NRG ONCOLOGY
NRG-HN001
ClinicalTrials.gov NCT02135042

RANDOMIZED PHASE II AND PHASE III STUDIES OF INDIVIDUALIZED TREATMENT FOR NASOPHARYNGEAL CARCINOMA BASED ON BIOMARKER EPSTEIN BARR VIRUS (EBV) DEOXYRIBONUCLEIC ACID (DNA)

This trial is part of the National Clinical Trials Network (NCTN) program, which is sponsored by the National Cancer Institute (NCI). The trial will be led by NRG Oncology with the participation of the network of NCTN organizations: the Alliance for Clinical Trials in Oncology, ECOG-ACRIN Medical Research Foundation, Inc., and SWOG.

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Protocol Agent/Device (10/9/14)

Agent/Device	Supply	NSC #	IND/IDE#
EBV DNA PCR	N/A	N/A	IDE# GI40026
Cisplatin	Commercially available	N/A	Exempt
5-FU	Commercially available	N/A	Exempt
Gemcitabine	Commercially available	N/A	Exempt
Paclitaxel	Commercially available	N/A	Exempt

Participating Sites
☐ U.S. Only
☐ Canada Only
☒ U.S. and Canada
☒ Approved International Member Sites

Document History

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<table>
<tr><th colspan="3">CANCER TRIALS SUPPORT UNIT (CTSU) CONTACT INFORMATION (23-Oct-2017)</th></tr>
<tr><th>For regulatory requirements:</th><th>For patient enrollments:</th><th>For study data submission</th></tr>
<tr><td>Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal:

Regulatory Submission Portal (Sign in at www.ctsu.org, and select the Regulatory Submission sub-tab under the Regulatory tab.)

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 to receive further instruction and support.

Contact the CTSU Regulatory Help Desk at 1-866-651-2878 for regulatory assistance</td><td>Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org

Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com</td><td>Data collection for this study will be done exclusively through Medidata Rave. Please see the data submission section of the protocol for further instructions.</td></tr>
<tr><td colspan="3">The most current version of the study protocol and all supporting documents must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' web site is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password.</td></tr>
<tr><td colspan="3">For clinical questions (i.e. patient eligibility or treatment-related): Contact the Study PI of the Lead Protocol Organization.</td></tr>
<tr><td colspan="3">For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or e-mail:
CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.</td></tr>
<tr><td colspan="3">The CTSU Website is located at https://www.ctsu.org.</td></tr>
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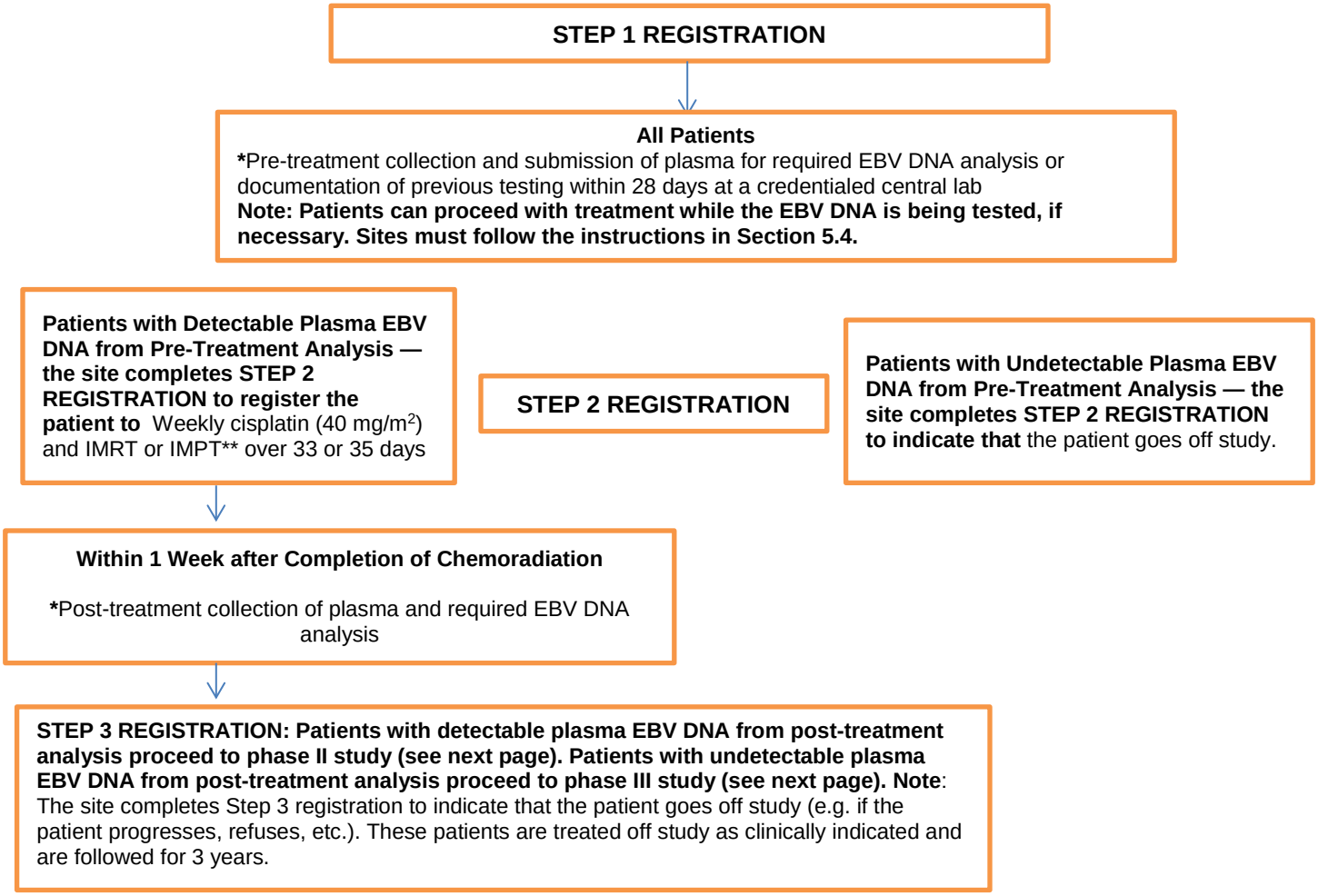
Randomized Phase II and Phase III Studies of Individualized Treatment for Nasopharyngeal Carcinoma Based on Biomarker Epstein Barr Virus (EBV) Deoxyribonucleic Acid (DNA)

SCHEMA (04May2017)



* Sites are required to complete to Step 1 registration before submitting specimens for EBV DNA analysis. Plasma will be collected from all patients for the mandatory plasma EBV DNA testing at pre-treatment and within 1 week after concurrent chemoradiation but prior to the start of adjuvant chemotherapy. Blood also will be collected for translational science from patients consenting to participate. See Section 10.0 for details. For patients who have detectable plasma EBV DNA tested at one of the credentialed central labs (listed on the EBV DNA Testing Specimen Transmittal form) within 28 days prior to Step 1 registration: that test result can be used for eligibility without the need for re-testing. To use this test result for eligibility, the central lab must enter the test result through the pathology portal, and the site must follow the instructions in Section 5.4. **Note: If the patient needs to start chemoradiation prior to the results of the pre-treatment plasma EBV DNA being known, then sites must follow the instructions in Section 5.4.**

** IMRT or IMPT over 33 or 35 fractions: PTV69.96 or 70 Gy; for the GTV69.96 or 70 Gy; PTV59.4 or 56 Gy for the high risk CTV59.4 or 56 Gy; PTV54 for the low risk CTV54.12 Gy. See Section 5.0 for credentialing required prior to patient registration. See Section 7.0 for details of drug therapy.

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Randomized Phase II and Phase III Studies of Individualized Treatment for Nasopharyngeal Carcinoma Based on Biomarker Epstein Barr Virus (EBV) Deoxyribonucleic Acid (DNA)

SCHEMA (Continued)

STRATIFY	**N Stage** 1. N0-1 2. N2-3 **T Stage** 1. T1-2 2. T3-4 **Zubrod Performance Status** 1. 0 2. 1	**RANDOMIZE**	**Randomized Phase II: Detectable Plasma EBV DNA Cohort** **Arm 1** (Control Arm, "PF"): Cisplatin (80 mg/m^2) and 5-FU (1000 mg/m^2/d x 4 d IVCI) Every 28 days for 3 cycles beginning 4 weeks after completion of radiation **Arm 2** (Experimental Arm, "GT"): Gemcitabine (1000 mg/m^2) days 1 and 8 and Paclitaxel (80 mg/m^2) days 1 and 8 every 21 days for 4 cycles beginning 4 weeks after completion of radiation

STRATIFY	**N Stage** 1. N0-1 2. N2-3 **T Stage** 1. T1-2 2. T3-4 **Zubrod Performance Status** 1. 0 2. 1	**RANDOMIZE**	**Phase III: Undetectable Plasma EBV DNA Cohort** **Arm 3** (Control Arm, "PF"): Cisplatin (80 mg/m^2) and 5-FU (1000 mg/m^2/d x 4 d IVCI) Every 28 days for 3 cycles beginning 4 weeks after completion of radiation **Arm 4** (Experimental Arm): Observation

Patient Population: (See Section 3.0 for Eligibility)
Biopsy proven (from primary lesion and/or lymph nodes) diagnosis of stage II-IVB non-metastatic cancer of the nasopharynx; detectable pre-treatment plasma EBV DNA

Required Sample Size: **Randomized phase II: 126**
Phase III: 632

1.0 INTRODUCTION

1.1 Background (04May2017)

Based on the U.S. Intergroup 0099 trial, concurrent high dose cisplatin (CDDP; 100 mg/m^2 every 3 weeks for 3 cycles) and radiotherapy (RT) followed by adjuvant CDDP (80 mg/m^2) and 5-Fluorouracil (5-FU; 1000 mg/m^2 over 4 days every 28 days for 3 cycles) is a current standard of care for patients with loco-regionally advanced nasopharyngeal carcinoma (LA-NPC) (Al-Sarraf 1998). However, it is worth noting that Intergroup 0099 was initially criticized due to the poor results noted for the control (RT alone) arm and may not be an accurate reflection of outcomes of World Health Organization (WHO) type II and III patients, as a third of the patients in this trial had the type I histology, which is thought to be less radiosensitive. The results of the Intergroup 0099 trial have since been replicated in countries in which NPC is endemic. Wee, et al. (2005) conducted a trial of virtually identical design to the U.S. Intergroup study in Singapore and validated the U.S. findings. The Hong Kong NPC study group also have recently reproduced the U.S. Intergroup study design in NPC patients and found substantial improvements in failure-free and PFS with a trend towards improvement in OS (Lee 2005b; Lee 2011). Therefore, the U.S. Intergroup regimen remains a current accepted standard of care.

Over the past decade, advances in radiation techniques, such as IMRT, have allowed for precise targeting of the tumor while significantly reducing the dose to the surrounding normal tissues resulting in improved patient quality of life (Xia 2000). Several randomized trials have shown the benefits of IMRT in terms of salivary preservation when compared to conventional RT techniques (Kam 2003; Pow 2006). A recent phase III trial from China of over 600 patients showed that the benefits of IMRT were not limited to decreasing toxicities but also improved loco-regional recurrence-free survival when compared to conventional RT (Peng 2012). The pooled results from several single institutions as well as a trial conducted by the Radiation Therapy Oncology Group (RTOG 0225) have consistently shown excellent loco-regional control in excess of 90%, and today distant recurrences are the most common site of recurrence after combined concurrent chemoradiation followed by adjuvant chemotherapy (Lee 2002; Lee 2009). The distant metastasis rates can be as high as 35%. More effective systemic therapy for distant disease is needed.

Proton beam therapy has been used for the treatment for NPC with results comparable to those of IMRT (Chan 2012: Lewis 2016). In a prospective phase II trial by the Massachusetts General Hospital, double-scattering proton beam therapy has been shown to result in a locoregional control rate of 91% in patients with Stage III-IV NPC (Chan 2012). Intensity-modulated proton therapy (IMPT) is a powerful delivery technique which achieves comparable target dose as intensity-modulated radiation therapy (IMRT). IMPT has been recently used in the treatment of NPC (Lewis 2016). For this current trial, given the promising results for IMPT in NPC, IMPT will be allowed as a radiation modality in this trial. This should not affect the primary endpoint as both IMPT and IMRT are considered to be different modes of radiation therapy delivery but without evidence of difference in tumoricidal killing effect between them. Furthermore, as the quality of life and cost-effectiveness endpoints in this study are built around the detection of differences resulting from systemic therapy administration, these should also not be affected. The overall quality of life hypothesis is related to survival and EBV response and is not radiation-specific. The hearing quality of life endpoint is controlled to account for doses to the inner ear and is focused on the different effects of chemotherapy. Finally, the peripheral neuropathy and cost-effectiveness endpoints are only dependent on differences in chemotherapy.

When examining the results of past trials, due to the inclusion of 2 variables, namely concurrent and adjuvant chemotherapy on the backbone of definitive RT, it is not possible to parse the relative contribution of each component to the improved outcomes. It is well accepted that chemotherapy delivered concurrently with RT is the most significant contributor to improvement in loco-regional control and overall survival for LA-NPC based on published meta-analyses. In addition, at least 2 small randomized studies have shown that the addition of concurrent chemotherapy improved PFS (and OS in a subgroup of patients) with LA-NPC over radiation alone, and in both studies, adjuvant chemotherapy was not employed (Lin 2003; Chan 2002).

The extent to which adjuvant treatment can influence distant relapse rates remains uncertain. The feasibility of adjuvant CDDP and 5-FU is problematic as only 50-60% of the patients enrolled in past trials were able to complete the prescribed regimens. The question of the benefit of adjuvant chemotherapy in LA-NPC was raised by a recent randomized trial from China (Chen 2012). Chen, et al. (2012) compared RT with weekly CDDP followed either by 3 cycles of CDDP and 5-FU or no adjuvant treatment in 508 patients and reported no statistically significant improvement in either PFS or OS with adjuvant chemotherapy. However, numerically, the results favored the adjuvant chemotherapy arm with a 2% absolute difference in OS, failure-free survival (FFS, p=0.13), and distant failure-free survival (DFFS, p = 0.12) at 2 years. Unfortunately, since this trial was not designed as a non-inferiority trial against the current standard, it cannot be definitively concluded that adjuvant chemotherapy is of no value in LA-NPC. One possible explanation for the lack of adjuvant chemotherapy effect is that only 63% of the patients completed the adjuvant therapy in this trial. This low adjuvant therapy completion rate is consistent with what had been observed in other NPC trials using adjuvant CDDP and 5-FU, suggesting that it is still not feasible to administer planned doses of CDDP and 5-FU despite the use of a more tolerable concurrent weekly cisplatin. A second possibility is that adjuvant CDDP and 5-FU are inherently of marginal effectiveness against NPC because the fraction of cells sensitive to CDDP have already been killed during the concurrent phase of treatment and therefore, continuation of CDDP in combination with 1 new agent was not highly effective. A final possibility is that because outcomes with concurrent chemoradiation are very good for most patients, it is difficult to demonstrate the benefit of adjuvant chemotherapy in an unselected group of LA-NPC patients and that there might be a subset of patients for whom adjuvant chemotherapy will provide substantial benefit.

Recent exploratory analyses of 2 large NPC trials from Hong Kong have shown that the use of adjuvant chemotherapy reduced distant metastasis, and that the number of delivered cycles (3-4 versus 0-1) was critical for decreasing distant failures (Lee 2011b). Lin, et al. (2004) on subsequent re-analysis of their randomized NPC trial in Taiwan showed that the benefit of concurrent chemoradiation alone without adjuvant chemotherapy was not observed in patients who were at very high risk for developing distant metastasis. Lastly, although randomized NPC trials that compared concurrent chemoradiation with no adjuvant chemotherapy to RT alone have shown improvement in OS, a closer look at these trials has shown inadequate control of distant disease. Therefore, the key issue is to select the most appropriate NPC patients at high risk for distant treatment failure and treat them with the most appropriate adjuvant chemotherapy regimen.

The RTOG recently reported the results of a phase II trial, RTOG 0615, which incorporated bevacizumab each time chemotherapy was given into the Intergroup 0099 chemoradiation regimen (Lee 2012). Although the data have shown that the addition of bevacizumab to standard chemoradiation might delay the progression of subclinical distant disease, the feasibility of 3 cycles of adjuvant CDDP and 5-FU chemotherapy was low at 47%. Lastly, the data using bevacizumab to treat distant disease for other disease sites is not as convincing as we once thought (Kelly 2012; Miller 2007; Kindler 2012). Therefore, there is very little enthusiasm for the incorporation of bevacizumab in the treatment of NPC. Furthermore, our Asian colleagues who will enroll the majority of NPC patients on this trial have reported that it is not feasible to deliver bevacizumab to their NPC patients (personal communication, Chan 2012).

Of note, since the ability to deliver the prescribed adjuvant chemotherapy is poor, one logical strategy is to alter the sequencing from concurrent-adjuvant to induction-concurrent, since the induction sequence is substantially better tolerated. The results from a recently published phase II randomized trial comparing induction chemotherapy (CDDP, epirubicin, and paclitaxel) followed by concurrent chemoradiation (CDDP) versus concurrent chemoradiation (CDDP) failed to show any difference in FFS and OS at 3 years (Fountzilas 2012). Furthermore, recent reported results of 2 phase III non-NPC head and neck squamous cell carcinoma trials, DECIDE and PARADIGM, showed that that induction chemotherapy followed by concurrent chemoradiation was not

superior to concurrent chemoradiation alone in patients with loco-regionally advanced disease who were not otherwise stratified by risk, since no such prognostic markers exist for non-HPV, patients (Haddad 2012; Cohen 2012). To definitively test this chemotherapy sequence question, several investigators are currently conducting phase III trials (Hong Kong, Singapore, and GORTEC) aiming to test whether induction chemotherapy followed by concurrent chemoradiation is better than concurrent chemoradiation either alone or followed by adjuvant chemotherapy for LA-NPC.

Given the challenges of delivering full dose chemotherapy in addition to concurrent chemoradiation (whether induction or adjuvant) in an unselected group of patients and the robust data in using post-chemoradiation plasma EBV DNA for identifying patients at high risk of relapse, NRG Oncology has decided not to pursue the induction route in an unselected population of patients with loco-regional NPC. Instead, we are proposing to focus on determining which patients need adjuvant chemotherapy after concurrent chemoradiation using plasma EBV DNA as a biomarker and then asking whether treatment regimens other than the Intergroup 0099 standard of care will benefit this subset of patients at risk for recurrence.

1.2 Rationale for Incorporating the EBV DNA Biomarker in the Treatment of NPC

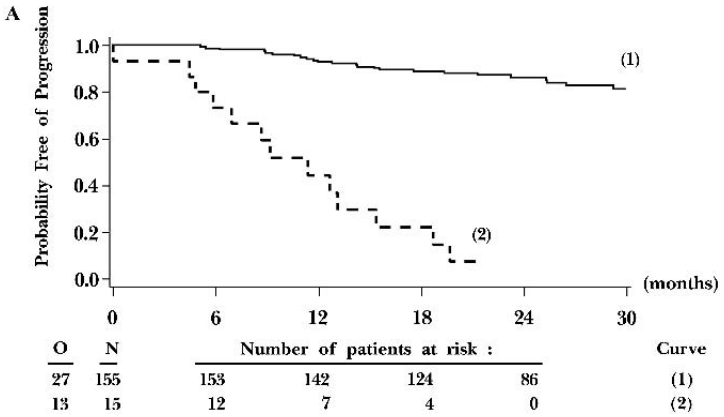
NPC, in particular undifferentiated and poorly differentiated subtypes, is unique among head and neck cancer in its association with the Epstein-Barr virus (EBV) (Liebowitz 1994). Real-time polymerase chain reaction (PCR) technology, can quantitatively detect circulating EBV DNA in the plasma in > 95% of the NPC patients (Lo 2000c). Tumor cells are hypothesized to release EBV DNA directly into the circulation such that the EBV DNA level reflects tumor burden and microscopic residual disease after RT (Lo 1999; Lo 2000; Lo 2000c). Multiple studies have demonstrated an association between the level of circulating EBV DNA and disease stage, tumor recurrence, and patient survival after chemoradiation (Lo 2000; Lo 2000c; Lo 1999b). Therefore, plasma EBV DNA analysis is a valuable tool in monitoring response to therapy for NPC.

Pre-treatment EBV DNA in plasma has been proven to correlate with cancer stage, clinical outcome, and prognosis in patients with endemic NPC (Lo 2000; Lo 2000c; Lo 1999b). However, post-radiation plasma EBV DNA has an even better correlation with prognosis and has been used to monitor recurrence after definitive therapy (Lin 2004b; Hong 2004; Chan 2002b; Le 2005; Wang 2012). Rising post-treatment plasma EBV DNA has been shown to predate clinical recurrence by 3 to 7 months (Lo 2000b; Ngan 2001; Chan 2004; Kondo 2004). Undetectable levels of plasma EBV DNA are observed in patients who remained in remission.

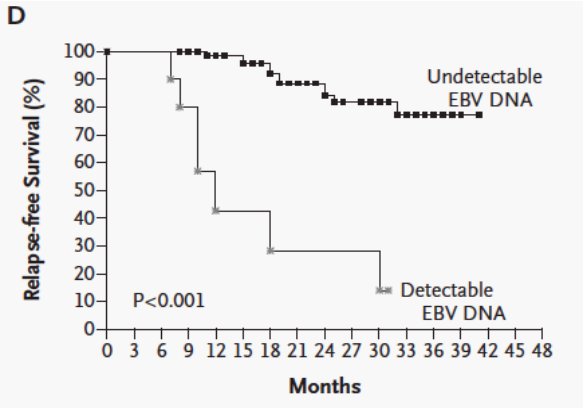
In a large (n=170) NPC study in which most patients were treated uniformly with definitive RT (with only 15 patients also receiving weekly CDDP at 40mg/m^2 during RT), the levels of post-treatment plasma EBV DNA strongly predicted for progression-free survival (PFS) ($p<0.001$) and OS ($p<0.001$), and this post-treatment EBV DNA dominated the effect of pre-treatment EBV DNA. The 1-year PFS was 93% among patients with post-treatment EBV DNA ≤ 500 copies/mL, and 48% for those with > 500 copies/mL (Figure 1A, Chan 2002). Two other studies also showed the prognostic significance of post-treatment EBV DNA, and both studies used DNA detectability (any copy number above 0) as a cut-point. Le, et al. (2005) showed that any detectable post-treatment EBV DNA levels after completion of RT or chemoradiation was highly significant for predicting treatment outcomes for 58 NPC patients, and this was independent of stage or the pre-treatment EBV DNA levels. The 2-year freedom from relapse rate was 92% versus 37% for patients with undetectable versus detectable levels. Similar to studies by other investigators, EBV DNA levels were detected several months prior to documentation of tumor recurrence. In another NPC RT study (Lin 2004; n=99) in which all patients also received neoadjuvant chemotherapy followed by RT, the investigators also showed that NPC patients with persistently detectable plasma EBV DNA had significantly worse OS ($p<0.001$) and relapse-free survival (RFS; $p<0.001$) than patients with undetectable EBV DNA 1 week after the completion of RT. Extrapolating from the curves in Figure 1B, the 2-year RFS was approximately 85% for patients with undetectable versus approximately 28% for those with a detectable post-treatment level. In a validation study of 111 patients treated uniformly with induction chemotherapy followed by RT, Lin, et al. confirmed their

initial report that post-treatment EBV DNA was the strongest prognostic factor in this patient group. The 2-year RFS was approximately 90% for patients with undetectable level versus 28% for those with detectable level (Figure 1C, Wang 2012). Table 1 summarizes survival results by post-treatment EBV DNA level in the published literature. One question that has come up is whether there is a significant difference in the relapse rate for the 2 different cut-points (500 versus 0 copy/mL) that have been used in the literature for classifying high-risk patients based on post-radiation EBV DNA level. The data shown in Table 2 suggest that there is no significant difference in the rate of distant relapse, which is the predominant pattern relapse of these patients, for the different cut-points (courtesy JC Lin).

