnel. For each institution participating in the study two separate randomization lists will be generated for cohort 1--- one for patients with a smoking history of ≤ 20 pack years and one for patients with a smoking history of > 20 pack years. In each list the probability of receiving the reduced dose of radiation in cohort 1 will be twice the probability of receiving the standard dose. These lists will be generated prior to opening the trial for patient enrollment. For each institution participating in the study, one randomization list will be generated for cohort 2, which will be separate from the list generated for cohort 1. In the list for cohort 2, the probability of receiving the reduced dose of radiation will be just as likely as the probability of receiving the standard dose. At the time of randomization for each patient, the eRAP system will prompt the person making the randomization to verify that all eligibility requirements have been satisfied and that informed consent has been obtained. Each person authorized to perform randomizations will be assigned a unique personal code which (s)he will enter into the database at the time of randomization. The system will capture the date and time the randomization is done, as well as the identity of the person obtaining the treatment assignment.

20.5 Analysis of Primary Endpoints

The primary endpoints are PFS and LRC at 3 years. Kaplan-Meier curves will be estimated for the standard therapy and the experimental therapy groups. Ninety-percent one-sided confidence intervals will be calculated for the differences between the cumulative PFS and between the cumulative LRC at 3 years in the standard therapy and experimental therapy groups. If the lower confidence limit for the differences is less than or equal to 0.10, the Margin of Non-inferiority, it will be concluded that the experimental treatment is non-inferior to the standard therapy (da Silva et al., 2008).

20.6 Analysis of Secondary Endpoints

The secondary endpoint of overall survival will be analyzed using Kaplan-Meier curves and a log-rank test for the difference between the two therapy groups. Five year OAS, PFS and LRC will be calculated using a log-rank test will be used to test for differences between the two treatment groups.

Toxicity is another secondary endpoint. We will compute for each arm the toxicity rate and provide the corresponding 90% confidence intervals based on the exact binomial distribution.

Reporting and Exclusions

Not Applicable.

21 PUBLICATION PLAN

The results should be made public within 24 months of the end of data collection. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes should be made public no later than three (3) years after the end of data collection.

22 REFERENCES

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23 APPENDICES

Appendix 1: Performance Status Criteria

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

Appendix 2: Video Swallowing

The video swallow study report will include the following information:

Impressions:

1. Oropharyngeal findings
 - a. Penetration-Aspiration-Scale
 - b. Severity rating of OP function
 - i. Within Normal Limits
 - ii. Mild
 - iii. Mild-Moderate
 - iv. Moderate
 - v. Moderate-Severe
 - vi. Severe
2. Cervical Esophageal findings
 - a. No stenosis
 - b. Partial stenosis
 - c. Complete stenosis

Recommendations:

1. Diet
 - a. Regular diet
 - b. Soft diet
 - c. Puree diet
 - d. Liquid diet
 - e. G-tube w/trials
 - f. G-tube, NPO
2. Liquids
 - a. Regular
 - b. Thickened
3. Therapeutic precautions/interventions
 - a. Implement postures/strategies to decrease penetration/aspiration or residue

Consider esophageal dilation Yes or No

Appendix 3: QOL Questionnaires

Name _____ Date _____ Hospital Number _____

The M. D. Anderson Dysphagia Inventory

This questionnaire asks for your views about your swallowing ability. This information will help us understand how you feel about swallowing.

The following statements have been made by people who have problems with their swallowing. Some of the statements may apply to you.

Please read each statement and circle the response which best reflects your experience in the past week.

My swallowing ability limits my day-to-day activities.

Strongly Agree Agree No Opinion Disagree Strongly Disagree

E2. I am embarrassed by my eating habits.

Strongly Agree Agree No Opinion Disagree Strongly Disagree

F1. People have difficulty cooking for me.

Strongly Agree Agree No Opinion Disagree Strongly Disagree

P2. Swallowing is more difficult at the end of the day.

Strongly Agree Agree No Opinion Disagree Strongly Disagree

E7. I do not feel self-conscious when I eat.

Strongly Agree Agree No Opinion Disagree Strongly Disagree

E4. I am upset by my swallowing problem.

Strongly Agree Agree No Opinion Disagree Strongly Disagree

P6. Swallowing takes great effort.

Strongly Agree Agree No Opinion Disagree Strongly Disagree

E5. I do not go out because of my swallowing problem.

Strongly Agree Agree No Opinion Disagree Strongly Disagree

F5. My swallowing difficulty has caused me to lose income.

Strongly Agree Agree No Opinion Disagree Strongly Disagree

P7. It takes me longer to eat because of my swallowing problem.

Strongly Agree Agree No Opinion Disagree Strongly Disagree

P3. People ask me, "Why can't you eat that?"

Strongly Agree Agree No Opinion Disagree Strongly Disagree

E3. Other people are irritated by my eating problem.

Strongly Agree Agree No Opinion Disagree Strongly Disagree

P8. I cough when I try to drink liquids.