A. Progression-free survival in 170 LA-NPC patients by post-treatment plasma EBV DNA



B. Relapse-free survival in 99 LA-NPC patients by post-treatment plasma EBV DNA



C. Relapse-free survival in the 111 patient validation group confirming the results previously reported in Figure 1B

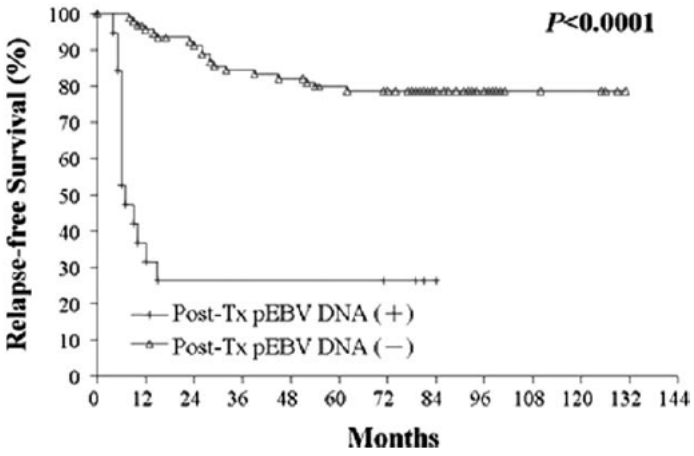


Table 1: Summary of prognostic effects of post-treatment EBV DNA in the literature

Series	# Pts	Stage	Treatment	Cutoff	OS	Other survival
Chan 2002	170	I-IV	RT±Ch	500	1yr 76% vs. 97%	1y PFS 48% vs. 93%
Le 2005	46	II-IV	RT±Ch	0	2yr 55% vs. 94%	2yr FFR 37% vs. 92%
Lin 2007	152	II-IV	CCRT	0	5yr 39% vs. 83%	5yr RFS 27% vs. 83%
Hou 2011	69	III-IV	RT±Ch	0	5yr 50% vs. 91%	
Lin 2004	99	III-IV	IndCT+RT	0	2yr 56% vs. 97%	2yr RFS 29% vs. 84%
Lin 2012*	210	II-IV	IndCT+RT	0	5yr 33% vs. 79%	5yr RFS 23% vs. 76%

* Including the 99 patients from Lin 2004

Table 2: Effects of the Plasma EBV DNA in Predicting Distant Failures (n=210, Courtesy JC Lin)

Post-Treatment Plasma EBV DNA Cutoff	Percent Distant Failure
1000	22.5
100	20.2
10	18.6
0	18.3

Based on these data, Chan, et al. (2012) are presently conducting a prospective randomized phase II study testing the efficacy of adjuvant gemcitabine (1000 mg/m^2) and cisplatin (40 mg/m^2) on days 1 and 8 every 21 days for 6 cycles compared to observation alone in patients with detectable EBV DNA after concurrent chemoradiation with weekly cisplatin (40 mg/m^2/week). From the interim results of this study, approximately 30% (157 out of 514) patients had detectable EBV DNA after concurrent chemoradiation, and half of these patients (15%) were eligible and randomized to adjuvant chemotherapy or observation (Chan 2012). Based on these data, we plan to use any detectable EBV DNA as the cut point for risk stratification (Please see rationale for the randomized study below). We also estimate that somewhere between 15-30% of enrolled patients will fall into the high-risk group.

A question was raised as to whether all NPC patients enrolled on this study have EBV positive tumors based on EBV (Epstein-Bar Virus)-Encoded RNA (Ribonucleic Acid) In Situ Hybridization (EBER ISH). Unlike the U.S. NPC cohort in which up to 20% of the patients are EBV negative, patients with NPC in the Asian countries are almost exclusively EBV positive. As a result, EBER ISH is not routinely performed on primary tumor tissue in the Asian countries. The overall sensitivity of detecting EBV DNA in the plasma of patients with EBV(+) NPC has been reported to be 98% of the stage III/IV tumors, which supports the assumption that the tumor tissues of almost all NPC patients in Hong Kong are positive for EBV (Leung 2004; Lo 1999). In addition, the false positive detection rate for circulating EBV DNA in healthy volunteers without NPC is < 2% (Leung 2004); therefore, circulating EBV DNA can be attributed to the presence of an EBV+ NPC tumor. Based on these data, we will limit our trial enrollment only to NPC patients with detectable circulating EBV DNA at diagnosis (pre-treatment). We will not require EBV testing to be performed on the tumor tissue because EBV negative NPC will not have circulating EBV DNA for detection.

1.3 Rationale for EBV DNA Harmonization Study (04May2017)

In an ideal setting, every center participating in this study would send their samples to a single CLIA certified center for central testing of EBV DNA. The Study Chairs have extensively investigated this approach and found that it would be impossible for several Asian centers to do

this. The cost of shipping fresh plasma samples on dry ice to the U.S. for every single enrolled patient in Asia is high and prohibitive. Moreover, several Asian centers are highly restrictive in allowing patient plasma samples to be shipped out of their countries, as these centers will require not only institutional approval but also central government approval. Nonetheless, these centers are outstanding, fully accredited NRG Oncology members in good standing and are enthusiastic about this study. These centers treat a high percentage of the world's cases of NPC, and thus, it is appropriate that they engage in this biomarker-driven trial, firstly for success of the study, but more importantly, to demonstrate future applicability of this study's results in the real world.

These considerations led the Study Chairs to initiate a harmonization process across clinical laboratories in different countries for measurement of plasma EBV DNA. The harmonization process will allow a uniform approach in the detection of plasma EBV DNA by investigators around the world in their respective laboratories. Under the leadership of Quynh-Thu Le, MD, an international collaboration study to harmonize the quantitative plasma EBV DNA assay for a biomarker-guided NPC study was completed. Four centers participated in this study: Stanford University (Clinical Laboratory Improvement Amendments, CLIA certified), Chinese University of Hong Kong, National Taiwan University, and Chung Gung University. The clinical laboratories of these Asian sites also had to undergo a rigorous accreditation process similar to the U.S. CLIA certification process. Pre-harmonization, there was a large variability in detecting and measuring plasma DNA levels among the 4 labs using 40 plasma samples from patients with either newly diagnosed or treated NPC. The intraclass correlations for each site when compared to the index site (SU) were 0.62 (95% CI: 0.39-0.78), 0.70 (0.50-0.83) and 0.59 (0.35-0.76). During harmonization, the largest variability noted was the use of different PCR master mix and calibrator sets, exceeding that of interoperator variability, which were standardized. Post-harmonization, the intraclass correlation for each site when compared to the index site improved to 0.83 (0.5-0.95), 0.95 (0.83-0.99) and 0.96 (0.86-0.99), respectively.

In addition, testing of un-infected plasma samples with different concentrations of EBV DNA added, which closely resembled fresh plasma samples, showed that correlations were > 0.99 ($p<0.0058$) between Stanford and the other 3 labs.

We also have established the detection limit of this assay for all involved laboratories. For this study, we analyzed 10-20 replicates of diluted DNA from the Namalwa cell line at a concentration of 0.5, 1.25, 2.5, 5, 25 and 100 copies/reaction. Although the assay showed positive signals in several replicates at concentrations below 5 copies/reaction, the coefficient of variation (CV) for the number of PCR threshold cycle (Ct) was greater than the 10% that is normally accepted for a clinical test. At 5 copies/reaction, the CV was consistently less than 10% for all 4 sites. However, even at these low CVs, the standard deviation (SD) for Ct can be up to 1.1 cycles. If we use a fixed Ct cut-point (mean or median value), up to ~50% of the samples having that concentration would be falsely excluded. Therefore, the initial plan was to use the mean Ct value + 2 standard deviations (SDs) at the concentration of 5 copies/reaction as a cutoff for defining a detectable level in the subsequent clinical trial. Theoretically, this would include 95% of the samples having an actual concentration of 5 copies/reaction, which translated to 60 copies/ml. This detection limit was originally used to assign patients into either low or high-risk for randomization in the first year. However, at the recommendation of the FDA, in order to further reduce the chance of having false negative results, we have modified our protocol to report any exponential curve that crosses the defined fluorescence threshold as detectable.

The harmonization study showed that it was important to harmonize the plasma EBV DNA detection assay for all clinical labs (Le 2012). Going forward, all clinical labs will use the same PCR protocol for the assay. In addition, if new labs were to participate, a process is now in place for credentialing these labs for EBV DNA measurement.

1.3.1 EBV DNA Measurement Procedure

- **DNA Extraction** will be performed using the ***QIAsymphony DSP Virus/Pathogen Midi kit*** (Qiagen Cat. 937055) on the QIAsymphony Extraction Instrument according to the

manufacturer's instructions. DNA extraction may also be performed using the ***QIAamp DNA Blood Mini Kit*** (Qiagen, Cat. 51304 (50) or 51306 (250)) following the manufacturer's instructions.

- **Real-Time PCR**: DNA samples are tested for EBV DNA using a real-time PCR targeting the *Bam*HI-W fragment region of the EBV genome. Assay primers and probes are shown in the table below. ***2X TaqMan reagent*** (Roche, Cat. NO. 04673450001) must be used as PCR mastermix. Thermal cycling will be initiated with an initial denaturation step of 10 min at 95°C, and then **45** cycles of 95°C for 15 seconds and 56°C for 30 seconds will be carried out.

Name	Sequence	Forward/reverse/probe
W-44F	CCCAACACTCCACCACACC	Forward primer
W-119R	TCTTAGGAGCTGTCCGAGGG	Reverse primer
W-67T	CACACACTACACACACCCACCCGTCTC	Probe (Reporter: FAM; Quencher: TAMRA)

- **Calibrates:** Calibration materials are available from Dr. Allen Chan's lab (Chinese University, Hong Kong) and Dr. Pinsky's lab (Stanford University, U.S.A.) to generate standard curves for quantitation.

  The Hong Kong calibrates are composed of DNA extracted from the Namalwa cell line. The Stanford calibrates are comprised of a bacterial plasmid containing the BamHI-W target sequence and are harmonized to the Namalwa copy. Either set of calibrates may be used. Calibrate aliquots have lot-specific concentrations that will be provided by Hong Kong or Stanford.

- **Cut-Point Identification**: Any exponential curve that crosses the defined fluorescence threshold (as described in the instructions for use) prior to the completion of cycling will be considered detected. This cut-point was selected in response to FDA concerns regarding false-negatives. Plasma samples meeting this threshold will be regarded as having a detectable level of EBV DNA and will be reported as "Detected". Quantitative values in copies/mL plasma will be collected for future analysis but will not be utilized for the protocol.

1.4 Rationale for Concurrent Weekly Cisplatin Chemotherapy (3/4/15)

Since the publication of the Intergroup 0099 trial, the use of cisplatin (100 mg/m^2 every 3 weeks) concurrently with RT has become an accepted standard of care approach for LA-NPC (NCCN v. 2, 2010). However, many LA-NPC patients cannot tolerate 100 mg/m^2 cisplatin chemotherapy, and as cited above, in the U.S. Intergroup trial, in which 300 mg/m^2 (three 100 mg/m^2 doses) was the intent, only 63% of the patients received 3 cycles of CDDP concurrent with RT. This lack of feasibility beyond 200 mg/m^2 administered in high doses every 3 weeks during RT is a consistent theme across trials using high-dose CDDP with RT (Lee 2011; Wee 2005). It is worth noting that the CDDP regimen used by Wee, et al. was 25 mg/m^2 daily x 4 days, 3 times during RT, supporting the notion that high-dose bolus cisplatin is not necessary to obtain a survival advantage over RT alone. Lin and colleagues also have demonstrated a robust survival advantage (72% versus 54% 5-year OS) for the combination of cisplatin and 5-FU (PF) given concurrently with RT in NPC patients, and in this case, the CDDP was administered as 80 mg/m^2 in a continuous infusion over 96 hours during weeks 1 and 5 of RT. (Lin JC, 2003) Weekly cisplatin has been investigated in several doses/schedules. Several trials comparing RT alone to RT + weekly cisplatin (40 mg/m^2/w) have demonstrated survival advantages to the weekly concurrent CDDP approach (Chan 2002b; Chen 2008; Qi, 2011). One trial also has demonstrated an OS advantage for a concurrent weekly CDDP dose of 30 mg/m^2 (Chen 2011). It also has been noted that the cumulative dose of CDDP during RT is an independent prognostic factor for NPC patients (Loong 2012). What all of the above trials have in common (as do other positive chemoradiation trials) is that a cumulative dose of 200 mg/m^2 of CDDP, administered concurrently with RT according to 1 of several schedules (high-dose bolus, by infusion, low-dose weekly) is associated with survival improvement. There are no data to support claims of superiority of any particular administration schedule in this setting.

We conclude from these data that the major determinant of benefit of CDDP concurrent with RT is a cumulative dose of at least 200 mg/m^2 and that the schedule of administration of CDDP during RT is less relevant. A weekly single-agent cisplatin regime is more attractive as it seems to avoid toxicities such as hearing loss and renal damage associated with 100 mg/m^2 dosing and based on prior trial experience, is more feasible. Based on this, we propose using weekly cisplatin at 40 mg/m^2 as the backbone for concurrent chemoradiation in this trial. This dosing in NPC patients has been shown to be very feasible, with greater than 90% of all treated patients receiving at least a cumulative dose of 200 mg/m^2 when treated with 40 mg/m^2 weekly with radiation in 2 large studies (Chen 2008; Hui 2009). While there are some data with lower doses of CDDP administered weekly, such as 30 mg/m^2, many of these patients had earlier stage disease (Chen 2012; Qi 2011). Because treating with 30 mg/m^2 or less weekly is less than a cumulative 200 mg/m^2 dose and because the comparative efficacy data in local-regionally advanced NPC for weekly cisplatin dosing with RT versus RT alone is primarily at the 40 mg/m^2 dose, we have chosen this dose regimen rather than a lower and potentially less toxic dosing plan.

1.5 Rationale for Choosing Gemcitabine and Paclitaxel as Adjuvant Chemotherapy for Loco-Regionally Advanced NPC at High Risk of Failure

1.5.1 Taxanes

Taxanes are among the most active anti-cancer agents available for squamous cell carcinoma of the head and neck (SCCHN), with single agent response rates of 40% or higher reported in patients with prior platinum exposure (Dreyfuss 1996). The strategy of using a taxane and cisplatin combination has been tested in NPC. The combination of docetaxel 75 mg/m^2 plus cisplatin 75 mg/m^2 achieved a response rate of 63% in patients with metastatic NPC (Chua 2005). Even in patients with metastatic NPC whose tumors have progressed on prior palliative cisplatin-containing chemotherapy, response rates of 37% with single agent docetaxel have been seen (Ngeow 2011). While there are no direct comparisons between cisplatin and 5-FU versus cisplatin and docetaxel, indirect comparisons suggest that their activity against NPC is at least equivalent (Xie 2007). A randomized phase II trial of cisplatin-based concurrent chemoradiation with or without neoadjuvant cisplatin and docetaxel suggested a dramatic improvement in 3 year PFS (88 vs. 60%) and OS (94 vs. 68%) with the cisplatin and docetaxel arm (Hui 2009). Phase III trials of docetaxel-containing neoadjuvant studies in NPC are currently enrolling in Europe and Asia.

Paclitaxel is very active against NPC as well. In the metastatic setting, single agent response rates of 22% have been reported (Au 1998). The combination of paclitaxel and carboplatin in patients with metastatic NPC has delivered response rates of 59-75% (Tan 1999; Yeo 1998) and the combination of paclitaxel and cisplatin in the induction setting in NPC patients is very active, with overall response rates of 80% reported (Mostaga 2006). Therefore, based upon single agent and combination agent activity and safety data of the taxanes in patients with NPC and based on safety data in the post-RT setting in many cancer types, further study of the taxanes in patients with NPC is warranted. We know of no data which support the choice of paclitaxel or docetaxel as the superior agent in this setting, so we have chosen to incorporate paclitaxel, since it is generically available globally, while the access to docetaxel is more limited, especially in Asian countries.

1.5.2 Gemcitabine

Gemcitabine has been studied extensively in patients with NPC. As a single agent, response rates of 30% are typical in patients with recurrent disease, and a study of patients with pre-treatment cisplatin demonstrated a response rate of 43% (Ma 2002; Foo 2002; Zhang 2008). The combination of cisplatin and gemcitabine in NPC delivers response rates of 64% in patients with metastatic recurrent disease. There are several clinical trials studying adjuvant gemcitabine plus cisplatin in patients with loco-regionally advanced NPC. A large phase II effort by AT Chan and colleagues (2012) in Hong Kong using gemcitabine 1000 mg/m^2 and cisplatin 40 mg/m^2 on days 1 and 8 every 21 days for 6 cycles following chemoradiation had demonstrated that it is feasible to give a gemcitabine-containing combination after RT to NPC patients (Chan 2012). The safety data for this trial, demonstrated that 56% of patients receiving adjuvant gemcitabine and cisplatin

completed 6 cycles, and 65% completing 5 cycles, suggesting that this doublet may be more feasible than the cisplatin and 5-FU adjuvant treatment used in the U.S. Intergroup study in which only 55% could complete 3 cycles. It is also notable that no radiation recall from gemcitabine-based adjuvant treatment was seen in the Chan study. Gu, et al. (2012) have demonstrated that gemcitabine and CDDP incorporated into a sequential chemoradiation plan for NPC patients substantially improved response rates and disease-free survival (DFS) and OS compared in a randomized controlled trial to sequential chemoradiation based upon 5-FU and CDDP chemotherapy. In this study, the 3-year OS was 95% versus 74% for the gemcitabine and CDDP versus 5-FU and CDDP, respectively, with a p value of <0.001. Therefore, based upon single agent activity of gemcitabine against NPC and based upon promising preliminary activity and safety data of gemcitabine incorporated into sequential chemoradiation treatment plans of patients with NPC, further study of gemcitabine in this setting is worthwhile.

1.5.3 Gemcitabine and Taxane Combinations

Gemcitabine and docetaxel have been studied extensively in cancer patients with recurrent, metastatic disease. The combination of gemcitabine and docetaxel is a well-accepted standard of care for patients with metastatic or recurrent NSCLC, pancreatic, breast, urothelial cancer, and sarcomas (Hainsworth 2004; Hensley 2008; Hirsh 2004; Jacobs 2006; Georgoulias 2005; Gitlitz 2003; Estevez 2007; Founzilas 2000; Fumoleau 2003). The combination of gemcitabine and docetaxel as well as gemcitabine and paclitaxel has been shown to be active and tolerable in patients with SCCHN who have had prior RT (Labourey 2007). The gemcitabine and docetaxel combination has been shown to be safe and feasible following cisplatin-based chemoradiation in NSCLC (Movsas 2010; Huang 2008). Typical dosing regimens are gemcitabine 800-1000 mg/m^2 every 2 out of 3 weeks or 3 out of 4 weeks combined with docetaxel, 75-100 mg/m^2 every 4 weeks or 30-40 mg/m^2 weekly for 2 weeks every 3 or 4 weeks.

The combination of gemcitabine and paclitaxel has been shown to be active and tolerable in patients with SCCHN who have had prior irradiation. The combination of gemcitabine (1000 mg/m^2), carboplatin (AUC 2.5) , and paclitaxel (70 mg/m^2) administered on days 1 and 8 every 21 days in patients with metastatic NPC is very active and feasible, with an 11% CR rate and 86% overall response rate (Leong 2008). The treatment was well tolerated, with 22 of 28 patients completing 6 cycles. Similar data demonstrating high anti-cancer activity, but more toxicity, with the combination of gemcitabine, paclitaxel, and carboplatin when the latter agent was administered at higher doses q21 in patients with metastatic, recurrent NPC suggests that a weekly treatment regimen in the adjuvant setting is likely to be better tolerated (Leong 2005). Based upon the efficacy data and safety data from multiple studies of gemcitabine plus paclitaxel in metastatic, recurrent carcinomas, including previously irradiated head and neck cancer patients (Bickel 2010; Fountzilas 1999; Khoo 2006; Xu 2010; Androulakis 1998), recommended doses would be paclitaxel 80-90 mg/m^2 and gemcitabine 1000 mg/m^2, both on days 1 and 8 every 21 days.

While we maintain that the combination of paclitaxel and gemcitabine is worthy of study in this setting, we are also cognizant of the fact that there is not a large body of data confirming the feasibility and activity of this combination as adjuvant treatment for NPC patients following concurrent cisplatin and RT. Our hypothesis is that the combination of cisplatin and 5-FU (PF) contributes only marginally to the intergroup recipe both because of the inability to deliver adequate doses of PF following chemoradiation and because PF fails to overcome drug resistance that develops during chemoradiation. We believe that gemcitabine and paclitaxel will be more active following CDDP because their mechanism of action is different from cisplatin. We believe that a major dose-limiting problem with the PF following RT is the mucositis associated with 5-FU, that the mucositis-related adverse event profile of gemcitabine and paclitaxel will be less, and therefore, a higher percentage of planned dose delivery will be possible.

Because the clinical benefit of PF adjuvant treatment in unselected NPC patients is marginal (Chen 2012) and because outcomes of chemoradiation in unselected patients are relatively good, we are proposing to limit study of this gemcitabine plus paclitaxel adjuvant regimen to patients with high-risk disease as defined by elevated post-RT blood EBV DNA levels. There is a

great unmet need for effective treatment of these patients, because their long-term survival free from relapse is minimal (Wang 2012). However, because the gemcitabine and paclitaxel regimen has not been tested in this setting, a phase III design versus the present standard of care would be premature. Yet an uncontrolled phase II trial also would be sub-optimally informative because there is no well-established historical outcome data for the control arm on the population proposed. Therefore, we are proposing a randomized phase II study with early stopping points for unexpectedly inferior tolerability or efficacy for the gemcitabine and paclitaxel arm when compared to the current PF arm. Furthermore, we are only interested in further study of this regimen if the analysis of this preliminary randomized phase II study demonstrates substantial clinically relevant improvement in outcomes for these high-risk patients. Therefore, we have chosen a high bar of improvement of PFS at 1 year from 40% to 55% reported for patients who have persistent detectable plasma EBV DNA after chemoradiation (Chan 2002).

1.6 Rationale for Studying Quality of Life (QOL) Changes Related to Administration of Adjuvant Chemotherapy (4/14/16)

For head and neck cancer patients, QOL is an increasingly important research issue. Particularly for scenarios in which differing oncologic decisions may affect tradeoffs in survivorship or toxicity, QOL concerns take on greater relevance, and the ethical responsibility to advise patients increases (Movsas 2003). Therapeutic treatment intensification affects varying domains of QOL over both the short- and long-term, and specifically in NPC patients, increases in clinician-reported toxicities are known to correlate with patient-reported QOL decreases (Liu 2012). With improvements in loco-regional control and survivorship in NPC, there is a need to validate high-quality, longitudinal QOL assessment methodology specific to this disease subsite, which is unique in its natural history and internationally-related demographic distribution. Quantification of the QOL impact will assist in decision-making about treatment intensification or de-intensification for patient subpopulations considered to be at more or less risk of poor outcome.

1.6.1 General and Physical Well-Being Patient Reported Outcomes (PROs)

A major PRO hypothesis in this study is to evaluate the predictive value of the general and physical well-being scores for metastasis and survival outcomes. There are strong suggestions that overall QOL and physical well-being subscale scores may have independent prognostic value for DFS and OS in both head and neck and nasopharyngeal cancer (Hwang 2004, Meyer 2009, Tsai 2012, Urba 2012). However, prior limitations in research have resulted from a paucity of NPC-appropriate PRO instruments. General scales and even those specific to head and neck cancer, such as Functional Assessment of Cancer Therapy-Head and Neck (FACT-HN) do not fully address the concerns unique to NPC survivorship (Tong, 2009). PRO assessment in this study is uniquely challenging in that the longitudinal assessment will be conducted in an international multi-institutional setting. Few PRO instruments are translated for or cross-culturally validated in the Chinese-speaking population. Therefore, for the general PRO assessment, the study chairs have chosen FACT-NP, which is a nasopharyngeal-specific PRO instrument that is validated and available in traditional and simplified Chinese. The FACT-NP assessment generates general and physical well-being subscale scores. Because the FACT-NP was developed for use in a radiation oncology setting, it is a uniquely appropriate instrument to measure both short- and long-term impacts on the population included in this study.

Furthermore, because distant metastasis is a major cause of death in the NPC population targeted in this study, evaluation of the predictive value of PRO measures and their relationship at baseline and over time to the predictive biomarker of EBV is highly relevant. Thus, in an exploratory fashion, changes in these general and physical well-being subscale scores will be correlated to changes in the objective measurement of EBV DNA to determine their relative predictive value. We will investigate the ability of the general and physical well-being subscales to predict the 2-year rate of distant metastases and perform exploratory correlations with plasma EBV DNA quantitation obtained at baseline and at the conclusion of radiation therapy.

We anticipate collecting data for this hypothesis at the pretreatment baseline, in order to obtain a range of patients who will clear or not clear EBV DNA from the blood and who will or will not be at higher risk of distant metastases. These patients will be followed with FACT-NP at the time points

of pretreatment baseline, after EBV re-testing, and at 1 and 2 years from the end of RT. The following specific hypotheses will be formally tested as to whether:

1) Higher general and physical well-being QOL scores across all time points will predict for a lower rate of distant metastases and death;
2) General and physical well-being QOL scores at 4 months and 1 and 2 years will be improved in patients who cleared EBV compared to those who did not.

1.6.2 Hearing and Peripheral Neuropathy PROs

The phase II study offers a unique opportunity to quantify QOL changes related to adjuvant chemotherapy. Decreases in many QOL domains, especially over the long term, are attributed to RT for NPC (Chie 2003). However, because 3D conformal radiation therapy (3D-CRT) and IMRT are now standard practice for NPC, radiation-related QOL has improved, and the impact of chemotherapy has become relatively more important (Fang 2007, Pow 2012). Chemotherapy-related decreases in QOL domains are most clearly related to concurrent chemotherapy, remaining significant even when adjusted for related clinical parameters (Talmi 2002, Lee 2012). However, adjuvant chemotherapy is known to produce additional toxicity. Clinician-reported toxicities are high due to adjuvant chemotherapy administration, as indicated by the 55% compliance rates reported in large studies (Al-Sarraf 1998, Chan 1995).In the phase II trial, organ-specific QOL hypotheses in hearing impairment and peripheral neuropathy will be studied in order to provide guidance about the neuropathic PRO-related impacts of the cisplatin/5FU versus gemcitabine/paclitaxel arms.

Due to the anatomic location of NPC tumors, being close to the auditory apparatus and because of the use of lengthy concurrent and adjuvant cisplatin administration, permanent tinnitus and hearing loss are very common sequelae of cisplatin-based treatment for NPC. Measurement of the toxicity impact of hearing impairment is a critical and understudied issue in NPC treatment, and it is of importance in this study of competing regimens of adjuvant chemotherapy with potential differing ototoxic effects. Significant improvement in hearing outcomes could be a justification for changing the adjuvant standard of care from cisplatin/5FU to gemcitabine/paclitaxel. Thus, the patients with known detectable EBV DNA titers who are scheduled to enter the phase II study will be tested for these neuropathic outcomes of hearing loss and peripheral neuropathy, in order to gauge the effect of the adjuvant chemotherapy regiments on these endpoints.

The self-perceived impact of hearing loss on the individual is referred to as hearing handicap. The Hearing Handicap Inventory for the Elderly Screening Version (HHIE-S) is a widely accepted measure of hearing impairment-related PROs (Ventry 1982, Weinstein 1986) and was adopted for use in the U.S. cooperative oncology group setting as part of the RTOG 0522 trial. In addition, this self-reported PRO instrument has been validated in a limited fashion based on correlations to measured changes in audiometry (Lichtenstein 1988; Sindhusake 2001; Wiley 2000). Most importantly for this cancer population, the HHIE-S has been linguistically and culturally adapted for use in the Chinese speaking population in the U.S. (Jupiter 2001). Since its translation, the HHIE-S also has been used in a number of international settings including studies conducted in Hong Kong and Taiwan (Chang 2009, Wong 2010, Wong 2012).

In patients in the phase II study, the HHIE-S will be collected after EBV re-testing and at 4 months and 1 and 2 years from the end of RT to test the following specific hearing-related hypothesis: There will be improvement in HHIE-S scores at 4 months and 1 year and 2 years from the end of RT resulting from the substitution of adjuvant cisplatin/5-FU chemotherapy with gemcitabine/paclitaxel.

The second organ-specific hypothesis to be tested in the phase II trial relates to peripheral neuropathy. Cisplatin and paclitaxel are each particularly associated with this side effect. The Functional Assessment of Cancer Therapy-Taxane (FACT-Taxane) scale contains a neurotoxicity subscale and includes multiple items focused on peripheral neuropathy. FACT-Taxane has been validated for use in multi-agent chemotherapy regimens, with PRO scores correlated to

cumulative chemotherapy burden (Cella 2003; Saibil 2010). It has been translated and validated in traditional and simplified Chinese. This assessment will be used in the phase II trial at the time points of end of RT and at 1 and 2 years from end of RT to determine if patients who have completed more cycles of concurrent cisplatin by the time of the post-RT baseline have worsened FACT-Taxane scores. This data will be formally used to test the following peripheral neuropathy related hypothesis: FACT-Taxane scores at 4 months and 1 and 2 years from the end of RT will show no worsened peripheral neuropathy effects resulting from the substitution of adjuvant cisplatin/5-FU chemotherapy with gemcitabine/paclitaxel.

Compatibility of scales, internal validity, and cross-cultural translatability were carefully considered in the choice of instruments. Time points of administration have been tailored to minimize patient burden while still obtaining high quality, longitudinal data.

1.6.3 Audiometric Procedures

An objective measurement of hearing changes will be obtained through pure tone audiometry (PTA). Audiometry will be obtained at pretreatment baseline, at the end of RT, and at approximately 1 year (+/- 4 months) from the end of RT.

A standard (i.e. 250-8000Hz) frequency range audiometric assessment is not sufficient for the purposes of this study. Because we are interested in the degree of hearing preservation and its effects on hearing handicap, an ototoxic monitoring protocol will be followed, which incorporates threshold measurement to the highest measurable frequency. The goal of the audiometric assessment is to establish baseline hearing thresholds for pure tone stimuli at both standard (octave and half octave frequencies between 250 and 8000Hz) and high frequency (octave and half octave frequencies from 8000-20,000Hz) test regions. Subsequent test results can then be compared to the baseline audiogram to assess the prevalence and severity of cisplatin-related threshold shifts. A threshold refers to the softest decibel level (intensity) of a stimulus frequency required to elicit a response 50% of the time; thresholds within the normal adult hearing range are 0 to 20 dBHL (decibel Hearing Level). The audiogram graphically represents how an individual has responded (pushing a button or raising the hand) to a series of calibrated sounds at varied frequency and decibel levels presented via ear-inserts or headphones (air conduction) or via a transducer on the mastoid bone (bone conduction). Each ear is tested individually, and results recorded and compared to that ear.

Audiometric assessment will be completed by licensed audiologists. A short procedures manual with PowerPoint slides will be provided to audiologists explaining the study procedures to be followed. The audiology studies (pure tone thresholds and tympanometry results in tabular format) will be submitted to NRG Oncology and then sent to University of California, San Francisco Medical Center for quality assurance and analysis by Dr. Anand, the Audiology Co-Chair. The difference in hearing sensitivity at octave and half-octave frequencies will be quantified as the dB difference in threshold between baseline and post-treatment audiometry results. Thus, a numeric difference that is negative indicates a worsening in sensitivity at a particular test frequency. Audiometric test results will be subdivided into low frequency (250, 500, 1000 Hz), mid frequency (2000, 3000, 4000), high frequency (6000, 8000, 12,000), and very high frequency (16,000 and 20,000 Hz) regions. The arithmetic mean of the thresholds (the Pure Tone Average) in each region will be used to describe the severity and configuration of the hearing loss. When differences between bone conduction and air conduction thresholds are >10 dB, a notation will be added to the patient file indicating the presence of a conductive component of the hearing loss. A shift in bone conduction thresholds suggests the effect of cisplatin-induced ototoxicity, while a shift in air conduction threshold without a bone conduction threshold shift (i.e. the introduction of a conductive hearing loss) will be attributed to radiation-induced inflammatory changes. The incidence of conductive hearing loss is expected to be constant between treatment groups. If a cochlea has received greater than 4000 cGy median dose, sensorineural worsening will be attributed to radiation-induced damage (Hitchcock 2009). Group mean shift in hearing threshold will be compared between low-dose and high-dose cisplatin groups. Threshold shifts in low, mid, high and very high frequency regions will be compared in a mixed model ANOVA (two way ANOVA with repeated measures in one variable) where the dependent variable is the difference

in hearing threshold (in dB) between baseline and post-treatment audiograms and the independent variable is the treatment group.

PTA can be obtained in a culturally appropriate manner in an international trial setting and provides a clear-cut means of assessing toxicity using an objective common denominator across populations. PTA will provide a means to assess the impact of cisplatin-based chemotherapy on hearing sensitivity. PTA provides not only a quantifiable measurement of the degree of hearing impairment or loss but can also provide information about the characteristics and etiology of the change, which cannot be provided by patient-reported outcomes (PROs), which are considered complementary but not redundant to PTA.

The HHIE-S specifically assesses hearing-related PRO concerns as opposed to the Functional Assessment of Cancer Therapy-Nasopharyngeal (FACT-NP), which contains 2 hearing-related items but is more oriented towards patient reporting of the existence of impairment rather than exploring multidimensional PRO-related impacts. Therefore, we plan to compare the FACT-NP hearing domain scores to those obtained on the HHIE-S; given recent evidence arguing for the superiority of HHIE-S over single-question screening in an Asian population (Tomioka 2012), we expect to establish the HHIE-S as a more sensitive PRO assessment that should become the standard for evaluating hearing-related PROs in this population. Thus, in this study, PTA will be used to:

1) Determine eligibility for trial participants at initial screening by identifying disqualifying baseline sensorineural hearing loss versus conductive hearing loss (see Section 3.2.4);
2) Assist clinicians in the assessment of ototoxicity in patients scheduled to receive multiple cycles of chemotherapy;

If the PTA data is available to test in conjunction with acquired PRO instruments, then one specific hypothesis will be formally evaluated as to whether: loss of high frequency hearing on PTA will be more readily detected by HHIE-S rather than FACT-NP (among patients in the phase II trial who are tested with both instruments).

1.6.4 Optional Online Completion of QOL Assessments

Missing data are a significant problem, particularly for QOL assessments. Unlike data for traditional endpoints, such as survival, QOL data can never be obtained retrospectively if it is not provided by the patient at the appropriate time point. This limits researchers' ability to accurately perform QOL statistical analyses and negatively impacts the clinical relevance of this effort. Typically, QOL forms are filled out in hardcopy (paper). To provide a more convenient method of completing QOL assessments, NRG Oncology is working with VisionTree Software, Inc., San Diego, CA. VisionTree offers patients on this study the option of completing their QOL forms online from any location that has a computer with Internet access, including the patient's home, and provides reminders to patients to complete the assessments.

VisionTree has developed a tool, VisionTree Optimal Care (VTOC), a HIPAA-secure, user friendly, web-based software system (Gorgulho 2005; Gorgulho 2007; Pedroso 2006). The VTOC tool contains a web-based system for global patient and trial administration access, which allows improved compliance and accuracy of data collection, validation, and reporting. It is compliant with the Title 21, Code of Federal Regulations, Part 11 statistical process control system and provides a mobile solution for clinical trials. QOL data are collected with Microsoft Excel and PDF export of reports. VTOC also has mobile messaging and e-mail reminders. Surveys can be "pushed" to patients for completion at timed intervals (see http://www.visiontree.com for details). This technology allows consenting patients on this study to fill out their QOL forms online from any location and to receive e-mail reminders to complete assessments. E-mail reminders also can be sent to research associates (RAs) at the appropriate institutions to remind them that a QOL time point window is about to close so that a patient can be contacted to fill out QOL information on time, before it becomes "missing data".

In a pilot RTOG study (RTOG 0828), the compliance rate of patients completing QOL assessments at 6 months significantly improved using electronic technology. Based on this pilot data, NRG Oncology is offering VisionTree as an option in other studies, including this one. Patients preferring to complete hardcopy QOL assessments can do so.

For this trial, the baseline QOL forms must be completed in hardcopy at the time of enrollment. To complete subsequent QOL forms online, patients will be asked for an e-mail address that they consent to use so that e-mail reminders may be sent to them. The patient's e-mail address also will be used for password-protected access to VTOC. Patients who are interested in participating but do not yet have an e-mail address can obtain one for free from a number of sources (e.g. Yahoo!, Hotmail, or AOL). **Note: The site RA is responsible for setting up the patient's account on VTOC. The RA may do so by logging on the VTOC portal at the following link: https://rtog.optimalcare.com - medical team. RA login information will be provided by VTOC after the patient is randomized to the study. The patient's VTOC account must be set up within 14 days after randomization.** Patients will receive a login card (either printed or sent via e-mail) with which to log in using the secure, web-based VTOC portal. VTOC meets all HIPAA guidelines and is encrypted (via 128-bit SSL) for the security, privacy, and confidentiality of QOL information. It is similar to the secure login commonly used when performing online banking. The login card can then be kept and maintained by the patient.

The patient's e-mail address only will be used by NRG Oncology for this purpose. Patients will be sent e-mail reminders to complete QOL forms. A typical e-mail reminder would read: "Your Quality of Life forms for the study, NRG-HN001, are now due. Please go to http://www.optimalcare.com, use your secure login, and complete the online forms. If any questions make you feel uncomfortable, you may skip those questions and not give an answer. If you have any questions, please e-mail or call your research associate at [insert RA e-mail address] or [insert RA telephone number]. Thank you for participating in this study." The reminders will be created by NRG Oncology and placed into a study template that will be sent to patients at customized intervals (at the time points when QOL forms are due). The first reminder will be sent at the beginning of the "window" to complete a QOL form, with a second reminder halfway through the window period if the QOL forms are not yet completed at that time point. A maximum of 3 reminders will be sent for each of the 4 QOL time points (following the baseline QOL forms, which are completed in hardcopy). After a patient has completed all forms in the VTOC portal, a dialogue box will appear that says "Thank you for completing your Quality of Life forms," and the patient will no longer receive any remaining notices for that time point. The site RA or study administrator will be informed through the VTOC "At-A-Glance" form management system when QOL forms have been completed.

1.7 Rationale for Studying Cost-Effectiveness Related to the Administration of Adjuvant Chemotherapy

For nasopharyngeal cancer treatment, costs accrued both by individual patients and the health care system are considerable. From the patient perspective, QOL is highly correlated to patients' socioeconomic status and financial burden (Fang 2002, Fang 2007). From the health care system perspective, the incorporation of additional forms of treatment, whether therapeutic or supportive in nature, can dramatically change the incremental cost-effectiveness ratio. In past studies, the RTOG has successfully developed decision models informed with actual clinical trial data to perform economic analyses (Konski 2005, Konski 2009). Costs have been estimated from single-institution data, as well as by retrospective collection from select institutions or administrative claims (Owen 2001; Konski 2008). Cost-effectiveness analysis will be incorporated into this trial using measurement of health-related QOL (HRQOL) from the EuroQol (EQ-5D) instrument.

The EQ-5D is available in simplified and traditional Chinese language translation, and its use in measuring health state has been validated for populations in Taiwan and Hong Kong (Chang 2007; Cheung 2008). HRQOL obtained from this instrument enables the derivation of quality adjusted life years (QALYs) associated with various forms of therapeutic intervention. Quality adjusted life years can be measured by numerous methods but the use of the EQ-5D instrument

is the simplest. Furthermore, the EQ-5D has been used to evaluate patient reported outcomes in previous studies of head and neck cancer patients with sensitivity adequate for distinguishing between differing modalities of treatment (Nijdam 2008) and accounting for chronic treatment related effects such as xerostomia and dysphagia (Ramaekers 2011). Time points of collection for the EQ-5D will be minimal, at the pre-treatment baseline, 1 year, and 2 years. Markov decision modeling will be developed based on cycling health states, rates of complications, and chronic toxicities of treatment up to 2 years.

1.8 Molecular Biomarker Studies

1.8.1 Cisplatin combined with RT has become the standard of care in locally advanced NPC. The addition of cisplatin to RT, however, leads to increase of acute and late treatment toxicity and narrows the ultimate therapeutic gain. Therefore, to identify the group of patients who do not benefit from the addition of cisplatin can render a more personalized therapy and maximize the therapeutic ratio.

ERCC1 plays the rate-limiting step in the nuclear excision repair pathway that recognizes and removes cisplatin-DNA adducts. A large body of pre-clinical evidence suggests that *ERCC1* expression levels correlate with cisplatin resistance in human cancer. In clinical studies, *ERCC1* mRNA or its protein expression level has been shown to be predictive for response to platinum-based chemotherapy and clinical outcome in a variety of cancer studied. Preliminary results supported the hypothesis that *ERCC1* expression is predictive of treatment response and survival in NPC.

Single nucleotide polymorphisms (SNPs) in *ERCC1* could confer sub-optimal DNA repair capacity, thus determining the response to chemotherapy and RT and thereby, cancer outcome. Polymorphisms of *ERCC1* have been shown to influence response to platinum-based chemotherapy treatment and clinical outcome in several cancer types studied. The hypothesis that low or negative *ERCC1* expression is predictive of platinum sensitivity has yet to be established outside lung cancer, because most studies employed small and heterogeneous patient populations treated non-uniformly. One important reason may be the lack of effective and reproducible methods for quantification of *ERCC1* expression, be it protein or mRNA. The *ERCC1* SNP genotyping methods is therefore a rational alternative and may circumvent many of the unresolved problems regarding mRNA and protein determination in clinical samples, since it required only a simple blood sample without too many variables. We plan to correlate certain *ERCC1* SNPs with PFS in all patients. Since everyone in the trial receives cisplatin concurrently with RT, we hypothesize that certain SNPs, which associate with higher *ERCC1* expression, may be associated with worse PFS in these patients due to potential resistance to cisplatin.
The large subunit of ribonucleotide reductase, RRM1, is involved in the regulation of cell proliferation, cell migration, tumor and metastasis development, and the synthesis of deoxyribonucleotides for DNA synthesis. It is also a cellular target for the chemotherapeutic agent, gemcitabine. RRM1 mRNA expression, and genetic variants have been studied in a large number of patients with different types of cancer, such as non-small-cell lung cancer, pancreatic cancer, breast cancer, and biliary tract cancer, to establish their prognostic or predictive value when these patients were treated with gemcitabine. Some studies have shown that RRM1 mRNA expression have been associated with clinical outcome of patients with certain neoplasm (Lars 2011; Zheng 2007); however, mRNA levels are hard to measure from archival tissues and require large tumor biopsies, which is not feasible in NPC. Results of some studies also suggest that RRM1 genotypes (certain SNPs) can be predictive of treatment outcome in some patient cohorts, but these findings need confirmation in large groups of patients. We hypothesize that certain RRM1 genotypes can predict for benefit from gemcitabine and can be useful in identifying high-risk LA-NPC patients who would do well (in terms of PFS) with the adjuvant gemcitabine-paclitaxel treatment. In contrast, these genotypes will not have any predictive effect for treatment outcome in high-risk patients treated on the CDDP-5-FU arm.

1.8.2 Specific Hypotheses

We propose a companion translational study performed on stored blood samples collected as part of the screening procedures in the prospective phase III NRG Oncology trial of NPC to confirm 2 prior hypotheses:

1. Certain *ERCC1* genotypes, which correlate with higher expression of *ERCC1*, are associated with worse PFS in all patients treated on this trial, since all will be receiving cisplatin chemotherapy concurrently with RT
2. RRM1 genotype can be used to predict for high-risk LA-NPC patients who would benefit from adjuvant gemcitabine chemotherapy.

Given the above results, for this current study, we will obtain research blood samples 4 weeks into concurrent chemoradiation, and at 4 and 12 months after radiation therapy from all patients who consent to participate in tissue/blood submission (see Section 10.0 for details of collection and submission).

1.9 Rationale for the Proposed Study

The majority of the loco-regionally advanced NPC patients treated with cisplatin and radiation followed by adjuvant cisplatin and 5-FU chemotherapy will be cured by present standard chemoradiation. When the tumors recur, the predominant failure pattern is distant metastasis. Exploratory analyses on several randomized trials as stated above have shown that concurrent chemoradiation alone was insufficient in reducing distant failures. It is not feasible to administer all planned cycles of adjuvant chemotherapy in many NPC patients after concurrent chemotherapy. Therefore, the current NRG Oncology proposal seeks to use plasma EBV DNA as a biomarker to select the most appropriate candidates for adjuvant chemotherapy after concurrent chemoradiation.

In this proposed trial, post-chemoradiation plasma EBV DNA will be used for risk stratification, and patients will be randomized to different treatments based on their risk. Those who have an undetectable post-treatment EBV DNA level are considered good risk and will be randomized to either observation or the current standard cisplatin and 5-FU. The aim is to see if omitting adjuvant chemotherapy for a group of patients at low risk for treatment failure will compromise overall survival (OS). Patients whose EBV DNA is detectable will be randomized to receive current standard adjuvant cisplatin and 5-FU versus gemcitabine and paclitaxel to test whether the latter regimen can further improve PFS in this high-risk population.