Strongly Agree Agree No Opinion Disagree Strongly Disagree

F3. My swallowing problems limit my social and personal life.

Strongly Agree Agree No Opinion Disagree Strongly Disagree

F2. I feel free to go out to eat with my friends, neighbors, and relatives.

Strongly Agree Agree No Opinion Disagree Strongly Disagree

P5. I limit my food intake because of my swallowing difficulty.

Strongly Agree Agree No Opinion Disagree Strongly Disagree

P1. I cannot maintain my weight because of my swallowing problem.

Strongly Agree Agree No Opinion Disagree Strongly Disagree

E6. I have low self-esteem because of my swallowing problem.

Strongly Agree Agree No Opinion Disagree Strongly Disagree

P4. I feel that I am swallowing a huge amount of food.

Strongly Agree Agree No Opinion Disagree Strongly Disagree

F4. I feel excluded because of my eating habits.

Strongly Agree Agree No Opinion Disagree Strongly Disagree

Thank you for completing this questionnaire!

Date: / /
(month) (day) (year)

Study Name: _____

Protocol #:

P1:

BLACK INK PEN

Study Subject #

Revision: 07/01/05

Revision: 07/01/05

Revision: 07/01/05

M. D. Anderson Symptom Inventory - Head & Neck (MDASI-HN)

Part I. How severe are your symptoms?

People with cancer frequently have symptoms that are caused by their disease or by their treatment. We ask you to rate how severe the following symptoms have been ***in the last 24 hours***. Please fill in the circle below from 0 (symptom has not been present) to 10 (the symptom was as bad as you can imagine it could be) for each item.

Date:

--	--

 /

--	--

 /

--	--

(month) (day) (year)

study Name: _____

Subject's Initials: _____

Patient #: _____

Study Subject #

--	--	--	--

PI: _____

Revision: 07/01/06

PLEASE USE
BLACK INK PEN

	NOT PRESENT										A 10 BAD AS YOU CAN IMAGINE	
	0	1	2	3	4	5	6	7	8	9	10	
16. Your choking/coughing (food/liquids going down the wrong pipe) at its WORST?	<input type="radio"/>											
17. Your difficulty with voice/speech at its WORST?												
18. Your skin pain/burning/rash at its WORST?	<input type="radio"/>											
19. Your constipation at its WORST?												
20. Your problem with tasting food at its WORST?	<input type="radio"/>											
21. Your mouth/throat sores at their WORST?												
22. Your problem with your teeth or gums at its WORST?	<input type="radio"/>											

Part II. How have your symptoms interfered with your life?

Symptoms frequently interfere with how we feel and function. How much have your symptoms interfered with the following items in the last 24 hours:

	Did not Interfere										Interfered Completely	
	0	1	2	3	4	5	6	7	8	9	10	
23. General activity?												
24. Mood?	<input type="radio"/>											
25. Work (including work around the house)?												
26. Relations with other people?	<input type="radio"/>											
27. Walking?												
28. Enjoyment of life?	<input type="radio"/>											

Name _____ Date _____ Hospital Number _____

Xerostomia Questionnaire (XQ)

This questionnaire asks your view about your dry mouth issue. This information will help us understand how you feel about dry mouth. Please rate your response which best reflects your experience in the past week. The higher the score, the worse your dry mouth.

1. Rate your difficulty in talking due to dryness

0 ____ 1 ____ 2 ____ 3 ____ 4 ____ 5 ____ 6 ____ 7 ____ 8 ____ 9 ____ 10

2. Rate your difficulty in chewing due to dryness

0 ____ 1 ____ 2 ____ 3 ____ 4 ____ 5 ____ 6 ____ 7 ____ 8 ____ 9 ____ 10

3. Rate your difficulty in swallowing solid food due to dryness

0 ____ 1 ____ 2 ____ 3 ____ 4 ____ 5 ____ 6 ____ 7 ____ 8 ____ 9 ____ 10

4. Rate the frequency of your sleeping problems due to dryness

0 ____ 1 ____ 2 ____ 3 ____ 4 ____ 5 ____ 6 ____ 7 ____ 8 ____ 9 ____ 10

5. Rate your mouth or throat dryness when eating food

0 ____ 1 ____ 2 ____ 3 ____ 4 ____ 5 ____ 6 ____ 7 ____ 8 ____ 9 ____ 10

6. Rate your mouth or throat dryness while not eating

0 ____ 1 ____ 2 ____ 3 ____ 4 ____ 5 ____ 6 ____ 7 ____ 8 ____ 9 ____ 10

7. Rate the frequency of sipping liquids to aid swallowing food

0 ____ 1 ____ 2 ____ 3 ____ 4 ____ 5 ____ 6 ____ 7 ____ 8 ____ 9 ____ 10

8. Rate the frequency of sipping liquids for oral comfort when not eating

0 ____ 1 ____ 2 ____ 3 ____ 4 ____ 5 ____ 6 ____ 7 ____ 8 ____ 9 ____ 10

Thank you for completing this survey.