In summary, this proposed trial will seek to answer several questions:

1) By using post-treatment plasma EBV DNA levels, we ask whether adjuvant chemotherapy is necessary among patients with an undetectable EBV DNA level after concurrent chemoradiation.
2) Can we more reliably demonstrate a benefit in terms of PFS with the addition of adjuvant chemotherapy for LA-NPC by enriching the population with poor prognosis patients using post-chemoradiation blood EBV DNA levels, i.e. those with plasma EBV DNA level?
3) Are there drugs that have mechanisms of action different from cisplatin and that can be given in the adjuvant setting that would demonstrate clinical benefit superior to adjuvant cisplatin and 5-FU?
4) Are these drugs more tolerable than adjuvant standard cisplatin and 5-FU?
5) Do general or physical well-being QOL scores predict for the risk of distant metastases or survival, and do general or physical well-being QOL scores predict outcomes in a manner similar to EBV DNA levels?
6) Will hearing-related QOL be improved from reduced cisplatin administration, and what is the optimal PRO instrument that correlates to objective audiometric testing?
7) Will peripheral neuropathy-related QOL remain stable or worsened by substitution of gemcitabine/paclitaxel for cisplatin/5FU?
8) Are alternative options of observation or gemcitabine/paclitaxel cost-effective, as compared to the administration of standard adjuvant cisplatin/5FU chemotherapy?

These questions are important to establish new standard of care in LA-NPC and will establish an important role for plasma EBV DNA as a biomarker for risk stratification.

2.0 OBJECTIVES

2.1 Primary Objectives for Randomized Phase II and Phase III Studies

2.1.1 Detectable Plasma EBV DNA Cohort (randomized phase II): The primary objective is to determine whether substituting adjuvant CDDP and 5-FU with gemcitabine and paclitaxel will result in superior progression-free survival.

2.1.2 Undetectable Plasma EBV DNA Cohort (phase III): The primary objective is to determine whether omitting adjuvant CDDP and 5-FU (observation alone in the adjuvant setting) will result in noninferior overall survival as compared with those patients receiving adjuvant CDDP and 5-FU chemotherapy.

2.2 Secondary Objectives for Randomized Phase II and Phase III Studies

To compare the following between arms:

- Time to distant metastasis;
- Time to local progression;
- Time to regional progression;
- Progression-free survival (Undetectable Cohort);
- Overall survival (Detectable Cohort)
- Acute and late toxicity profiles based on clinician-reported CTCAE, v. 4;
- Death during or within 30 days of end of protocol treatment;
- Quality of life (general and physical well-being);
- Quality of life (hearing);
- Quality of life (peripheral neuropathy);
- Cost effectiveness.

3.0 PATIENT SELECTION (4/14/16)

NOTE: PER NCI GUIDELINES, EXCEPTIONS TO ELIGIBILITY ARE NOT PERMITTED. For questions concerning eligibility, please contact the study data manager.

3.1 Conditions for Patient Eligibility (23-Oct-2017)

3.1.1 Biopsy proven (from primary lesion and/or lymph nodes) diagnosis of cancer of the nasopharynx;

3.1.2 Sites are required to complete Step 1 registration before submitting specimens for EBV DNA analysis.

- Patients must have detectable pretreatment plasma EBV DNA, determined by the central lab prior to Step 2 registration (see Section 10.2 for details of specimen submission).
- For patients who have detectable plasma EBV DNA tested at one of the credentialed central labs (listed on the EBV DNA Testing Specimen Transmittal form) within 28 days prior to Step 1 registration: that test result can be used for eligibility without the need for re-testing. To use this test result for eligibility, the central lab must enter the test result through the pathology portal, and the site must follow the instructions in Section 5.4.

3.1.3 Stage II-IVB disease (AJCC, 7th ed.) with no evidence of distant metastasis, based upon the following minimum diagnostic workup:

- History/physical examination by a Medical Oncologist or Clinical Oncologist or Radiation Oncologist or ENT, which must include an endoscopic evaluation, a complete list of current medications, and assessment of weight and weight loss in the past 6 months within 21 days prior to registration;
- Evaluation of tumor extent with one of the following combinations required within 28 days prior to registration:
    a) MRI of the nasopharynx and neck; or CT of the nasopharynx and neck with ≤ 3 mm contiguous slices with contrast and bone windows (to evaluate base of skull involvement).
    b) MRI of the nasopharynx and PET/CT (with contrast) of the neck.

Note: If a treatment planning CT scan is used, it must be with ≤ 3 mm contiguous slices with contrast and be read by a radiologist.
Please refer to section 6.3.2 for MRI requirement for target delineation.

- To rule out distant metastasis, patients must undergo the following imaging within 28 days prior to registration:
  1) a CT scan with contrast of the chest and abdomen (required), and the pelvis (optional), or a total body PET/CT scan (non-contrast PET/CT is acceptable);
  2) a bone scan only when there is suspicion of bone metastases (a PET/CT scan can substitute for the bone scan).

3.1.4 Zubrod Performance Status 0-1 within 21 days prior to registration;
3.1.5 Age ≥ 18;
3.1.6 CBC/differential obtained within 21 days prior to registration, with adequate bone marrow function defined as follows:
- Absolute neutrophil count (ANC) ≥ 1,500 cells/mm^3;
- Platelets ≥ 100,000 cells/mm^3;
- Hemoglobin ≥ 8.0 g/dl (Note: The use of transfusion or other intervention to achieve Hgb ≥ 8.0 g/dl is acceptable.);

3.1.7 Adequate hepatic function within 21 days prior to registration, defined as follows:
- Total bilirubin ≤ 1.5 x institutional ULN;
- AST or ALT ≤ 1.5 x institutional ULN;
- Alkaline phosphatase ≤ 1.5 x institutional ULN.

3.1.8 Adequate renal function within 21 days prior to registration, defined as follows:
- Serum creatinine ≤ 1.5 mg/dl or calculated creatinine clearance (CC) ≥ 50 ml/min determined by 24-hour urine collection or estimated by Cockcroft-Gault formula:

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

$$\text{CCr female} = 0.85 \times (\text{CrCl male})$$

3.1.9 Negative serum pregnancy test within 14 days prior to registration for women of childbearing potential;
3.1.10 Women of childbearing potential and male participants who are sexually active must agree to use a medically effective means of birth control throughout protocol treatment;
3.1.11 Patient must provide study specific informed consent prior to study entry, including the mandatory pre-treatment plasma EBV DNA assay.

3.2 Conditions for Patient Ineligibility
3.2.1 Prior invasive malignancy (except node negative, non-melanomatous skin cancer) unless disease free for a minimum of 1095 days [3 years] (For example, carcinoma in situ of the breast, oral cavity, or cervix are all permissible);
3.2.2 Prior systemic chemotherapy for the study cancer; note that prior chemotherapy for a different cancer is allowable; however, at least 6-weeks recovery is necessary if the last regimen included nitrosourea or mitomycin.
3.2.3 Prior radiotherapy to the region of the study cancer that would result in overlap of radiation therapy fields;
3.2.4 Patients with hearing loss assessed to be primarily sensorineural in nature, requiring a hearing aid, or intervention (i.e. interfering in a clinically significant way with activities of daily living); a conductive hearing loss from tumor-related otitis media is allowed.
3.2.5 ≥ grade 2 peripheral sensory neuropathy (CTCAE, v. 4.0);
3.2.6 Severe, active co-morbidity, defined as follows:
- Major medical or psychiatric illness, which in the investigator's opinion would interfere with the completion of therapy and follow up or with full understanding of the risks and potential complications of the therapy;

- Unstable angina and/or uncontrolled congestive heart failure;
- Myocardial infarction within the last 6 months;
- Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration; note that patients switched from IV antibiotics and currently on oral antibiotics whose infection is assessed to be adequately treated or controlled are eligible.
- Chronic Obstructive Pulmonary Disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy within 30 days prior to registration**;**
- Acquired Immune Deficiency Syndrome (AIDS) based upon current CDC definition; note, however, that HIV testing is not required for entry into this protocol. The need to exclude patients with AIDS from this protocol is necessary because the treatments involved in this protocol may be significantly immunosuppressive.

3.2.7 Pregnancy or women of childbearing potential and men who are sexually active and not willing/able to use medically acceptable forms of contraception;

3.2.8 Prior allergic reaction to the study drug(s) involved in this protocol;

3.2.9 Patients with undetectable pre-treatment plasma EBV DNA.

4.0 PRETREATMENT EVALUATIONS/MANAGEMENT (4/14/16)

NOTE: This section lists baseline evaluations needed before the initiation of protocol treatment that do not affect eligibility. Failure to perform one or more of these tests may result in assessment of a protocol violation.

4.1 Required Evaluations/Management

4.1.1 Pre-treatment collection of plasma for the required EBV DNA analysis; sites are required to complete Step 1 registration before submitting specimens for the DNA analysis.

For patients who have detectable plasma EBV DNA tested at one of the credentialed central labs (listed on the EBV DNA Testing Specimen Transmittal form) within 28 days prior to Step 1 registration: that test result can be used for eligibility without the need for re-testing. To use this test result for eligibility, the central lab must enter the test result through the pathology portal, and the site must follow the instructions in Section 5.4.

4.1.2 If the patient consents to participate in the patient-reported outcomes (PROs) and quality adjusted survival assessments in the study, sites are required to administer the following baseline assessments prior to the start of protocol treatment: Hearing Handicap Inventory for the Elderly Screening Version (HHIE-S), Functional Assessment of Cancer Therapy-Nasopharyngeal (FACT-NP), Functional Assessment of Cancer Therapy-Taxane (FACT-Taxane), and EuroQol (EQ-5D).

Patients who consent to participate in the quality of life (QOL) component of this study have the option of completing QOL forms online from any location, including home, via VisionTree Optimal Care (VTOC). Patients without e-mail or Internet access are still able to participate in the QOL component of the study by completing hardcopy (paper) forms. Indeed, at any time, any patient may choose to fill out their QOL form using the hardcopy form.

If the patient wishes to complete QOL assessments online, the patient must have an e-mail address that they consent to use for this purpose. Patients' e-mail addresses are necessary so that e-mail reminders may be sent to them to remind them to fill out QOL forms that are due. The patient's e-mail address also will be used for password-protected access to VTOC. Patients who are interested in participating but do not yet have an e-mail address can obtain one for free from a number of sources (e.g.,Yahoo!, Hotmail, or AOL). **Note: The site RA is responsible for setting up the patient's account on VTOC. The RA may do so by logging on the VTOC portal at the following link: https://rtog.optimalcare.com - medical team. RA login information will be provided by VTOC after the patient is randomized to the study. The patient's VTOC account must be set up within 14 days after randomization.**

See Section 11.2 for details.

4.1.3 Baseline audiogram within 180 days (6 months) prior to treatment.

4.2 Highly Recommended Evaluations/Management

The following evaluations/interventions are highly recommended as part of good clinical care of patients on this trial but are not required.

4.2.1 Nutritional evaluation for a prophylactic gastrostomy (PEG) tube or gastrostomy-jejunostomy (G-J) tube placement is encouraged for patients who have experienced > 10% weight loss prior to treatment. For patients who do not have a feeding tube placed prophylactically and who subsequently require placement during treatment, it is strongly encouraged that these patients do not stop their radiation treatments. It is recommended that patients be counseled to continue swallowing as much as they are able, despite placement of a feeding tube.

4.2.2 Dental evaluation within 180 days (6 months) prior to treatment.

5.0 REGISTRATION PROCEDURES (04May2017)

Access requirements for OPEN, Medidata Rave, and TRIAD:

Site staff will need to be registered with CTEP and have a valid and active CTEP Identity and Access Management (IAM) account. This is the same account (user id and password) used for the CTSU members' web site. To obtain an active CTEP-IAM account, go to https://eapps-ctep.nci.nih.gov/iam.

Note: IMRT or IMPT is mandatory for this study. IGRT is optional (Exception: IGRT is mandatory when using reduced margins, as defined in Section 6.4).

5.1 Pre-Registration Requirements for IMRT or IMPT Treatment Approach (04May2017)

5.1.1 In order to utilize IMRT on this study, the institution must have met specific technology requirements and have provided baseline physics information as indicated in the table below. Instructions for completing these requirements or determining if they already have been met are available on the IROC Houston web site. Visit http://irochouston.mdanderson.org and select "Credentialing".

IMPT may be used on this protocol if the proton therapy treatment modality to be used has been approved by the IROC Houston QA Center and other credentialing procedures described below have been met. Investigators using proton therapy must comply with the NCI proton guidelines for the Use of Proton Radiation Therapy in NCI Sponsored Cooperative Group Clinical Trials, which are available on the website of IROC Houston.

For detailed information on the specific technology requirement required for this study, please refer to the table below and utilize the web link provided for detailed instructions. The check marks under the treatment modality columns indicate whether that specific credentialing requirement is required for this study. IROC Houston will be the entity to notify your institution when all credentialing requirements have been met and the institution is RT credentialed to enter patients onto this study.

- Credentialing documentation received from IROC Houston for this trial—see Section 5.1.1 Table for details.

RT Credentialing Requirements	Web Link for Procedures and Instructions: http://irochouston.mdanderson.org		
	Treatment Modality		
	IMRT	IMPT	**Key Information**
Facility Questionnaire	x	x	The IROC Houston electronic facility questionnaire (FQ) should be completed or updated with the most recent information about your institution. To access this FQ, email irochouston@mdanderson.org to receive your FQ link. For facilities using IMPT, proton facility questionnaire is found at (http://rpc.mdanderson.org/RPC/Forms2/Proton_questionnaires/Registration.aspx)
Credentialing Status Inquiry Form	x	x	To determine whether your institution needs to complete any further credentialing requirements, please complete the "Credentialing Status Inquiry Form" found under credentialing on the IROC Houston QA Center website (http://irochouston.mdanderson.org)
Phantom Irradiation	x	x	An IMRT H&N phantom study provided by the IROC QA Center Houston must be successfully completed. Instructions for requesting and irradiating the phantom are found on the IROC Houston web site (http://irochouston.mdanderson.org). Tomotherapy and Cyberknife treatment delivery modalities must be credentialed individually. For IMPT, successful irradiation of IROC Houston's proton H&N phantom is required. Instructions for requesting and irradiating the phantom are found on the IROC Houston web site (http://irochouston.mdanderson.org.
IGRT Verification Study	x	x	Only institutions interested **in using reduced margins** will be required to complete this credentialing step. The institution must submit a series of daily treatment images along with a spreadsheet of IGRT data from an anonymized head and neck cancer patient. This series must include a minimum of 3 daily pre-treatment images. Pre-treatment images may include three-dimensional (3D) volumetric images (either fan- or cone-beam CT with Megavoltage (MV) or kilovoltage (KV) x-ray or Orthogonal (MV or KV) 2D images. These images and the spreadsheet will be reviewed by the Medical Physics Co-Chair, Ping Xia, PhD, prior to certification. The IGRT credentialing details along with the spreadsheet are available on the IROC Houston web site: http://irochouston.mdanderson.org
Beam calibration		x	Annual monitoring of output calibration by IROC Houston.
On-site dosimetry review		x	Successful completion of an on-site dosimetry review visit, to occur only after the center has been routinely treating patients for a minimum of 6 months and no fewer than 3 anatomical disease sites, and completion of the site visit report by IROC Houston

			recommending approval.
Credentialing Notification Issued to:			
Institution			IROC Houston QA Center will notify the site that all desired credentialing requirements have been met. The site will need to upload a PDF of approval email from IROC Houston to the CTSU Regulatory Portal for RSS to be updated.

5.2 Digital RT Data Submission Using TRIAD

TRIAD is the American College of Radiology's (ACR) image exchange application and it is used by NRG Oncology. TRIAD provides sites participating in NRG Oncology clinical trials a secure method to transmit DICOM RT and other objects. TRIAD anonymizes and validates the images as they are transferred.

TRIAD Access Requirements:

- Site physics staff who will submit images through TRIAD will need to be registered with The Cancer Therapy Evaluation Program (CTEP) and have a valid and active CTEP Identity and Access Management (IAM) account. Please refer to Section 5.0 of the protocol for instructions on how to request a CTEP-IAM account.
- To submit images, the site physics user must have been assigned the 'TRIAD site user' role on the relevant Group or CTSU roster. Users should contact your site Lead RA to be added to your site roster. Users from other cooperative groups should follow their procedures for assignment of roster roles.
- RAs are able to submit standard of care imaging through the same method.

TRIAD Installations:

When a user applies for a CTEP-IAM account with proper user role, he/she will need to have the TRIAD application installed on his/her workstation to be able to submit images. TRIAD installation documentation can be found on the NRG Oncology/RTOG website Core lab tab.

This process can be done in parallel to obtaining your CTEP-IAM account username and password.

If you have any questions regarding this information, please send an e-mail to the TRIAD Support mailbox at TRIAD-Support@acr.org.

5.3 Regulatory Pre-Registration Requirements (23-Oct-2017)

5.3.1 CTEP Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to OPEN, RAVE, or TRIAD or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) (https://ctepcore.nci.nih.gov/rcr). Documentation requirements per registration type are outlined in the table below.

Documentation Required	IVR	NPIVR	AP	A
FDA Form 1572	✔	✔		
Financial Disclosure Form	✔	✔	✔	
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔	
HSP/GCP training	✔	✔	✔	
Agent Shipment Form (if applicable)	✔			
CV (optional)	✔	✔	✔	

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and IRBs covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Added to a site roster
- Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol PI on the IRB approval

Additional information can be found on the CTEP website. For questions, please contact the RCR ***Help Desk*** by email at < RCRHelpDesk@nih.gov >.

5.3.2 CTSU Registration Procedures

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

IRB Approval

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients.

Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to: an active Federal Wide Assurance (FWA) number, an active roster affiliation with the Lead Network or a participating organization, a valid IRB approval, and compliance with all protocol specific requirements.

In addition, the site-protocol Principal Investigator (PI) must meet the following criteria:

- Active registration status
- The IRB number of the site IRB of record listed on their Form FDA 1572
- An active status on a participating roster at the registering site.

Sites participating on the NCI CIRB initiative that are approved by the CIRB for this study are not required to submit IRB approval documentation to the CTSU Regulatory Office. For sites using the CIRB, IRB approval information is received from the CIRB and applied to the RSS in an

automated process. Signatory Institutions must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB via IRBManager to indicate their intent to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office. In order for the SSW approval to be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study.

Downloading Site Registration Documents:

Site registration forms may be downloaded from the NRG-HN001 protocol page located on the CTSU members' web site. Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password

- Click on the Protocols tab in the upper left of your screen
- Either enter the protocol # in the search field at the top of the protocol tree, or
- Click on the By Lead Organization folder to expand
- Click on the NRG Oncology link to expand, then select trial protocol NRG-GI001
- Click on LPO Documents, select the Site Registration documents link, and download and complete the forms provided.

Requirements for NRG-HN001 site registration:

- IRB approval letter (For sites not participating via the NCI CIRB); local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted.
- IROC Credentialing Status Inquiry (CSI) Form

NOTE: For studies with a radiation and/or imaging (RTI) component, the enrolling site must be aligned to a RTI provider. To manage provider associations access the Provider Association tab on the CTSU website at https://www.ctsu.org/RSS/RTFProviderAssociation, to add or remove associated providers. Sites must be linked to at least one IROC credentialed provider to participate on trials with an RT component.

- IRB/REB approved consent (International and Canadian sites only; English and native language versions*)
  *Note: Institutions must also provide certification/verification of consent translation to NRG Oncology.
- IRB/REB assurance number renewal information, as appropriate
- See the additional pre-registration requirements in Sections 5.1 and 5.2.
- Credentialing documentation received from IROC Houston must be uploaded to the CTSU Regulatory Portal for RSS to be updated

Non-English Speaking Canadian and Non-North American Participating Sites

*****Translation of documents is critical. The institution is responsible for all translation costs. All regulatory documents, including the IRB/REB approved consent, must be provided in English and in the native language. Certification of the translation is optimal but due to the prohibitive costs involved NRG Oncology will accept, at a minimum, a verified translation. A verified translation consists of the actual REB approved consent document in English and in the native language, along with a cover letter on organizational/letterhead stationery that includes the professional title, credentials, and signature of the translator as well as signed documentation of the review and verification of the translation by a neutral third party. The professional title and credentials of the neutral third party translator must be specified as well.

Submit required forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal, where they will be entered and tracked in the CTSU RSS.

Regulatory Submission Portal: www.ctsu.org (members' section) → Regulatory Submission Portal

When applicable, original documents should be mailed to:

CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

Checking Your Site's Registration Status:
Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU member web site by entering credentials at https://www.ctsu.org. For sites under the CIRB initiative, IRB data will automatically load to RSS.

You can verify your site registration status on the members' section of the CTSU website.

Check the status of your site's registration packets by querying the RSS site registration status page of the members' section of the CTSU web site.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

5.3.3 Pre-Registration Requirements FOR CANADIAN INSTITUTIONS
In addition to the requirements noted above, Canadian institutions must also complete and submit the following documents via the Regulatory Submission Portal to the CTSU Regulatory Office:

- Health Canada's Therapeutic Products Directorates' Clinical Trial Site Information Form,
- Qualified Investigator Undertaking Form, and
- Research Ethics Board Attestation Form.

5.4 Summary of Registration Procedures (04May2017)
The patient must be determined to meet pre-registration requirements. The study incorporates a 3-step registration process. See Section 5.5 below for OPEN Registration Instructions.

Step 1 is an initial registration for the required pre-treatment EBV DNA analysis. Sites are required to complete Step 1 registration before submitting specimens for the EBV DNA analysis or to document detectable EBV DNA within 28 days of Step I registration.

- If the institution expects to enroll a patient, the institution should request a kit for collection and shipment of the required plasma sample from the NRG Oncology Biospecimen Bank (see Section 10.2). The kit can take 7-10 days to arrive. If the institution needs to expedite testing, then the site can use an EDTA collection tube and a tube for the plasma and can provide a FedEx account number for priority overnight shipping (see Section 10.2 and Appendix IV for packing /shipping details).
- The site will register the patient and will collect the patient's plasma (including buffy coat)per Section 10.2.1.

- The institution will ship the patient's plasma to the appropriate lab (see Section 10.2 and Appendix IV for packing/shipping details) for EBV DNA analysis. The specimens should be accompanied by the study-specific EBV DNA Testing Specimen Transmittal Form.
- Registered patients can proceed to chemoradiation so long that there is proof from the institution that blood was drawn for testing for plasma EBV DNA prior to starting chemoradiation. The institution must provide the shipping tracking number and the date of blood draw to the NRG HQ. This information will be entered on a CRF in Medidata Rave prior to Step 2 registration (see Section 12.1 for details).
- The turnaround time for EBV DNA (from shipping of the sample to receipt of the result) is anticipated to be 7-10 business days.
- NRG Oncology will provide the EBV DNA analysis results to the institution in an e-mail. For patients who have detectable plasma EBV DNA tested at one of the credentialed central labs (listed on the EBV DNA Testing Specimen Transmittal form) within 28 days prior to Step 1 Registration: The site must provide the date of testing, the name of the central lab, and the EBV DNA results to the central lab in order for the central lab to submit the EBV DNA results through the pathology portal.

Step 2 is to register patients with detectable plasma EBV DNA to chemoradiation.

- If the patient's plasma EBV DNA is detectable, the patient continues with protocol treatment.
- If the patient's plasma EBV DNA is undetectable, the site must complete Step 2 registration to indicate that the patient goes off study.

Step 3 is for randomization of the patient based on the results of the required EBV DNA analysis post-chemoradiotherapy.

- The site will collect the patient's plasma (including buffy coat) within 1 week after completion of chemoradiation.
- The institution will ship the patient's plasma to the appropriate lab (see Section 10.2 and Appendix IV for packing/shipping details) for EBV DNA analysis. The specimens should be accompanied by the study-specific EBV DNA Testing Specimen Transmittal Form.
- The turnaround time for EBV DNA (from shipping of the sample to receipt of the result) is anticipated to be 7-10 business days.
- NRG Oncology will provide the EBV DNA analysis results to the institution in an e-mail.
- Patients with detectable plasma EBV DNA will be randomized to Arm 1 or Arm 2.
- Patients with undetectable plasma EBV DNA will be randomized to Arm 3 or Arm 4.
- The site must complete Step 3 registration to indicate that the patient goes off study (e.g. if the patient progresses, refuses, etc.). These patients are treated off study as clinically indicated and are followed for 3 years.
- For patients who are deemed ineligible prior to randomization, the site must complete step III registration to indicate that the patient goes off study. Ineligible patients must not be randomized to an arm. These patients are treated off study as clinically indicated and are followed for 3 years.

5.5 Registration (23-Oct-2017)

5.5.1 OPEN Registration Instructions

Patient registration can occur only after evaluation for eligibility is complete, eligibility criteria have been met, and the study site is listed as 'approved' in the CTSU RSS. Patients must have signed and dated all applicable consents and authorization forms.

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at https://eapps-ctep.nci.nih.gov/iam/index.jsp) and a 'Registrar' role on either the LPO or participating organization roster. See Section 5.0 for obtaining a CTEP-IAM account.

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at https://ctepcore.nci.nih.gov/iam) and a 'Registrar' role on either the LPO or participating organization roster. Registrars must hold a minimum of an AP registration type. See Section 5.0 for obtaining a CTEP-IAM account. All site staff will use OPEN to enroll patients to this study. . It is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient position in the Rave database. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' web site https://www.ctsu.org. To assign an IVR or NPIVR as the treating, crediting, consenting, drug shipment (IVR only), or investigator receiving a transfer in OPEN, the IVR or NPIVR must list on their Form FDA 1572 in RCR the IRB number used on the site's IRB approval.

Prior to accessing OPEN site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes.
- All patients have signed an appropriate consent form and HIPPA authorization form (if applicable).

The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

Further instructional information is provided on the CTSU members' side of the website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 orctsucontact@westat.com.

In the event that the OPEN system is not accessible, participating sites can contact web support for assistance with web registration: websupport@acr.org or call the Registration Desk at (215) 574-3191, Monday through Friday, 8:30 a.m. to 5:00 p.m. ET. The registrar will ask the site to fax in the eligibility checklist and will need the registering individual's e-mail address and/or return fax number. This information is required to assure that mechanisms usually triggered by the OPEN web registration system (e.g. drug shipment, confirmation of registration, and patient-specific calendar) will occur.

6.0 RADIATION THERAPY (04May2017)

Note: See Section **5.2 for information on installing TRIAD for submission of digital RT data prior to enrolling patients.**

Note: Radiotherapy must be given with IMRT or IMPT techniques. IGRT is optional (Exception: IGRT is mandatory when using reduced margins). See Section 5.1 for credentialing requirements.

Protocol treatment must begin at the latest within 21 days after Step 2 Registration. In order to minimize protocol deviation, it is recommended that the patient not be registered until there is a treatment start date established. If the start date is beyond 21 days after Step 2 registration, contact the Principal Investigator, Dr. Lee.

Whether patients undergo IMRT or IMPT, the dose specifications and target volume delineation principles outlined below are the same.

6.1 Dose Specifications (04May2017)

Treatment will be delivered once daily, 5 fractions per week, over 6.5 to 7 weeks (33 or 35 fractions) in accordance with accepted standards of care. All targets will be treated simultaneously.

Prescription dose for IMRT and IMPT plans are specified separately, and shall be according to the following (also see Section 6.4):

6.1.1 IMRT Dose Prescription to PTVs

For patients treated in 33 fractions, the $PTV_{69.96}$ ($CTV_{69.96}$ + margin) will receive 69.96 Gy at 2.12 Gy per fraction.

For patients treated in 35 fractions, the PTV_{70} (CTV_{70} + margin) will receive 70 Gy at 2 Gy per fraction.

The treating Radiation Oncologist has the option of prescribing a dose of 62.7 or 63 Gy, $PTV_{62.7 \text{ or } 63}$, to small volume lymph nodes (those nodes ≤ 2 cm) in the level IB region with the goal of limiting dose to the mandible or to level IV and VB lymph nodes to limit the dose delivered to the brachial plexus.

For patients treated in 33 fractions, the $PTV_{62.7}$ ($CTV_{62.7}$ + margin) will receive 62.7 Gy at 1.9 Gy per fraction.

For patients treated in 35 fractions, the PTV_{63} (CTV_{63} + margin) will receive 63 Gy at 1.8 Gy per fraction.

The most common example of the appropriate application of this intermediate dose is the clinical scenario in which there are small lymph nodes in the lower neck close to the brachial plexus. The maximum point dose (defined as to the maximum dose encompassing a volume of 0.03 cc) to the brachial plexus should not exceed 66 Gy and will be scored as a Deviation Unacceptable when 69.96 Gy is exceeded (see the Table in Section 6.7).

6.1.2 **For patients treated in 33 fractions,** the high-risk subclinical region $PTV_{59.4}$ ($CTV_{59.4}$ + margin) can receive 59.4 Gy at 1.8 Gy per fraction.

For patients treated in 35 fractions, the high-risk subclinical regions will receive 63 Gy in 1.8 Gy per fraction. The radiation oncologist also has the option to treat the high-risk subclinical region to 56 Gy at 1.6 Gy per fraction.

For patients treated in 33 fractions, the treating physician may choose to use a single IMRT plan to treat the entire elective neck. In this case, the low neck and supraclavicular region, which is considered the low-risk subclinical region $PTV_{54.12}$ ($CTV_{54.12}$ + margin) will receive 54.12 Gy at 1.64 Gy per fraction.

For patients treated in 35 fractions, the low neck also can be treated to 56 Gy in 1.6 Gy per fraction.

6.1.3 The low neck and supraclavicular region may also be treated with conventional AP or AP/PA field(s) (matched to the IMRT plan for the upper neck). In this case, the low neck and supraclavicular field(s) will receive 50.4 Gy at 1.8 Gy per fraction or 50 Gy in 2 Gy per fraction. If using a single AP field, the prescription depth is dependent on the thickness of the low anterior neck, which is typically at a depth of 3 cm. For AP/PA fields, the prescription point will be at midplane for an AP field or midline for AP/PA fields. The investigator should place a midline cord block. However, if there are grossly involved nodes in the low neck, these nodes should receive the same dose as the $PTV_{69.96 \text{ or } 70}$, except for small volume lymph nodes which can receive a total dose of 62.7 or 63 Gy (see above). Should the treating physician choose to use a low anterior neck field in the presence of gross nodal disease, electrons or photons can be used to boost these nodes.

6.1.4 The prescription dose % coverage for the $PTV_{69.96 \text{ or } 70}$, $PTV_{62.7 \text{ or } 63}$, $PTV_{59.4 \text{ or } 56}$, and $PTV_{54.12}$ (see Sections 6.1.1-6.1.2 and Section 6.7) will be used to evaluate treatment plans. Additionally, the

maximum point dose (to a small volume of 0.03 cc) for each PTV will be used for evaluation. Specific plan compliant criteria are provided in Section 6.7.

At the discretion of the treating physician, $PTV_{62.7 \text{ or } 63}$ is also allowed for gross small volume nodal disease (see Sections 6.1.1 and 6.1.3).

6.1.5 IMPT Dose Prescription

For proton planning, each beam has an individual and unique expansion from the CTV. In the plane perpendicular to the proton beam axis, the PTV expansion from the CTV is up to 5mm while the distal and proximal range margins is based on the proton range uncertainty (see eg Paganetti, Phys. Med. Biol. 57 (2012) R99–R117) and will be calculated using established methods and determined by the individual institution's practice based on their local machine characteristics for the modality. Both single-field and multi-field optimization are allowed for IMPT if the institution has the capability to do it. For dose evaluation purposes, robust optimization and evaluation can be used for IMPT and the worst case CTV dose distribution corresponding to a setup error of at least 3 mm and 2% range uncertainty will be used for dose optimization, evaluation and dose reporting in place of the PTV. If robust optimization and evaluation method is not available, the IMRT dose prescription to the PTV described above may be used.

6.1.6 For IMPT, a spot size with an in-air median sigma at isocenter that is 8mm or greater (without range shifter-200Mev) requires the use of aperture to improve the beam profile (Moteabbed 2015).

6.1.7 Guideline for pencil beam proton planning: Due to the complex geometry of the target volumes, different beam directions to treat the primary and nodal disease are required. The primary disease and upper neck nodes are usually treated with a posterior field as well as anterior and/or posterior oblique fields. The lower neck nodes are treated with an anterior approach.

6.2 Technical Factors (04May2017)

6.2.1 External Beam Equipment and Beam Delivery Methods

Megavoltage equipment capable of delivering static-gantry intensity modulation beams with a multileaf collimator or dynamic intensity modulation (using a multileaf collimator or tomotherapy) is required. Other techniques are acceptable as long as dose specifications and constraints are satisfied. This includes tomotherapy and Volumetric Modulated Arc Therapy (VMAT) techniques.

Conventional anterior low-neck field(s) is/are allowed. The junction between an IMRT dose distribution and a conventional dose distribution is dependent upon the IMRT technique used and on institutional philosophy. Institutions are required to protect the spinal cord at all times. Dosimetric details regarding the match between this field and the upper neck therapy should be provided.

Proton Therapy Equipment and Beam Delivery Methods

Only proton beam systems capable of pencil beam scanning and IMPT are allowed. Uniform scanning, single scattering, and double-scattering protons are not allowed in this protocol.

Note: Due to the sensitivity of IMPT dose distribution to anatomical change, weekly verification CT or conebeam CT scans are required to ensure that a high quality IMPT plan is maintained throughout the course of treatment. The need for IMPT plan adaptation for each patient will be determined by the institution based on the verification CT or conebeam CT scans.

6.2.2 Image Guidance for IGRT When Using Reduced Margins

Daily image guidance of IMRT or IMPT may be achieved using any one or more of the following techniques:

- Orthogonal kilovoltage (KV) images, e.g. ExacTrac
- In room CT
- Linear-accelerator or proton system mounted kV and MV helical conebeam CT images
- Linear-accelerator or proton mounted MV CT images (e.g. Tomotherapy)
- Other Mechanism, after discussion with the Radiation Oncology Co-chair

The institution's procedure to register treatment day imaging dataset with the reference dataset should comply with the following recommendations:

- Region-of-Interest (ROI) or "clip box" for fusion should be set to encompass the high dose PTV and adjacent spinal cord; if the supraclavicular region is a part of the target volume the ROI should extend to the C6 level;
- If the fusion software allows the user to create an irregular ROI (e.g., ExacTrac), treatment room objects seen on in-room X-rays should be excluded from the registration;
- Both manual (e.g., based on bony anatomy) and automatic (e.g., based on mutual information) types of registration can be used; the result of the fusion must be visually checked for the alignment of the bony anatomy, such as vertebral bodies and applicable soft tissue structures (e.g., optic nerves and/or optic chiasm).

Following the registration, the translational and (if the appropriate technology is available) rotational corrections should be applied to the treatment couch. If all the variances are less than 3 mm, the treatment can proceed without correction (however, the physician/team may elect to perform adjustments even for a variance < 3 mm). If one or more corrections are 3-10 mm, adjustment is necessary prior to treatment; however, re-imaging is not mandatory. If one or more of the corrections are larger than 10 mm, the imaging must be repeated in addition to performing table/positioning adjustments. However, the use of numerous repeat IGRT studies should be avoided (see next section).

Management of Radiation Dose to the Patient from IGRT

According to the literature, the estimates of patient doses per imaging study for various imaging systems vary considerably. The doses are in the range of 1 mGy for Cyberknife's and BrainLab's ExacTrac planar kV-systems and can be considered negligible compared with doses from MV portal imaging and kV and MV CT. The doses from helical MV CT scan on a tomotherapy unit were estimated to be in range from 1 to 3 cGy for head and neck studies, similar to doses reported for kV cone beam CT on Elekta Synergy machine. The doses for MV cone beam CT were reported to be in range from 10 cGy for a pelvis study to 6 cGy for a head and neck study. Thus, the doses for 3D imaging systems are in the range from 1 to 6 cGy for head and neck imaging and can contribute from 0.5 to 3% to the daily dose of 2.0 Gy. These are small enough dose contributions that if there is only one imaging study done per treatment session, the dose does not need to be incorporated into treatment planning and is not expected to have any clinical relevance to the patient. However, the imaging dose to the patient may become significant if repeated studies are done for patients with severe set up problems (e.g., requiring frequent corrections of more than 10 mm). It is recommended that patients demonstrating severe set up problems during the first week of treatment be moved to a treatment with larger margins.

6.3 Treatment Planning, Imaging, and Localization Requirements (10/9/14)

Note: If a treatment planning CT scan is used to determine the extent of disease at the time of radiation simulation (which can occur after registration but prior to treatment), it must be with ≤ 3 mm contiguous slices with contrast and be read by a radiologist.

6.3.1 The immobilization device should at least include the head and neck. It is strongly encouraged that the participating centers also include the shoulders in the immobilization. This is to further ensure accurate patient set-up on a daily basis.

6.3.2 Treatment planning CT scans will be required to define gross target volume(s), and clinical target volume(s). MRI scans (required unless medically contraindicated) aid in delineation of the treatment volume on planning CT scans. Special attention should be paid to the skull base. The

treatment planning CT scan should be acquired with the patient in the same position and using the same immobilization device as for treatment.

All tissues to be irradiated must be included in the CT scan. CT scan thickness should be ≤ 0.3 cm slices through the region that contains the primary target volumes. The regions above and below the target volume may be scanned with 0.5 cm slice thickness. MRI scans assist in definition of target volumes, especially when targets extend near the base of skull. If possible, the patient undergoing an MRI scan should be set up as close as possible to the treatment planning position. Image registration and fusion applications, if available, should be used to help in the delineation of target volumes. Image registration should be performed in a region of interest encompassing the GTV, skull base, brainstem, and optic chiasm.

6.3.3 The GTV and CTV (see Section 6.4), and normal tissues must be outlined on all CT slices in which the structures exist.

6.4 Treatment Planning/Target Volumes (23-Oct-2017)

6.4.1 The Gross Tumor Volume (GTV) is defined as all known gross disease determined from CT, MRI, clinical information, and endoscopic findings. Grossly positive lymph nodes are defined as any lymph nodes ≥ 1 cm or nodes with a necrotic center. It is strongly encouraged that the Radiation Oncologist outlines the radiologic extent of the primary tumor and neck nodes along with a Neuro-Radiologist. Whenever possible, it is recommended that the diagnostic images be fused to the planning CT scan image dataset to more accurately define the GTV. To further subdivide the GTV, gross disease at the primary site is designated as GTVp and clinically involved gross lymph nodes are designated GTVn.

6.4.2 The Clinical Target Volume (CTV): See the bulleted list and Table 3 for delineation details. For the split beam technique [IMRT asymmetrically matched to low neck AP or AP/PA field(s)], two separate CTVs will be defined, namely $CTV_{69.96 \text{ or } 70}$ and $CTV_{59.4 \text{ or } 56}$ superior to the junction point between IMRT fields and the low neck AP or AP/PA field(s). In terms of the GTV (GTVp and GTVn), a margin of 3 mm should be given circumferentially around the $GTV_{69.96 \text{ or } 70}$ ($GTVp_{96 \text{ or } 70}$ and $GTVn_{69.96 \text{ or } 70}$) and this volume will be called the $CTV_{69.96 \text{ or } 70}$ ($CTVp_{69.96 \text{ or } 70}$ and $CTVn_{69.96 \text{ or } 70}$). This margin may be reduced to as low as 0 mm near critical structures at the discretion of the treating Radiation Oncologist. For subclinical regions deemed to be at high risk for microscopic disease, all potential routes of spread for primary and nodal GTVs should be delineated by the treating radiation oncologist. This volume is known as the $CTV_{59.4 \text{ or } 56}$.

The low neck and supraclavicular region can be separately treated with conventional AP or AP/PA portal(s). This low risk subclinical region and can receive a lower dose of 50.4 or 50.0 Gy in 1.8 to 2 Gy per fraction. For patients treated in 33 fractions with a single IMRT plan, the $CTV_{69.96}$ and $CTV_{59.4}$ are defined exactly the same as in the split beam technique. However, the low neck and supraclavicular region, which is considered the low-risk subclinical region $CTV_{54.12}$ will receive 54.12 Gy at 1.64 Gy per fraction or CTV_{56} will receive 56 Gy at 1.6 Gy per fraction for 35 fractions.

As noted above (see Section 6.1.3), at the discretion of the treating physician, a $CTV_{62.7 \text{ or } 63}$ may also be used for small volume lymph node disease.

In all directions, the margin between each GTV and its CTV should be at least 3 mm. This margin can be reduced to 0 mm at the discretion of the treating Radiation Oncologist. CTV margins may also be limited to exclude bone or air NOT at risk for subclinical disease.

- To summarize, $CTV_{69.96 \text{ or } 70}$ should include the gross disease at the primary disease site or any grossly involved lymph nodes ($CTVp_{69.96 \text{ or } 70}$ and $CTVn_{69.96 \text{ or } 70}$), except when an intermediate 62.7 or 63 Gy dose may be appropriate for small volume nodal disease, $CTVn_{62.7 \text{ or } 63}$ when using a single IMRT plan.
- To define the high risk subclinical region at the primary disease site, $CTVp_{59.4 \text{ or } 56}$ includes the entire nasopharynx, anterior 1/3 of the clivus, (the entire clivus if involved), skull base (foramen ovale where V3 resides and rotundum where V2 resides bilaterally), bilateral pterygoid fossae, bilateral parapharyngeal space, inferior sphenoid sinus (in T3-T4 disease, the entire sphenoid sinus) and posterior fourth of the nasal cavity and maxillary sinuses (as

long as the coverage of the pterygopalatine fossae, where V2 resides is adequate).The ipsilateral or bilateral cavernous sinus, if needed, should be included in high-risk patients (T3, T4).

Note: The outermost boundary of $CTVp_{59.4 \text{ or } 56}$ should be 8 mm from the GTVp. Typically, it is larger as coverage of the anatomic subclinical regions defined above is necessary. However, this margin can be reduced to 0 mm at the discretion of the treating radiation oncologist if the GTV is close to critical structures, such as the optic structures, brainstem, or spinal cord.

Regarding the high risk lymph nodal regions, $CTVn_{59.4 \text{ or } 56}$ includes:

a. Upper deep jugular (junctional, parapharyngeal): bilaterally;
b. Subdigastric (jugulodigastric [level II]): bilaterally;
c. Midjugular (level III): bilaterally;
d. Ipsilateral or bilateral low jugular (level IV) and supraclavicular region (for heminecks with grossly involved low neck nodes);
e. Upper and mid-posterior cervical (upper and mid-level V, corresponding to the same level as level II and III): bilaterally;
f. Retropharyngeal: bilaterally;
g. Ipsilateral or bilateral submandibular (level IB [for heminecks with direct involvement of level IB or II on that side]).

Note: The outermost boundary of the $CTVp_{59.4 \text{ or } 56}$ should be 8 mm away from the GTVn. This margin should at least be 8 mm from the retropharyngeal lymph nodes, except when the CTV is in air in neck region or in bone. This margin may be reduced to as small as 0 mm at the discretion of the treating Radiation Oncologist.

Bilateral IB lymph nodes may be spared if the patient is node positive. The treatment of level IB may result in the delivery of clinically significant radiation doses to normal structures such as the submandibular glands, mandible, and upper pharyngeal mucosa above the hyoid. At the discretion of the treating Radiation Oncologist, level IB may also be spared in low risk node positive patients. Patients presenting with isolated retropharyngeal nodes or isolated level IV nodes are considered low risk for level IB involvement. Treatment of level IB should be considered in node negative patients with extensive involvement of the hard palate, nasal cavity or maxillary antrum.

When IMRT or IMPT is used to treat the entire plan, the low risk lymph nodal regions, $CTVn_{54.12}$ includes the level IV, VB, and supraclavicular nodal regions unless there are grossly enlarged nodes in these regions for which it is encouraged to treat these regions to $CTVn_{59.4 \text{ or } 56}$. For patients receiving 35 fractions, these regions can also be treated to 63 Gy.

Note: The consensus guideline for head and neck cancer is for **NODE NEGATIVE** patients only. One can use this guideline to treat the appropriate nodal levels only for **NODE NEGATIVE** patients. http://www.rtog.org/CoreLab/ContouringAtlases/HNAtlases.aspx

Table 3: Volumes required to deliver IMRT treatment in either 33 fractions (PTV_6996, PTV_6270, PTV_5940, PTV_5412) or 35 fractions (PTV_7000, PTV_6300, PTV_5600).

	Description
GTVp	Primary site gross disease based on imaging and clinical examination findings
GTVn	Nodal gross disease based on imaging and clinical examination findings

GTV	GTVp + GTVn
CTV_6996 or 7000	GTV + *3 mm *May be reduced to as low as 0 mm at the discretion of the radiation oncologist, typically when tumors abut critical structures
PTV_6996 or 7000	CTV_6996 or CTV_7000 + *5 mm *May be reduced to 3 mm if daily IGRT is used *May be reduced to 0 mm near critical structures such as brain stem and chiasm When reporting the dose, refer to protocol for PTV_eval guidelines
CTV_6270 or 6300 (For GTVn ≤2 cm involving levels IB, IV, or VB)	GTVn + *3 mm *May be reduced to as low as 0 mm at the discretion of the Radiation Oncologist typically when tumors abut structures
PTV_6270 or 6300	CTV_6270 or 6300 + *5 mm *May be reduced to 3 mm if daily IGRT is used *May be reduced to 0 mm near critical structures such as brain stem and chiasm When reporting the dose, refer to protocol for PTV_eval guidelines
CTV_5940p or 5600p [Note: high risk regions can also be treated to 6300cGy]	GTVp + *8 mm *May be reduced to as low as 0 mm if abutting critical structures Include the following at-risk sites: • Entire nasopharynx • Anterior 1/3 of the clivus (the entire clivus if involved) • Skull base (foramen ovale and rotundum bilaterally) • Bilateral pterygoid fossae • Bilateral parapharyngeal space • Inferior sphenoid sinus (in T3-T4 disease, the entire sphenoid sinus) • Posterior fourth of the nasal cavity and maxillary sinuses (as long as coverage of the pterygopalatine fossae is adequate) • Ipsilateral or bilateral cavernous sinus, if needed, should be included in high-risk patients (T3/T4)
CTV_5940n or 5600n	GTVn + *8 mm *May be reduced to as low as 0 mm if abutting critical structures Include the following at risk nodal levels: • Upper deep jugular (junctional, parapharyngeal): bilaterally; • Subdigastric (jugulodigastric) [level II]: bilaterally; • Midjugular (level III): bilaterally; • Ipsilateral or bilateral low jugular (level IV) and supraclavicular region (for heminecks with grossly involved low neck nodes); • Upper and mid-posterior cervical (upper and mid-level V, corresponding to the same level as level II and III): bilaterally; • Retropharyngeal: bilaterally; • Ipsilateral or bilateral submandibular (level IB) [for heminecks with direct involvement of level IB or II on that side].