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:

--	--	--	--

Your birthdate (Day, Month, Year):

--	--	--	--	--	--

Today's date (Day, Month, Year):

31

--	--	--	--	--	--

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a <u>long</u> walk?	1	2	3	4
3. Do you have any trouble taking a <u>short</u> walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:

	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your <u>family</u> life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your <u>social</u> activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1 2 3 4 5 6 7

30. How would you rate your overall quality of life during the past week?

1 2 3 4 5 6 7

EORTC QLQ - H&N35

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:	Not at all	A little	Quite a bit	Very much
31. Have you had pain in your mouth?	1	2	3	4
32. Have you had pain in your jaw?	1	2	3	4
33. Have you had soreness in your mouth?	1	2	3	4
34. Have you had a painful throat?	1	2	3	4
35. Have you had problems swallowing liquids?	1	2	3	4
36. Have you had problems swallowing pureed food?	1	2	3	4
37. Have you had problems swallowing solid food?	1	2	3	4
38. Have you choked when swallowing?	1	2	3	4
39. Have you had problems with your teeth?	1	2	3	4
40. Have you had problems opening your mouth wide?	1	2	3	4
41. Have you had a dry mouth?	1	2	3	4
42. Have you had sticky saliva?	1	2	3	4
43. Have you had problems with your sense of smell?	1	2	3	4
44. Have you had problems with your sense of taste?	1	2	3	4
45. Have you coughed?	1	2	3	4
46. Have you been hoarse?	1	2	3	4
47. Have you felt ill?	1	2	3	4
48. Has your appearance bothered you?	1	2	3	4

Please go on to the next page

During the past week:	Not at all	A little	Quite a bit	Very much
49. Have you had trouble eating?	1	2	3	4
50. Have you had trouble eating in front of your family?	1	2	3	4
51. Have you had trouble eating in front of other people?	1	2	3	4
52. Have you had trouble enjoying your meals?	1	2	3	4
53. Have you had trouble talking to other people?	1	2	3	4
54. Have you had trouble talking on the telephone?	1	2	3	4
55. Have you had trouble having social contact with your family?	1	2	3	4
56. Have you had trouble having social contact with friends?	1	2	3	4
57. Have you had trouble going out in public?	1	2	3	4
58. Have you had trouble having physical contact with family or friends?	1	2	3	4
59. Have you felt less interest in sex?	1	2	3	4
60. Have you felt less sexual enjoyment?	1	2	3	4

During the past week:	No	Yes
61. Have you used pain-killers?	1	2
62. Have you taken any nutritional supplements (excluding vitamins)?	1	2
63. Have you used a feeding tube?	1	2
64. Have you lost weight?	1	2
65. Have you gained weight?	1	2

Appendix 5: Smoking Questionnaire for Stratification

To be Filled out by Study Personnel

Have you ever smoked? Yes No

If yes:

At what age did you begin to smoke?

Are you a Current smoker Former Smoker?

If you are a former smoker, how long ago did you stop smoking? _____ years

What is/was the total number of cigarettes packs you use/used per Day?

Do you use any other forms of tobacco? Cigars Pipe Other

For how many years did you smoke?

Have your spouse/partner ever smoked? Yes No

Calculate Pack Years (Packs/day x Years = PYR) _____

< 20 PY \geq 20 PY

Information Obtained By: _____

Appendix 6: Inclusion Exclusion Check List

See Attached File

Appendix 7: Randomization Check List

See attached File

Appendix 8: Multi-Center SOP

1. Enrollment

Bi-weekly screening/enrollment logs will be sent to MSSM coordinator via email or fax.

2. Central Registration

Upon consenting a patient in the trial, the external site coordinator will e-mail coordinator at Mt. Sinai to alert to a potential patient. Once a patient has met the eligibility criteria and is ready to enroll, the external site coordinator will fax/e-mail the eligibility checklist with lab values provided where necessary and subject registration form. The following sections in the registration form should be completed:

- a. Subject Information
- b. Study Information
- c. Screening Information

The PI/ research team at Mt. Sinai will confirm eligibility and a completed and signed registration form with subject ID # will be sent to back to the external site coordinator via e-mail. At this point, the patient can begin treatment and the coordinator can enter the patient into Erap.

3. SAE Reporting

The external site will complete and email Medwatch form 3500A, lab reports and local IRB submission to MSSM PI and MSSM Regulatory Coordinator no later than 5 business days. The PI will review the form and reports. If PI finds serious adverse event to be related to study drug it will be reported to FDA, drug sponsor, all external sites and MSSM IRB.

4. Bi-weekly teleconference

Teleconferences twice a month will be held among all the sites participating in the trial and will be a forum to discuss patient progress, enrollment, new risks, protocol amendments, and any other issues sites may be having.

5. Off Site Monitoring

Clinical trials conducted at a facility other than MSSM will be monitored by the OCR monitor- following the OCR SOP. Erap will be monitored regularly and onsite monitoring visits will occur **quarterly** depending on site's accrual.