CTV_5940 or 5600	CTV_5940p or 5600p + CTV_5940n or 5600n
PTV_5940 or 5600	CTV_5940 or 5600 + *5 mm *May be reduced to 3 mm if daily IGRT is used *May be reduced to 0mm when near critical structures such as brain stem and chiasm When reporting the dose, refer to protocol for PTV_eval guidelines
CTV_5412 ([†]May be used for 33 fraction single IMRT plans on heminecks without grossly involved low-lying neck nodes) [note: this subclinical region can also be treated to 5600cGy in 35 fractions}	Include the following at risk nodal levels: • Level IV, VB, and supraclavicular nodes
PTV_5412	CTV_5412 + *5 mm *May be reduced to 3 mm if daily IGRT is used *May be reduced to 0mm near critical structures When reporting the dose, refer to protocol for PTV_eval guidelines

[†]Alternatively, the low neck can be separately treated for patients receiving either of the above fractionations with conventional AP or AP/PA field(s) to a dose of 50.4 or 50 Gy in 1.8 or 2 Gy fractions. (Table created with help from James M. Melotek, University of Chicago.)

Table 4: Volumes required to deliver IMPT treatment with robust optimization and evaluation in either 33 fractions or 35 fractions.

	Description
GTVp	Primary site gross disease based on imaging and clinical examination findings
GTVn	Nodal gross disease based on imaging and clinical examination findings
GTV	GTVp + GTVn
CTV_6996 or 7000	GTV + *3 mm *May be reduced to as low as 0 mm at the discretion of the radiation oncologist, typically when tumors abut critical structures
CTV*_6996 or 7000	CTV*_6996 or CTV*_7000 CTV* is referred to as worst case CTV 6996 or worst case CTV 7000 during robust optimization and evaluation
CTV_6270 or 6300	GTVn + *3 mm

(For GTVn ≤2 cm involving levels IB, IV, or VB)	*May be reduced to as low as 0 mm at the discretion of the Radiation Oncologist typically when tumors abut structures
CTV*_6270 or 6300	CTV*_6270 or 6300 is referred to as worst case CTV 6270 or worst case CTV 6300 during robust optimization and evaluation
CTV_5940p or 5600p [Note: high risk regions can also be treated to 6300cGy]	GTVp + *8 mm *May be reduced to as low as 0 mm if abutting critical structures Include the following at-risk sites: • Entire nasopharynx • Anterior 1/3 of the clivus (the entire clivus if involved) • Skull base (foramen ovale and rotundum bilaterally) • Bilateral pterygoid fossae • Bilateral parapharyngeal space • Inferior sphenoid sinus (in T3-T4 disease, the entire sphenoid sinus) • Posterior fourth of the nasal cavity and maxillary sinuses (as long as coverage of the pterygopalatine fossae is adequate) • Ipsilateral or bilateral cavernous sinus, if needed, should be included in high-risk patients (T3/T4)
CTV_5940n or 5600n	GTVn + *8 mm *May be reduced to as low as 0 mm if abutting critical structures Include the following at risk nodal levels: • Upper deep jugular (junctional, parapharyngeal): bilaterally; • Subdigastric (jugulodigastric) [level II]: bilaterally; • Midjugular (level III): bilaterally; • Ipsilateral or bilateral low jugular (level IV) and supraclavicular region (for heminecks with grossly involved low neck nodes); • Upper and mid-posterior cervical (upper and mid-level V, corresponding to the same level as level II and III): bilaterally; • Retropharyngeal: bilaterally; • Ipsilateral or bilateral submandibular (level IB) [for heminecks with direct involvement of level IB or II on that side].
CTV_5940 or 5600	CTV_5940p or 5600p + CTV_5940n or 5600n
CTV*_5600 or 5940	CTV*_5940 or 5600 is referred to as worst case CTV 5940 or CTV 5600 during robust optimization and evaluation
CTV_5412 ([†]May be used for 33 fraction single IMRT plans on heminecks without grossly involved low-lying neck nodes) [note: this subclinical region can also be treated to 5600cGy in 35 fractions}	Include the following at risk nodal levels: • Level IV, VB, and supraclavicular nodes
CTV*_5412	CTV*_5412 is referred to as worst case CTV 5412 during robust optimization and evaluation

†Alternatively, the low neck can be separately treated for patients receiving either of the above fractionations with conventional AP or AP/PA field(s) to a dose of 50.4 or 50 Gy in 1.8 or 2 Gy fractions.

6.4.3 A separate planning Target Volume (PTV) will provide a margin around the CTVs to compensate for the variability of treatment set up and internal organ motion.

For IMRT, unless there are published peer review papers on the set-up errors of a given institution, specifically dealing with patient daily set-up for head and neck cancer, a margin of 5 mm around the CTVs is required in all directions to define each respective PTV (PTV69.96 or 70, PTV62.7 or 63, PTV59.4 or 56, PTV54.12). If the investigator wants to further reduce the PTV margin from 5 mm to 3 mm, daily IGRT must be employed and a credentialing procedure is required (see Table in Section 5.1.1). When an institution has results from a peer-reviewed, published study on head-and-neck set-up errors, upon submission of the material to the Medical Physicist Co-Chair and review/approval of the NRG Oncology Medical Physics Committee, the margins can be reduced to 3 mm without performing the credentialing described in Section 5.1.1. Careful consideration should be made when defining the superior and inferior margins in three dimensions.

Note that at any given point, the margin from the GTV at the primary site to the $PTV_{59.4 \text{ or } 56}$ typically should be 11 mm (8 + 3 mm) if daily IGRT is used or 13 mm (8 + 5 mm) if patients are treated without daily IGRT. Again, at the discretion of the treating radiation oncologist, $GTV_{69.96 \text{ or } 70}$ may be equivalent to $CTV_{69.96 \text{ or } 70}$, and in such cases, the respective $PTV_{59.4 \text{ or } 56}$ outermost boundaries are reduced accordingly. This margin can be as small as 0 mm especially when the tumor abuts critical normal tissues.

Robust optimization is preferred for IMPT plans and the worst case CTV may be used in place of the PTV for dose reporting when robustness evaluation (minimum of 3 mm setup error and 2% range uncertainty) is used. If robust optimization and evaluation method is not available, the IMRT dose prescription to the PTV described above may be used.

For some patients, a PTV will overlap critical organs, such as the brainstem, spinal cord, optic structures, and brachial plexus. The PTV may be modified in the following situations:

1) When a PTV overlaps a critical OAR (spinal cord and/or brainstem) and its associated PRV, the PTV should be modified to exclude the PRV so as to limit the dose delivered to the PRV within constraints defined in the table in Section 6.4.4.
2) When expansion of CTVs results in PTVs that extend beyond the patient's external contour, the PTVs should be constrained 5 mm within the external contour. For situations where gross disease is external to this constraint, the use of 5 mm tissue equivalent material (bolus) is required. No PTV constraint should be used underneath the bolus.

The true PTV as obtained by following the margin rules stated above must be contoured and identified as PTV without a subscript. It is acknowledged there will be compromise to the true PTV dose to meet critical OAR dose-volume criteria for the brainstem, spinal cord, optic structures, and brachial plexus. Additionally, it is recognized that it may not be possible to meet the study PTV dose compliance criteria in these cases. It is recommended that a PTV-subvolume, PTV_Eval, be generated during the planning process when it is necessary to avoid PTV overlap with the critical OARs (the brainstem, spinal cord, optic structures, and brachial plexus). In some cases, the OAR plus a maximum 3 mm margin may need to be excluded from the true PTV to generate the PTV_Eval. The additional margin should not exceed 3 mm, i.e. PTV_Eval = true PTV minus (OAR + 3mm). If the PTV exceeds the external skin, the PTV_Eval = true PTV with 5 mm extraction from the skin. If the CTV exceeds the external skin, a 5mm bolus is required to ensure the adequate dose coverage to the CTV. Institutions must submit all true PTVs (named simply PTV contours) and any PTV_Eval contours for review. PTV study nomenclature should be maintained for PTV_Eval, e.g. a subvolume for $PTV_{69.96 \text{ or } 70}$ will be PTV_6996_Eval or PTV_7000_Eval. PTV subvolumes, PTV_Eval can be generated automatically

by modern planning systems and therefore, significant additional planning workload should not be required. The use of PTV subvolumes, PTV_Eval is consistent with the principles of ICRU 83 definition and reporting of PTV: ICRU 83: Definition of volumes. *Journal of the ICRU*. 10(1): Report 83, 41-53, 2010. Oxford University Press.

If the delineation is done correctly, the results should be as follows: GTVp + 3 mm = $CTVp_{69.96 \text{ or } 70}$; GTVn + 3 mm = $CTVn_{69.96 \text{ or } 70}$; $CTVp_{59.4 \text{ or } 56}$ includes $CTVp_{69.96 \text{ or } 70}$ and $CTVn_{59.4 \text{ or } 56}$ includes $CTVn_{69.96 \text{ or } 70}$ but the outermost boundary of the $CTV_{59.4 \text{ or } 56}$ should be 8 mm away from GTVp and GTVn. $PTV_{69.96 \text{ or } 70}$ will be 5 mm away from $CTV_{69.96 \text{ or } 70}$.

Note: If daily IGRT is employed, $PTV_{69.96 \text{ or } 70}$ will be 3 mm away from $CTV_{69.96 \text{ or } 70}$ and $PTV_{59.4 \text{ or } 56}$ will be 11 mm away from GTV at the primary site and from the gross nodes including the retropharyngeal region.

Although not shown as an example, the treating physician has the option to treat small volume lymph nodes (those nodes ≤ 2 cm) to 62.7 or 63 Gy. **The margins at the primary and the nodal sites are crucial to ensure no marginal misses**.

However, when the GTV is abutting critical structures such as the brainstem, spinal cord, or optic apparatus, the margins can be reduced to as low as 0 mm. This is also true for all CTV target volumes with the goal to protect normal tissue.

6.4.4 Required Structures and Standard Names for Digital RT Submission

IMRT plans:

Note: All structures must be named for digital RT data submission as listed in the respective table below. The structures marked as "Required" in the table must be contoured and submitted with the treatment plan. Structures marked as "Required when applicable" must be contoured and submitted when applicable.

Resubmission of data may be required if labeling of structures does not conform to the standard DICOM name listed. Capital letters, spacing and use of underscores must be applied exactly as indicated.

Names		**Description**
33 Fractions	**35 Fractions**	
GTV	**GTV**	GTV **Required**
GTVp	**GTVp**	GTVp (Primary) **Required**
GTVn	**GTVn**	GTVn (Lymph Node) **Required**
CTV_6996	**CTV_7000**	$CTV_{69.96 \text{ or } 70}$ **Required**
CTV_6270	**CTV_6300**	$CTV_{62.7 \text{ or } 63}$ **Required when applicable**
CTV_5940	**CTV_5600**	$CTV_{59.4 \text{ or } 56}$ **Required**
CTV_5412		$CTV_{54.12}$ **Required when applicable**
PTV_6996	**PTV_7000**	$PTV_{69.96 \text{ or } 70}$ **Required**

PTV_6996_Eval	**PTV_7000_Eval**	$PTVsv_{69.96 \text{ or } 70}$ (PTV sub volume) **Required when applicable**
PTV_6270	**PTV_6300**	$PTV_{62.7 \text{ or } 63}$ **Required when applicable**
PTV_6270_Eval	**PTV_6300_Eval**	$PTVsv_{62.7 \text{ or } 63}$(PTV sub volume) **Required when applicable**
PTV_5940	**PTV_5600**	$PTV_{59.4 \text{ or } 56}$ **Required**
PTV_5940_Eval	**PTV_5600_Eval**	$PTVsv_{59.4 \text{ or } 56}$ (PTV sub volume) **Required when applicable**
PTV_5412		$PTV_{54.12}$ **Required when applicable**
PTV_5412_Eval		$PTVsv_{54.12}$(PTV sub volume) **Required when applicable**

Names for both 33 and 35 fractions	Description
BrainStem	Brain Stem **Required**
BrainStem_03	3 mm expansion of Brain Stem **Optional**
BrachialPlexus_R	Right Brachial Plexus **Required**
BrachialPlexus_L	Left Brachial Plexus **Required**
BrachialPlex_03R	3 mm expansion of Right Brachial Plexus **Optional**
BrachialPlex_03L	3 mm expansion of Left Brachial Plexus **Optional**
OpticChiasm	Optic Chiasm **Required**
OptChiasm_03	3 mm expansion of Optic Chiasm **Optional**
Cochlea_R	Right Cochlea **Required**
Cochlea_L	Left Cochlea **Required**
Ear_Inner_R	Right Inner Ear **Optional**
Ear_Inner_L	Left Inner Ear **Optional**
Ear_Middle_R	Right Middle Ear **Optional**
Ear_Middle_L	Left Middle Ear **Optional**
Esophagus_Up	Esophagus (including postcricoid pharynx) **Optional**
Eye_R	Right Eye **Required**
Eye_L	Left Eye **Required**
LarynxGSL	Glottic Larynx **Required**
Lens_R	Right Lens

	Required
Lens_L	Left Lens **Required**
Mandible	Mandible **Required**
OpticNerve_R	Right Optic Nerve **Required**
OpticNerve_L	Left Optic Nerve **Required**
OptNerv_R_03	3 mm expansion of Right Optic Nerve **Optional**
OptNerv_L_03	3 mm expansion of Left Optic Nerve **Optional**
OralCavity	Oral Cavity **Required**
Parotid_R	Right Parotid Gland **Required**
Parotid_L	Left Parotid Gland **Required**
Pituitary	Pituitary **Optional**
Lips	Lips **Optional**
SpinalCord	Spinal Cord **Required**
SpinalCord_03 or 05	3 mm or 5 mm expansion of Spinal Cord **Optional**
SkinOAR	3 mm thickness of external Skin (region of TV) **Optional**
TemporalLobe_R	Right Temporal Lobe **Required**
TemporalLobe_L	Left Temporal Lobe **Required**
TMjoint_R	Right TMJ **Required**
TMjoint_L	Left TMJ **Required**
External	Skin **Required**

For IMPT plans without robust optimization and evaluation capability, use the same table above as the IMRT plans.

For IMPT plans with robust optimization and evaluation: on table above, replace PTVs with corresponding worst case CTVs (i.e., PTV=worst case CTV, for data submission label as PTV(s)). Screen captures of the robustness evaluation should also be submitted for evaluation.

6.5 Critical Structures (4/14/16)

6.5.1 Critical Normal Structures

Surrounding critical normal structures, including the brainstem, spinal cord, optic nerves, chiasm, eyes, parotid glands, cochlea, skin (in the region of the target volumes), oral cavity, mandible, temporal lobes, brachial plexus, and glottic larynx must be outlined.

Physicians should assist the planner in identifying the critical normal structures. If planning organ at risk volumes (PRVs) are used, the spinal cord PRV will be defined as a three-dimensional margin at least 3 (if IGRT is used) or 5 mm (if IGRT is not used) larger than the spinal cord to ensure that the PRV margin is at least 3 or 5 mm from any portion of the spinal cord. The brainstem PRV, chiasm PRV, and optic nerve PRV will be defined as at least 3 mm larger in all directions than the corresponding structure. The normal tissues will be contoured and considered as solid organs. The tissue within the skin surface and outside all other critical normal structures and PTVs is designated as unspecified tissue.

DVH's must be generated for all critical normal structures, and the unspecified tissues. Dose constraints used for treatment planning can be extracted from the Table in Section 6.7.

All maximum doses stated in the table are defined as to the maximum dose for a volume of 0.03 cc (approximately 3x3x3 mm or typically, the size of the dose calculation grid).

Note: Protection of the brain stem, optic chiasm, and the spinal cord is essential. Using the subvolume (PTV_Eval) approach described in Section 6.4.3 can be used to mitigate the problem. It is necessary to balance the tradeoff between critical structure overdose and target underdose using the information from the table in Section 6.7. If the tumor invades the optic structures, the treating physician must discuss the possibility of blindness due to radiation therapy during the Informed Consent process.

6.5.2 The dose prescription is to be based on a dose distribution corrected for heterogeneities. A list of the approved Treatment Planning Systems (TPS) and algorithm for dose calculation can be found on the IROC Houston web site.

6.5.3 Planning Priorities

Critical normal structure constraints, specifically, the brain stem and spinal cord, which take priority over coverage of the tumor, followed by the prescription goals are the most important planning priorities. The priorities in addressing the protocol aims and constraints will be in the following order:

1) Critical Normal Structure Constraints (Section 6.7) specifically, the brain stem, optic chiasm, and spinal cord, which take priority over coverage of the tumor;
2) Dose Specifications (Section 6.1);
3) Planning Goals: Salivary glands (Section 6.7)*;*
4) Planning Goals: All other normal structures (Section 6.7).

6.6 Documentation Requirements (04May2017)

Verification and orthogonal films or images CT or cone beam images are required. For IMRT or IMPT dose delivery, orthogonal films or images, CT or cone beam images that localize the isocenter placement shall be obtained. This information should be archived by the submitting institution, so it can be made available for possible future review.

Note: Due to the sensitivity of IMPT dose distribution to anatomical change, weekly verification CT or conebeam CT scans are required to ensure that a high quality IMPT plan is maintained throughout the course of treatment. (Section 6.2.1)

6.7 Compliance Criteria (23-Oct-2017)

Treatment breaks must be clearly indicated in the treatment record along with the reason(s) for the treatment break(s). Treatment breaks, if necessary, should ideally not exceed 5 treatment days at a time and 10 treatment days total. Treatment breaks should be allowed only for resolution of severe acute toxicity and/or for intercurrent illness and not for social or logistical reasons. Unplanned treatment breaks should be avoided if at all possible and any breaks for reasons other than adverse events should be discussed with the Principal Investigator, Nancy Lee, MD, prospectively if possible, and the reasons for the break in treatment should be clearly documented.

Each submitted IMRT treatment plan will be judged as follows:

Target volume constraints and compliance criteria for 33 fractions

Name of Structure	Dosimetric parameter*	Per Protocol	Variation Acceptable
PTV_6996 or PTV_6996_Eval	V100%[%]	95	90
	D99%[%]	>=93	>=90
	D0.03cc[%]	<=115	<=120
PTV_6270 or PTV_6270_Eval	V62.7Gy[%]	>=95	>=90
PTV 5940 or PTV_5940_Eval	V59.4Gy[%]	>=95	>=90
PTV_5412 or PTV_5412_Eval	V54.12Gy[%]	>=95	>=90

Target volume constraints and compliance criteria for 35 fractions

Name of Structure	Dosimetric parameter*	Per Protocol	Variation Acceptable
PTV_7000 or PTV_7000_Eval	V100%[%]	95	90
	D99%[%]	>=93	>=90
	D0.03cc[%]	<=115	<=120
PTV_6300 or PTV_6300_Eval	V63Gy[%]	>=95	>=90
PTV_5600 or PTV_5600_Eval	V56Gy[%]	>=95	>=90

Normal Structure Constraints and Compliance Criteria for 33 and 35 fractions

Name of Structure	Dosimetric parameter	Per Protocol	Variation Acceptable
BrainStem	D0.03cc[Gy]	<=54	<=60
SpinalCord	D0.03cc[Gy]	<=45	<=50
OpticNrv_L/R	D0.03cc[Gy]	<=54	<=60
OpticChiasm	D0.03cc[Gy]	<=54	<=56
Bone_Mandible	D0.03cc[Gy]	<=70	<=75
Joint_TM_L/R	D0.03cc[Gy]	<=70	<=75
BrachialPlexus_L/R	D0.03cc[Gy]	<=66	<=70
Lobe_Temporal_L/R	D0.03cc[Gy]	<=70	<=72
Glnd_Parotid_L/R	Mean[Gy]	<=26	<=33

Per Protocol range is excluded from Variation Acceptable range.

*The subvolume (PTV_Eval) should be used for evaluation when the volume of a critical structure overlaps with the true PTV. Only the true critical structures, not the PRVs are evaluated. In overlap situations, treatment planning should attempt to balance the tradeoff between minimum dose to the CTV and protection of the critical structure.
If the treatment planning system does not calculate the mean dose, use the dose to 50% of the volume as an alternative.

For IMPT plans with robust optimization and evaluation, the worst case CTV will replace PTVs in table above for dose reporting purposes. For IMPT plans without robust optimization and evaluation, use the

same table as IMRT for plan compliance evaluation. Screen captures of the robustness evaluation should also be submitted for evaluation.

For proton, Gy is referred to as Gy(RBE), the radiobiologically equivalent dose.

Recommended Dose Acceptance Criteria for Other Normal Tissue (not to be used for plan score)

Oral cavity (excluding PTV's)	Mean dose less than 40 Gy
Each cochlea	Maximum dose ≤ 55 Gy * Mean dose ≤ 45 Gy
Eyes	Max dose less than 55 Gy*
Lens	Max dose less than 15 Gy*
Glottic Larynx	Mean dose less than 40 Gy
Esophagus, Postcricoid pharynx	Mean dose less than 50 Gy

* **Note**: The maximum dose is defined as the maximum dose to encompassing 0.03 cc volume.

6.8 R.T. Quality Assurance Reviews (04May2017)

The Principal Investigator/Radiation Oncologist, Nancy Lee, MD, will perform RT Quality Assurance Reviews. These reviews will be ongoing. IROC Philadelphia-RT QA center will facilitate these reviews. The scoring mechanism is: Per Protocol, Variation Acceptable, Deviation Unacceptable.

6.9 Radiation Therapy Adverse Events (10/9/14)

Grade 3-4 therapy-induced mucositis and/or dysphagia, which are enhanced by cisplatin, are expected to develop in about two thirds of patients. Nutritional evaluation prior to the initiation of therapy for a prophylactic gastrostomy (PEG) tube placement is highly recommended. Placement of a feeding tube should be recorded, as should use of a feeding tube during and after treatment (e.g., greater than or less than 50% of nutrition by tube). Other common radiation adverse events include: fatigue, weight loss, regional alopecia, xerostomia, hoarseness, transient ear discomfort, dysgeusia, and skin erythema and desquamation within the treatment fields.

Less common long-term treatment adverse events include: hypothyroidism, loss of hearing, chronic swallowing dysfunction requiring permanent feeding tube, and cervical fibrosis. Much less common radiation adverse events include: mandibular osteoradionecrosis (< 5% incidence), cranial nerve damage, temporal lobe necrosis, and cervical myelopathy (< 1% with restriction of spinal cord dose to ≤ 45 Gy).

6.9.1 *Treatment Interruptions*

Interruptions in radiotherapy may be necessitated by skin reaction, mucositis, ulceration, edema, or other acute complication. The reason for and the length of any such interruption must be documented. If the sum total of such interruptions exceeds five normally-scheduled treatment days, the treatment may be considered as a Deviation Unacceptable for the protocol. Radiation therapy will be continued without interruption if at all possible. Should confluent mucositis, moist desquamation unresponsive to topical dressings, or severe stomatitis resulting in weight loss greater than 15% occur, radiation may be interrupted in order to relieve morbidity, but this is strongly discouraged. The use of tube feedings in this situation is encouraged; it is anticipated to minimize treatment interruptions.

6.10 Radiation Therapy Adverse Event Reporting

See Section 7.12 for details.

7.0 DRUG THERAPY (9/2/15)

Protocol treatment must begin at the latest within 21 days after Step 2 Registration and within 28 days after the end of radiation. In order to minimize protocol deviation, it is recommended that the patient not be registered until there is a treatment start date established. If the start date is beyond 21 days after Step 2 registration, contact the Principal Investigator, Dr. Lee.

7.1 Treatment for Patients with Detectable EBV DNA from Pre-Treatment Analysis (04May2017)

7.1.1 Low-dose Cisplatin Administration Concurrent with Radiation

Cisplatin: 40 mg/m^2/day, weekly during radiation, with a maximum cumulative dose of **280 mg/m^2**.

No concurrent cisplatin will be administered after the final week of radiation, but the final dose of cisplatin may be administered following the last dose of radiation if it is administered within the same calendar week. **Cisplatin should be administered on Mondays or Tuesdays to maximize overlap of daily radiation with cisplatin exposure**. Administration on Wednesday prior to that day's radiation dose is acceptable but not preferred. For cisplatin given on Wednesdays because of holiday reasons, for example, cisplatin can be given before or after RT to prevent any logistical delays. Investigators should strive to administer cisplatin on the same day each week but variance of 1 day is acceptable for vacations, holidays, etc. If radiation treatments are held for toxicity, cisplatin dosing should also be held.

7.1.2 Low-dose Cisplatin Concurrent with Radiation Administration Guidelines

High dose cisplatin is highly emetogenic . While this protocol is using an intermediate dose of cisplatin when administered concurrently with radiation, investigators should be prepared to use aggressive prophylactic antiemetics and hydration. Many institutions will have standard guidelines for the administration of cisplatin at the doses used in this study. **For purposes of this protocol, individual investigators may use these local guidelines for cisplatin administration. One possible approach is outlined below.** This may need to be modified based on local guidelines and patient related factors (e.g. the substitution of normal saline in diabetic patients). Similarly, the anti-emetic regimen for this combination is to be determined by the local investigator.

- *Low-dose Cisplatin anti-emetic administration guidelines*: 5-HT3 antagonists (e.g. ondansetron 16 mg PO prior to cisplatin and 8 mg PO up to 3 times daily on days 2 and 3 following cisplatin weekly. Dexamethasone x 3 days starting prior to the cisplatin dose weekly, 12 mg on day 1 and 8 mg on days 2 and 3 each week. Use of other anti-nausea meds such as aprepitant, metoclopramide, or prochlorperazine is left to the discretion of the investigator.
- *Low-dose Cisplatin pre-hydration guidelines*: Pre-hydration with 1 liter D5 ½ NS and 40 meq KCL/ liter x 1 liter prior to cisplatin. Mannitol 12.5 gm IV immediately prior to cisplatin.
- *Low-dose Cisplatin administration*: Cisplatin, 40 mg/m2 over 30-60 minutes IV in 250 cc NS. See Section 7.9 for dose modifications. See above discussion on scheduling and number of doses concurrent with radiation.
- *Low-dose Cisplatin post-hydration guidelines*: Following the end of the cisplatin administration, an additional liter of ½ NS with 10 meq KCL/L, 8 meq MgSO4/L, and 25 g mannitol should be infused over 2 hours. On the second and third day following cisplatin, patient should be encouraged to take at least 2 liters of fluid per day orally. Patients unable to orally self-hydrate should be considered for additional IV hydration on these days with NS.

7.2 Randomized Phase II (Detectable EBV DNA): For Patients Randomized to Cisplatin and 5-Fluorouracil ("PF") (3/4/15)

Patients are scheduled to receive up to 3 adjuvant cycles of PF beginning 28 days (+/- 2 days) after the end of radiation. Initiation of PF and subsequent PF cycles may be delayed up to 14 days to allow patients to recover from chemoradiation adverse events (AEs).The initiation of all subsequent PF cycles would in this case be delayed so that PF is administered on a q28 day schedule. Patients who have not recovered from chemoradiation AEs in 14 days will not receive further protocol treatment but will be followed as specified in the protocol.

7.2.1 Requirements for Initiation of Each Adjuvant PF Cycle

- Zubrod Performance status < 3;
- CBC/differential and chemistries obtained within 1 day prior to beginning adjuvant PF, with adequate bone marrow function defined as follows: Absolute Neutrophil Count (ANC) ≥ 1,000 cells/mm^3 and Platelets ≥ 100,000 cells/mm^3;
- AST/ALT and total bilirubin < grade 2 (CTCAE, v. 4);
- Serum creatinine < grade 2 (CTCAE, v. 4);
- All AEs must be < grade 3 (CTCAE, v. 4).

7.2.2 Cisplatin Administration, PF Regimen

Cisplatin: 80 mg/m^2, q28 days for 3 cycles beginning 28 days (+/- 2 days) after completion of radiation.

High dose cisplatin is highly emetogenic . Many institutions will have standard guidelines for the administration of cisplatin at the doses used in this study. **For purposes of this protocol, individual investigators may use these local guidelines for cisplatin administration. One possible approach is outlined below.** This may need to be modified based on local guidelines and patient related factors (e.g. the substitution of normal saline in diabetic patients). Similarly, the anti-emetic regimen for this combination is to be determined by the local investigator.

- *High-Dose Cisplatin Anti-Emetic Administration Guidelines*: Substance P antagonist such as **aprepitant**, 125 mg PO on day 1 prior to cisplatin and 80 mg on days 2 and 3. 5-HT3 antagonists (e.g. **ondansetron**, 16 mg PO prior to cisplatin and 8 mg PO up to 3 times daily on days 2 and 3 following cisplatin. **Dexamethasone** x 3 days prior to cisplatin, 12 mg PO or IV on day 1 and 8 mg on days 2 and 3. Use of other anti-nausea meds such as metoclopramide, lorazepam, olanzapine, or prochlorperazine is left to the discretion of the investigator.
- *Cisplatin Pre-Hydration Guidelines*: Pre-hydration with 1 liter D5 ½ NS and 40 meq KCL/ liter x 1 liter prior to cisplatin. Mannitol 12.5 gm IV immediately prior to cisplatin.
- *Cisplatin Administration*: Cisplatin, 80 mg/m^2 over 60-120 minutes IV in 250 cc NS. See Section 7.9 for dose modifications. See above discussion on scheduling and number of doses concurrent with radiation.
- *Cisplatin Post-Hydration Guidelines*: Following the end of the cisplatin administration, at least an additional 1.5 liters of ½ NS with 10 meq KCL/L, 8 meq MgSO4/L, and 25 g mannitol should be infused over 2-4 hours. On the second and third day following cisplatin, patient should be encouraged to take at least 2 liters of fluid per day orally. Patients unable to orally self-hydrate should be considered for additional IV hydration on these days with NS.

7.2.3 5-Fluorouracil (5-FU) Administration, PF Regimen

5-FU, 1000mg/m^2/day is given intravenously in 5% glucose in ½ NS as a 96 hour (4 day) continuous infusion for a total dose of 4000 mg/m^2. The 5- FU continuous infusion may begin concurrently with the cisplatin or be initiated after the cisplatin is completed on the first day of the chemotherapy cycle. However, institutions may follow their standard guidelines for the administration of 5-FU at the dose specified in this study (e.g. the substitution of normal saline for diabetic patients).

7.2.4 Myeloid Growth Factor Use Following Adjuvant PF

Pegfilgrastim or Filgrastim may be used according to institutional guidelines. We recommend following the NCCN myeloid growth factor use guidelines (see NCCN.org).

7.3 Randomized Phase II (Detectable EBV DNA): For Patients Randomized to Gemcitabine and Paclitaxel ("GT") (23-Oct-2017)

Patients are scheduled to receive up to 4 adjuvant cycles of GT beginning 28 days (+/- 2 days) after the end of radiation. Initiation of GT and subsequent GT cycles may be delayed up to 14 days to allow patients to recover from chemoradiation adverse events (AEs).The initiation of all subsequent GT cycles would in this case be delayed so that GT is administered on a q21 day schedule. Patients who have not recovered from chemoradiation AEs in 14 days will not receive further protocol treatment but will be followed as specified in the protocol.

7.3.1 Requirements for Initiation of Each Adjuvant GT Cycle

- Zubrod Performance status < 3;
- CBC/differential and chemistries obtained within 1 day prior to beginning adjuvant GT, with adequate bone marrow function defined as follows: Absolute Neutrophil Count (ANC) ≥ 1,000 cells/mm^3 and Platelets ≥ 100,000 cells/mm^3;
- AST/ALT and total bilirubin < grade 2 (CTCAE, v. 4);
- Serum creatinine < grade 2 (CTCAE, v. 4);
- All AEs must be < grade 3 (CTCAE, v. 4).

7.3.2 GT Premedications

The premedication for gemcitabine and paclitaxel should account for the emetogenic potential and infusion reaction potential of these agents. There is no one universally accepted infusion reaction prophylaxis regimen for weekly paclitaxel dosing, but in general dexamethasone, diphenhydramine, and an H2 antagonist are used. Local institutional guidelines may be used. The regimen below is recommended. For patients who experience more than mild infusional reactions with the first dose of paclitaxel, more aggressive premedication regimens including dexamethasone 6 and 12 hours prior to paclitaxel infusion should be considered. Institutions should have a paclitaxel hypersensitivity management in place.

Diphenhydramine, 25 mg IV or PO 1 hour prior to paclitaxel;
Dexamethasone, 20 mg IV or PO 1 hour prior to paclitaxel;
Famotidine (or equivalent H2 blocker dose; however, CIMETIDINE SHOULD NOT BE USED), 20 mg IV or PO 1 hour prior to paclitaxel;
Ondansetron, 16 mg IV or PO prior to paclitaxel.

7.3.3 Paclitaxel Infusion: 80 mg/m^2 IV in 250 cc NS over 1 hour on days 1 (+/- 2 days) and 8 (+/- 2 days) of each 21 day cycle.

7.3.4 Gemcitabine infusion: 1000 mg/m^2 in 250 cc NS over 30 minutes immediately following the paclitaxel infusion on days 1 (+/- 2 days) and 8 (+/- 2 days) of each 21-day cycle. **Note**: The final concentration of the prepared drug must be in the range of 38 mg/ml to 0.1 mg/ml.

7.3.5 Myeloid Growth Factor Use Following Adjuvant PF

Pegfilgrastim or Filgrastim may be used according to institutional guidelines. We recommend following the NCCN myeloid growth factor use guidelines (see NCCN.org).

7.4 Phase III: Treatment for Patients with Undetectable EBV DNA

7.4.1 For patients randomized to cisplatin and 5-Fluorouracil ("PF"), see Section 7.2.

7.4.2 For patients randomized to observation, see Appendix I for study parameters.

7.5 Cisplatin

Refer to the package insert for detailed pharmacologic and safety information.

7.5.1 Formulation: Each vial contains 10 mg of DDP, 19 mg of sodium chloride, 100 mg of mannitol, and hydrochloric acid for pH adjustment. One vial is reconstituted with 10 ml of sterile water. The pH range will be 3.5 to 4.5. Cisplatin injection also is available from the manufacturer in aqueous solution, each ml containing 1 mg cisplatin and 19 mg NaCl and HCL or NaOH to adjust pH.

7.5.2 Mechanism of Action: The dominant mode of action of cisplatin appears to be inhibition of the incorporation of DNA precursors, although protein and RNA synthesis are also inhibited. Although this drug seems to act as an alkylating agent, there are data to indicate that its mode and sites of action are different from those of nitrogen mustard and the standard alkylating agents.

7.5.3 Administration: Cisplatin is highly emetogenic. After administering appropriate antiemetics, cisplatin will be infused over 30-60 minutes for the 40 mg/m^2 dose and 60-120 minutes for the 80 mg/m^2 dose along with vigorous hydration.

7.5.4 Storage and Stability: Reconstituted solution of cisplatin is stable for 20 hours when stored at 27°C and should be protected from light if not used within 6 hours. The vials and injection should not be refrigerated. Cisplatin has been shown to react with aluminum needles, producing a black precipitate within 30 minutes.

7.5.5 Adverse Events: Human toxicity includes nausea, vomiting, anaphylaxis, neuropathies, ocular disturbances, renal toxicity (with an elevation of BUN and creatinine and impairment of endogenous creatinine clearance, as well as renal tubular damage, which appears to be transient), ototoxicity (with hearing loss that initially is in the high-frequency range, as well as tinnitus), and hyperuricemia. Much more severe and prolonged toxicity has been observed in patients with abnormal or obstructed urinary excretory tracts. Myelosuppression, often with delayed erythrosuppression, is expected.

7.5.6 Supply: Cisplatin is commercially available. The use of drug(s) or combination of drugs in this protocol meets the criteria described under Title 21 CFR 312.2(b) for IND exemption.

Non-Canadian International Institutions

Please refer to your LOI Approval Notification. Your institution will be responsible for acquiring any drug noted in the protocol as commercially available and not provided for the study. Before drug can be provided your institution must comply with all pre-registration requirements and certifications and provide all necessary documentation listed in your LOI Approval Notification document.

7.6 5-Fluorouracil

Refer to the package insert for detailed pharmacologic and safety information.

7.6.1 Other Names: 5-FU, Adrucil

7.6.2 Formulation: 5-FU is supplied as a colorless-to-faint-yellow solution in 10-mL single-use vials. 5-FU is also available in 50 mL and 100 mL vials at a concentration of 50 mg/mL Each 10 mL of solution contains 500 mg 5-FU with pH adjusted to approximately 9.2 with sodium hydroxide. 5-FU is commercially available as a multisource product.

7.6.3 Administration: Continuous IV infusion over 96 hours.

7.6.4 Adverse Events: The following toxicities are anticipated:

- Hematologic: Leukopenia, thrombocytopenia, anemia (can be dose limiting, less common with continuous infusion);
- Dermatologic: Dermatitis, nail changes, hyperpigmentation, Hand-Foot Syndrome with protracted infusions, alopecia;
- Gastrointestinal: Nausea, vomiting, anorexia, diarrhea (can be dose limiting); mucositis (more common with 5-day infusion, occasionally dose limiting); severe, cholera-like diarrhea which can be fatal when given with leucovorin;
- Neurologic: Cerebellar Syndrome (headache and cerebellar ataxia);
- Cardiac: Angina, noted with continuous infusion;
- Ophthalmic: Eye irritation, nasal discharge, watering of eyes, blurred vision.

7.6.5 Drug Interactions

Cimetidine: Because cimetidine can decrease the clearance of 5-FU, patients should not enter on this study until the cimetidine is discontinued. Ranitidine or a drug from another anti-ulcer class can be substituted for cimetidine, as necessary.

Allopurinol: Oxypurinol, a metabolite of allopurinol, can potentially interfere with 5-FU anabolism via orotate phosphoribosyltransferase. Although this was originally used as a strategy to protect normal tissues from 5-FU-associated toxicity, further laboratory studies suggested possible antagonism of the anticancer activity of 5-FU in some tumor models. If a patient is receiving allopurinol, the need for taking this medicine should be ascertained. If possible, allopurinol should be discontinued prior to starting on this regimen, and another agent substituted for it.

7.6.6 Storage: Stable for prolonged periods of time at room temperature, if protected from light. Inspect for precipitate; resolubilize by heating to 140°F and shaking vigorously; allow to cool to body temperature before using. Do not allow to freeze.

7.6.7 Supply: 5-FU is commercially available. The use of drug(s) or combination of drugs in this protocol meets the criteria described under Title 21 CFR 312.2(b) for IND exemption.

Non-Canadian International Institutions

Please refer to your LOI Approval Notification. Your institution will be responsible for acquiring any drug noted in the protocol as commercially available and not provided for the study. Before drug can be provided your institution must comply with all pre-registration requirements and certifications and provide all necessary documentation listed in your LOI Approval Notification document.

7.7 Paclitaxel

Refer to the package insert for detailed pharmacologic and safety information.

7.7.1 Paclitaxel is a poorly soluble plant product from the western yew, Taxus brevifolia. The injection is a clear, colorless to slightly yellow viscous solution. Improved solubility requires further dilution with either 0.9% sodium chloride or 5% dextrose in water. All solutions of paclitaxel exhibit a slight haziness directly proportional to the concentration of drug and the time elapsed after preparation, although when prepared as described below, solutions of paclitaxel (0.3-1.2 mg/ml) are physically and chemically stable for 27 hours at ambient temperature (27°C).

7.7.2 Preparation: Paclitaxel injection is a sterile solution concentrate, 6 mg/ml in 5, 16.7, and 50 ml vials (30, 100, and 300 mg/vial) in polyoxyethylated castor oil (Cremophor EL) 50% and dehydrated alcohol, USP, 50%. Paclitaxel will be diluted to a final concentration of 0.3 to 1.2 mg/ml in D_5W, NS, or D_5NS, in glass or polyolefin containers due to leaching of diethylhexphthalate (DEHP) plasticizer from polyvinyl chloride (PVC) bags and intravenous tubing by the Cremophor vehicle in which paclitaxel is solubilized. Each bag/bottle should be prepared immediately before administration. NOTE: Formation of a small number of fibers in solution (NOTE: acceptable limits established by the USP Particular Matter Test for LVPs) have been observed after preparation of paclitaxel. Therefore, in-line filtration is necessary for administration of paclitaxel solutions. In-line filtration should be accomplished by incorporating a hydrophilic, microporous filter of pore size not greater than 0.22 microns (e.g.: Millex-GV Millipore Products) into the intravenous fluid pathway distal to the infusion pump. Although particulate formation does not indicate loss of drug potency, solutions exhibiting excessive particulate matter formation should not be used.

7.7.3 Administration: All patients should be premedicated prior to paclitaxel administration in order to prevent severe hypersensitivity reactions. See specific recommendations for pre-treatment in Section 7.3.

Paclitaxel, at the appropriate dose and dilution, will be given as an infusion as per standard of care guidelines. The paclitaxel is administered using an in-line filter with a maximum size of 0.22 micron. Paclitaxel will be administered via an infusion control device (pump) using non-PVC tubing and connectors, such as the intravenous administration sets (polyethylene or polyolefin) that are used to infuse parenteral nitroglycerin. Nothing else is to be infused through the line through which paclitaxel is administered.

Caution is warranted when paclitaxel is concomitantly administered with known substrate or inhibitors of CYP2C8 and CYP3A4.

7.7.4 Storage: Paclitaxel vials should be stored between 20°-25°C (68°-77°F).

7.7.5 Adverse Effects: Hematologic: Myelosuppression; Gastrointestinal: Nausea, diarrhea, vomiting, abdominal pain; Heart: Arrhythmias, heart block, hypertension; Neurological: Sensory and peripheral neuropathy; Allergy: Severe anaphylactic reactions; Other: Alopecia, fatigue, arthralgia, myopathy, myalgia, infiltration (erythema, induration, tenderness, rarely ulceration), hypotension, irritation to the injection site, mucositis

7.7.6 Supply: Paclitaxel is commercially available. The use of drug(s) or combination of drugs in this protocol meets the criteria described under Title 21 CFR 312.2(b) for IND exemption.

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

7.8 Gemcitabine

Refer to the package insert for detailed pharmacologic and safety information.

7.8.1 Formulation: Gemcitabine is a nucleoside metabolic inhibitor that exhibits antitumor activity. Gemcitabine HCl is 2´-deoxy-2´,2´-difluorocytidine monohydrochloride (-isomer) and is available as a lyophilized powder in sterile vials containing 200 mg or 1 gram of gemcitabine as the hydrochloric salt (*expressed as the free base)* formulated with mannitol and sodium acetate.

7.8.2 Preparation: Drug vials will be reconstituted with normal saline added to the vial to make a solution containing 38 mg/mL. The solution is further diluted to a concentration as low as 0.1 mg/mL.

7.8.3 Administration: An appropriate amount of drug will be prepared with normal saline and administered as a 30 minute infusion.

7.8.4 Dosage: See Section 7.3.

7.8.5 Storage and Stability: The lyophilized product should be stored at controlled room temperature (20° to 25° C; 68° to 79° F). Once the drug has been reconstituted it should be stored at controlled room temperature and used within 24 hours.

7.8.6 Adverse Events: The major side effects observed with gemcitabine include leukopenia, thrombocytopenia, anemia, and a collection of signs and symptoms referred to collectively as a flu-like syndrome with fever, headache, rigors, myalgia, and anorexia. Less common side effects include abnormal liver function tests, kidney damage, proteinuria, hematuria, chills, nausea, vomiting, diarrhea, constipation, itchy skin rash, malaise, anorexia, cough, runny nose, insomnia, sweating, hypotension, drowsiness, peripheral edema, dyspnea, difficulty in breathing and stomatitis.

7.8.7 Supply: Gemcitabine is commercially available.

7.9 Dose Modifications

Note: If adverse events prevent the administration of chemotherapy, the patient may continue to receive radiation therapy.

7.9.1 Cisplatin Dose Modifications During Concurrent Radiation

Patients will be examined and graded for subjective/objective evidence of developing toxicity weekly according to CTCAE, v. 4 while receiving concurrent cisplatin with radiotherapy.

Treatment interruptions are allowed if there is symptomatic mucositis or skin reaction that, in the judgment of the clinician, warrants a break. For chemotherapy attributable AEs requiring a break in treatment, resumption of concurrent CDDP may begin when AEs have recovered to the levels specified below. If an AE does not resolve to the levels specified in the sections below prior to the calendar week of the last radiation treatment (See Section 7.1.1 for details concerning parameters for timing of last allowable concurrent CDDP dose), treatment off protocol can continue according to the judgment of the treating physician.

There will be no dose re-escalation for concurrent cisplatin.

Chemotherapy dosage modifications are based upon lab values obtained within the 24 hours prior to cisplatin and interim non-hematologic toxicities during the week prior to a particular cisplatin dose.

The dose modifications for cisplatin (below) are intended to be permanent (i.e., if the patient's dose is reduced to dose level -1, it remains at the reduced dose level) but dose reductions for

cisplatin during the concurrent chemoradiation portion do not extend to adjuvant treatment dosing unless adverse events (AEs) are ongoing.

7.9.2 Cisplatin Dose Modifications for Hematologic Adverse Events during Concurrent Radiation

Starting Dose	Dose Level -1	Dose Level -2
40 mg/m^2	30 mg/m^2	23 mg/m^2

Chemotherapy must not be administered until the ANC is ≥ 1,000 and platelets are ≥ 75,000. If not, delay 7 days. Cisplatin should be held every week until the above ANC and platelet parameters are met. Dose reductions when cisplatin is resumed after delay for low ANC or platelets will be as follows, based upon counts at time cisplatin was held.

ANC		Platelets	Reduction
≥ 1000 mm^3	and	≥ 75,000	None
< 1000 mm3	or	< 75,000	One dose level

Note: **Hematologic growth factors for neutropenia or anemia are not allowed during concurrent cisplatin and radiation treatment.**

7.9.3 Cisplatin Dose Modifications for Non-Hematologic Adverse Events during Concurrent Radiation **(4/14/16)**

Neutropenic Fever: Temperature of 38.5° C with ANC < 1000 is an expected potential complication of concurrent chemotherapy and radiotherapy or chemotherapy alone. If neutropenic fever is noted, the chemotherapy dose reduction will be determined by the weekly blood counts. See above.

Renal Adverse Events: Dose will be modified based on the serum creatinine prior to each cisplatin dose. If the serum creatinine is ≤ 1.5 mg/dL, creatinine clearance is not necessary for treatment with full dose. If the serum creatinine is > 1.5 mg/dL, a creatinine clearance should be obtained by urine collection or nomogram calculation (valid only if serum creatinine is not changing rapidly).

Cisplatin must not be administered until creatinine is ≤ 1.5 or creatinine clearance ≥ 50. Once the creatinine has met the above parameters, cisplatin may be restarted with the below modifications based on the creatinine at the time the cisplatin was held: In general, cisplatin should be held for weekly intervals (rather than restarting cisplatin later in the same week that a dose limiting AE is seen)

Cisplatin dose modifications for creatinine during concurrent radiation			
Creatinine (mg/dL)		Creatinine clearance, measured or calculated ml/min	Cisplatin dose reduction
≤ 1.5	or	≥ 50	No change
> 1.5	and	40-50	One dose level
		< 40	Hold drug

Neurologic (neuropathy) adverse events:

Grade (CTCAE, v. 4)	Dose Reduction
0-1	None
2	One dose level
3-4	Hold drug

Ototoxicity: Should patients develop clinical evidence of ototoxicity, further audiometric

evaluation is required. A neurologic deficit should be distinguished from a conductive loss from obstruction of the Eustachian tube leading to a middle ear effusion. Because no AE scale, including the CTCAE, v. 4, has been validated in terms of correlation with clinically relevant hearing loss, there are no protocol mandates requiring dose reduction for audiogram-determined sensorineural hearing loss without an analogous clinical high grade (> grade 2) hearing loss. However, for clinical grade 3 or higher hearing loss, cisplatin should be held and for grade 2 clinical hearing loss, one dose level reduction.

All Other Non-Hematologic Adverse Events Attributable to Cisplatin during Concurrent Radiation: For > grade 2, hold cisplatin, re-evaluate weekly until AE grade falls to 0 or 1, then restart cisplatin at one lower dose level. **Note**: Do not hold cisplatin for > grade 2 lymphopenia, mucositis, or dysphagia.

7.9.4 Dose Modifications for Adjuvant PF (Cisplatin and 5-FU)

Cisplatin Dose Levels During Adjuvant PF		
Starting Dose	Dose Level -1	Dose Level -2
80 mg/m^2	60 mg/m^2	45 mg/m^2

5-FU Dose Levels During Adjuvant PF		
Starting Dose	Dose Level -1	Dose Level -2
4000 mg/m^2 as 96 hour IVCI	3000 mg/m^2 as 96 hour IVCI	2250 mg/m^2 as 96 hour IVCI

7.9.5 Dose Modifications for Hematologic Adverse Events during Adjuvant PF

Chemotherapy should not be administered until the ANC is at least 1000 cells/mm^3 and the platelet count is at least 100,000/mm^3. If these parameters are not met, then treatment should be delayed in weekly increments until they have recovered to this level, but no more than a 21-day delay is permitted.

Dose reductions for ANC and platelets based on counts at anticipated day of treatment (i.e. 28 days post-radiation or 28 days post day 1 of prior cycle), ONCE RECOVERY TO THE ABOVE LEVELS ARE ACHIEVED:

ANC		**Platelets**	**Reduction**
At least 1000 mm^3	and	At least 100,000	None
< 1000 mm3	or	< 100,000	One dose level of BOTH cisplatin and 5-FU

7.9.6 Dose Modifications for Non-Hematologic Adverse Events during Adjuvant PF **(4/14/16)**

GI and Skin Events Attributable to 5-FU (mucositis, stomatitis, diarrhea, hand-foot syndrome, other rash): Delay the chemotherapy cycle until ≤ grade 1, decrease 5-FU by one dose level for the remaining cycles. If ≥ grade 3 adverse events occur after dose reduction to the –2 level, discontinue 5-FU.

Neurological Events Attributable to Cisplatin (e.g. peripheral neuropathy): Grade 2, decrease cisplatin by one dose level. ≥ grade 3, hold cisplatin.

Neurological Events Attributable to 5-FU (cerebellar signs, confusion, somnolence, upper motor neuron signs): Discontinue 5-FU.

Ototoxicity: Should patients develop clinical evidence of ototoxicity, further audiometric evaluation is required. A neurologic deficit should be distinguished from a conductive loss from fluid in the Eustachian tube. Because no AE scale, including the CTCAE v. 4, has been validated in terms of correlation with clinically relevant hearing loss, there are no protocol mandates

requiring dose reduction for audiogram-determined sensorineural hearing loss without an analogous clinical high grade (> grade 2) hearing loss. However, for clinical grade 3 or higher hearing loss, cisplatin should be held, and for grade 2 clinical hearing loss, one dose level reduction.

Angina or Coronary Artery Syndrome: 5-FU is a known myocardial toxin. For patients who develop angina or other coronary syndromes without definite alternative explanation , permanently discontinue 5-FU.

Renal Adverse Events: Dose will be modified based on the serum creatinine prior to each cisplatin dose. If the serum creatinine is ≤ 1.5 mg/dL, creatinine clearance is not necessary for treatment with full dose. If the serum creatinine is > 1.5 mg/dL, a creatinine clearance should be obtained by urine collection or nomogram calculation (valid only if serum creatinine is not changing rapidly).

Cisplatin must not be administered until creatinine is ≤ 1.5 or creatinine clearance ≥ 50. Once the creatinine has met the above parameters, cisplatin may be restarted with the below modifications based on the creatinine at the time the cisplatin was held: In general, cisplatin should be held for weekly intervals (rather than restarting cisplatin later in the same week that a dose limiting AE is seen)

Cisplatin dose modifications for creatinine during PF			
Creatinine (mg/dL)		Creatinine clearance, measured or calculated ml/min	Cisplatin dose reduction
≤ 1.5	or	≥ 50	No change
> 1.5	and	40-50	One dose level

All Other Non-Hematologic Adverse Events during Adjuvant PF
For grade 3 or 4 events, drugs should be held until resolution to ≤ grade 1, then both cisplatin and 5-FU resumed with one dose level decrease. Study treatment should be stopped if > grade 2 AEs are not resolved to grade 1 within 3 weeks. For specific AEs clearly attributable exclusively to one or the other agent (cisplatin or 5-FU), then one level dose reduction only for that agent is required.

7.9.7 Dose Modifications for Adjuvant GT (Gemcitabine and Paclitaxel)

Note: Day 1 of GT may be delayed; however, held doses of gemcitabine or paclitaxel on day 8 will be considered missed doses and will not be delayed or made up.

Gemcitabine Dose Levels During Adjuvant GT		
Starting Dose	Dose Level -1	Dose Level -2
1000 mg/m^2	800 mg/m^2	600 mg/m^2

Paclitaxel Dose Levels During Adjuvant GT		
Starting Dose	Dose Level -1	Dose Level -2
80 mg/m^2	60 mg/m^2	45 mg/m^2

7.9.8 Dose Modifications for Hematologic Adverse Events during Adjuvant GT

Chemotherapy on day 1 of each GT cycle should not be administered until the ANC is at least 1000 cells/mm^3 and the platelet count is at least 100,000/mm^3. If these parameters are not met, then treatment should be delayed in weekly increments until they have recovered to this level, but no more than a 14-day delay is permitted.

Dose reductions for ANC and platelets based on counts at day 21 of the prior cycle, ONCE RECOVERY TO THE ABOVE LEVELS ARE ACHIEVED:

Day 1 Dose Reduction Parameters for Adjuvant GT Based on Prior Cycle Counts			
ANC		**Platelets**	**Reduction**
At least 1000 mm^3	and	At least 100,000	None
< 1000 mm3	or	< 100,000	One dose level of BOTH gemcitabine and paclitaxel

Chemotherapy on day 8 of each cycle should not be administered unless the ANC is at least 1000 and the platelet count at least 75,000. If these parameters are not met, then day 8 chemotherapy shall be held, and there will be a dose reduction of 1 level for both gemcitabine and paclitaxel for all subsequent cycles. There are no planned dose reductions on day 8 of each cycle based upon hematological AEs beyond the dose reductions specified for day 1, but the reduced doses for hematologic AEs applied to day 1 also will apply to day 8. That is, doses on day 1 and 8 will be the same within any GT cycle unless day 8 is held per the above criteria. There will be no intra- cycle escalation or de-escalation based upon hematological AEs

7.9.9 Dose Modifications for Non-Hematologic Adverse Events during Adjuvant GT

Neurotoxicity: Dose reductions only will be for paclitaxel. On any day of paclitaxel administration:

Grade (CTCAE, v. 4)	Paclitaxel Reduction	Note
0-1	None	Gemcitabine will not be held or reduced for neurotoxicity.
2	Reduce by 1 dose level	
3	Hold until neurotoxicity resolves to grade 0-1, then dose reduce 1 level	
4	Discontinue	

Anaphylaxis/Hypersensitivity: Dose reductions only will be for paclitaxel. On any day of paclitaxel administration:

Severity	Paclitaxel Reduction
Mild (e.g. mild flushing, rash, pruritus)	No treatment needed. Supervise at bedside and complete paclitaxel infusion.
Moderate (e.g. moderate flushing, rash, mild dyspnea, chest discomfort)	Stop paclitaxel. Administer diphenhydramine 25 mg and dexamethasone 10 mg IV. After recovery, resume infusion at half the previous rate for 15 minutes. If no further symptoms occur, complete the infusion at the full dose rate. Paclitaxel may be administered again at the investigator's discretion, with more aggressive anti-hypersensitivity prophylaxis. See Section 7.3. If symptoms recur despite more aggressive hypersensitivity prophylaxis, discontinue paclitaxel.
Severe (e.g. hypotension requiring pressors, angioedema, respiratory distress requiring bronchodilators)	Stop paclitaxel. Administer diphenhydramine 25 mg and dexamethasone 10 mg IV. Add epinephrine or bronchodilators as needed. Do not restart paclitaxel.

All Other Non-Hematologic Adverse Events During Adjuvant GT

For grade 3 or 4 events, drugs should be held until resolution to grade 1 or less, then both drugs resumed at dose level -1. Doses on day 8 of each GT cycle will not be made up but merely skipped for grade 3 or greater AEs occurring between days 1 and 8. Protocol treatment should

be stopped if greater than grade 2 AEs are not resolved to grade 1 within 2 weeks. For specific AEs clearly attributable exclusively to one or the other agent (paclitaxel or gemcitabine), one level dose reduction only for that agent is required.

7.10 Modality Review

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

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

7.11 Adverse Events

This study will utilize the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 for adverse event (AE) reporting. The CTCAE version 4.0 is 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 CTCAE version 4.0.

Adverse events (AEs) that meet expedited reporting criteria defined in the table(s) below will be reported via the CTEP-AERS (CTEP Adverse Event Reporting System) application accessed via either the CTEP web site (https://eapps-ctep.nci.nih.gov/ctepaers/pages/task?rand=1390853489613).

NRG Oncology is responsible for reporting adverse events to the FDA.

7.11.1 Adverse Events (AEs)

Definition of an AE: Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product (attribution of unrelated, unlikely, possible, probable, or definite). (International Conference on Harmonisation [ICH], E2A, E6). [CTEP, NCI Guidelines: Adverse Event Reporting Requirements. February 29, 2012; http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf]

7.11.2 Serious Adverse Events (SAEs)

Serious Adverse Events (SAEs) —Serious adverse events (SAEs) that meet expedited reporting criteria defined in the table in Section 7.12 will be reported via CTEP-AERS. SAEs that require 24 hour CTEP-AERS notification are defined in the expedited reporting table in Section 7.12. Contact the CTEP-AERS Help Desk if assistance is required.

Definition of an SAE: Any adverse drug event (experience) occurring at any dose after that results in any of the following outcomes:

- Death;
- A life-threatening adverse drug experience;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant disability/incapacity;
- A congenital anomaly/birth defect;
- Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE, when, based upon medical judgment, they may

jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition.

Due to the risk of intrauterine exposure of a fetus to potentially teratogenic agents, the pregnancy of a study participant must be reported via CTEP-AERS in an expedited manner.

7.11.3 Acute Myeloid Leukemia (AML) or Myelodysplastic Syndrome (MDS)

AML or MDS that is diagnosed as a secondary malignancy during or subsequent to treatment in patients on NCI/CTEP-sponsored clinical trials must be reported via the CTEP-AERS system within 30 days of AML/MDS diagnosis.

Secondary Malignancy:
A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

All secondary malignancies that occur following treatment must be reported via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (e.g., acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

Second Malignancy:
A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting via CDUS unless otherwise specified.

7.12 CTEP-AERS Expedited Reporting Requirements (10/9/14)

All serious adverse events that meet expedited reporting criteria defined in the reporting table below will be reported via CTEP-AERS, the CTEP Adverse Event Reporting System, accessed via the CTEP web site, https://eapps-ctep.nci.nih.gov/ctepaers/pages/task?rand=1390853489613

Submitting a report via CTEP-AERS serves as notification to NRG Oncology and satisfies NRG Oncology requirements for expedited adverse event reporting.

CTEP-AERS provides a radiation therapy-only pathway for events experienced that involve radiation therapy only. These events must be reported via the CTEP-AERS radiation therapy-only pathway.

In the rare event when Internet connectivity is disrupted, a 24-hour notification must be made to the NRG Oncology Operations Office at 1-800-227-5463, ext. 4189, for instances when Internet fails. Once internet connectivity is restored, an AE report submitted by phone must be entered electronically into CTEP-AERS.

- CTEP-AERS-24 Hour Notification requires that an CTEP-AERS 24-hour notification is electronically submitted within 24 hours of learning of the adverse event. Each CTEP-AERS 24-hour notification must be followed by an CTEP-AERS 5 Calendar Day Report. Serious adverse events that require 24 hour CTEP-AERS notification are defined in the expedited reporting table below.
- Supporting source document is not mandatory. However, if the CTEP-AERS report indicates in the *Additional Information* section that source documentation will be provided, then it is expected. If supporting source documentation accompanies an CTEP-AERS report, include

the protocol number, patient ID number, and CTEP-AERS ticket number on each page, and fax supporting documentation **the NRG Oncology dedicated SAE FAX, 215-717-0990.**

- A serious adverse event that meets expedited reporting criteria outlined in the following table but is assessed by the CTEP-AERS as "expedited reporting NOT required" must still be reported to fulfill NRG Oncology safety reporting obligations. Sites must bypass the "NOT Required" assessment; the CTEP-AERS allows submission of all reports regardless of the results of the assessment.

CTEP defines expedited AE reporting requirements for phase 2 and 3 trials as described in the table below. **Important:** All AEs reported via CTEP-AERS also must be reported on the AE section of the appropriate case report form (see Section 12.1).

Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under a non-CTEP IND within 30 Days of the Last Administration of the Investigational Agent/Intervention [1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">10 Calendar Days</td><td rowspan="2">24-Hour 5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR

Expedited AE reporting timelines are defined as:

- o "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- o "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

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

The following are protocol specific exceptions to expedited reporting via CTEP-AERS. Report the following AEs in an expedited manner only if they exceed the grade in parentheses next to the AE: lymphocyte count decrease (grade 4), nausea (grade 3), vomiting (grade 2), diarrhea (grade 2), dehydration (grade 2), mucositis (grade 3), and dysphagia (grade 3).

8.0 SURGERY

8.1 Neck Dissection

A neck dissection should be considered if a palpable or worrisome radiographic abnormality persists in the neck 56 days after completion of all therapy (i.e. adjuvant chemotherapy).

8.2 Cervical Lymphadenectomy

The type of neck dissection will depend on the extent of lymphadenopathy, and preservation of the accessory nerve, jugular vein, and sternocleidomastoid muscle will be at the discretion of the treating surgeon.

8.3 Pathology Report

If the patient has salvage surgery, sites must upload the pathology report into Rave.

9.0 OTHER THERAPY

9.1 Permitted Supportive Therapy

All supportive therapy for optimal medical care will be given during the study period at the discretion of the attending physician(s) within the parameters of the protocol and documented on each site's source documents as concomitant medication.

Pegfilgrastim or Filgrastim may be used in the adjuvant setting according to institutional guidelines. We recommend following the NCCN myeloid growth factor use guidelines (see NCCN.org).

9.2 Non-permitted Supportive Therapy

9.2.1 Prophylactic use of amifostine or pilocarpine is not allowed.

9.2.2 Treatment with dipyramidole (Persantine®), ticlopidine (Ticlid®), clopidogrel (Plavix®), or cilostazol (Pleta®) is not allowed.

10.0 TISSUE/SPECIMEN SUBMISSION (9/2/15)

NOTE: Patients must be offered the opportunity to participate in the correlative components of the study, such as tissue/specimen submission. If the patient consents to participate in the tissue/specimen component of the study, the site is required to submit the patient's specimens as specified in Section 10.0 of the protocol. **Note:** Sites are not permitted to delete the tissue/specimen component from the protocol or from the sample consent.

10.1 Tissue/Specimen Submission

The NRG Oncology Biospecimen Bank-San Francisco, located at the University of California San Francisco acquires and maintains high quality specimens from NRG Oncology trials. Tissue from each block is preserved through careful block storage and processing. The NRG Oncology encourages participants in protocol studies to consent to the banking of their tissue. The NRG Oncology Biospecimen Bank provides tissue specimens to investigators for translational research studies. Translational research studies integrate the newest research findings into current protocols to investigate important biologic questions**.**

10.2 Mandatory Plasma Collection for EBV DNA Measurement: (23-Oct-2017)

Each enrolling institution will do the following:

1. Collect the patient's plasma for mandatory EBV DNA measurement anytime between Step 1 registration and start of chemoradiation. Sites are required to complete Step 1 registration before submitting specimens for the EBV DNA analysis OR to document detectable plasma EBV DNA tested at one of the credentialed central labs (listed on the EBV DNA Testing Specimen Transmittal form) within 28 days prior to Step 1 registration (see Sections 4.1.1 and 5.4). If EBV DNA is undetectable, the patient goes off study, and no further biospecimen will be collected or submitted.
2. For patients who continue on study, collect the patient's plasma for mandatory EBV DNA measurement within 1 week after the end of chemoradiation.

10.2.1 Collection and Shipment of Plasma Samples for EBV DNA Measurement

The NRG Oncology Biospecimen Bank-San Francisco will provide kits for the collection and shipment of the required plasma samples to the centralized Asian labs (see the specimen transmittal (ST) form on the CTSU website) as well as to individual U.S. and Canadian sites. **Institutions in Asia can request the kits from centralized Asian laboratories (see the EBV DNA Testing Specimen Transmittal form on the NRG-HN001 page on CTSU website, www.ctsu.org, for contact information for these labs). U.S. and Canadian institutions can request kits from the NRG Oncology Biospecimen Bank (NRGBB@ucsf.edu or 415-476-7864).**

Note: Since the kit can take 7-10 days to arrive, the institution should anticipate enrollment and request a kit in advance of patient registration. If the institution needs the testing completed earlier, then the site can provide its own EDTA collection tube, a cryovial tube (3.5 ml Sarstedt cat# 60.549.001 cryovials preferred) shipping kit and label for the plasma.

Required Samples and Documentation

The following material must be shipped to one of the central clinical laboratories listed on the EBV DNA Testing Specimen Transmittal form (on CTSU website) for testing:

- Patient must be registered and have an NRG case number before shipping samples for EBV testing.
- For U.S. and Canadian sites : Two 3.5 ml Sarstedt cryovials (cat# 60.549.001), each with 2 mls of plasma

- For Asian sites: 5-10 ml of plasma (collected in an EDTA tube and processed according to Appendix IV) for each required EBV DNA measurement;
- The plasma for EBV DNA should be collected and frozen on the same day. The sample should then be shipped frozen by priority overnight per **Appendix IV packing/shipping details.**
- Sites must label the cryovial tubes with the same information that is on the ST form for EBV analysis.
  - The study and case number should be in this format: HN001-0000. Include the leading zeroes for the case numbers.
  - Vials should also include date of procedure and the EBV Plasma labeled on them. For example: HN001-0046, EBV plasma, 1/7/17.
  - The information on the ST form must match the vials.
  - Failure to properly label the samples may result in the CLIA lab being unable to perform the required testing
- A study-specific EBV DNA Testing Specimen Transmittal form stating that the plasma is being submitted for central testing. The form must include the samples being shipped, the NRG Oncology protocol number, the patient's case number, collection time point, and the submitting institution name and institution NRG Oncology number

A slide set providing collection & shipping instructions for EBV DNA can be accessed on the HN001 protocol page of CTSU's website, www.ctsu.org.

Specimen Collection Summary for Mandatory EBV DNA Testing			
Specimens taken from patient:	**Collected when:**	**Submitted as:**	**Shipped:**
PLASMA for EBV DNA: 5-10 mL of anticoagulated whole blood in EDTA tube #1 (purple/ lavender top)	1) Pre-treatment (any time between Step 1 Registration and start of chemoradiation) 2) Within 1 week after the end of chemoradiation	If being tested within 6 hours, do not process; instead, provide the sample in EDTA collection tube. If being shipped by overnight courier, then process the plasma and aliquot 2.0 mL per aliquot in 3.5 mL cryovials . Freeze at -80°C until ready to ship	Frozen Plasma: ship with 4-6 frozen cold packs inside Ziplock bag. Ship by overnight courier to appropriate laboratory (see shipping/contact information below).

When the institution has collected the plasma, the sample will be shipped to one of the central clinical labs listed on the EBV DNA Testing Specimen Transmittal form (on the CTSU website) **with 2-6 frozen cold packs by overnight courier.**

Note: Due to possible degradation of plasma EBV DNA, sites should freeze the samples at -80°C and ship the same or following day (Monday-Wednesday) or wait until Monday to ship with 4-6 frozen cold packs inside a Ziplock bag and tight-fitting Styrofoam box with outer cardboard box (see photos in Appendix IV). Utek 1ºC silver cold packs or frozen Polar packs are recommended. DO NOT use Utek -23ºC silver cold packs, as these can thaw more rapidly.

Shipping and Contact Information: See the EBV DNA Testing Specimen Transmittal form on the NRG-HN001 page of the CTSU website, www.ctsu.org, for the contact information for each central clinical laboratory.

10.2.2 EBV DNA Plasma Sample Testing

EBV PCR testing is performed on one day each week. If the sample arrives before the scheduled testing, the turnaround time from shipping of the sample to receipt of the result is anticipated to

be between 7-10 days or less. However, if the sample arrives after scheduled day of testing for that week, the sample will wait until the next week's testing run. Note: The labs cannot accept Saturday deliveries, and the labs do not have the flexibility to accommodate changes to the testing schedules.

10.3 Specimen Collection for Tissue Banking and Translational Science: Highly Recommended (but Optional) (04May2017)

For patients with detectable plasma EBV DNA and who consent to participate in the tissue/blood component of the study (see sample informed consent).

10.3.1 Tissue Collection

Tumor tissue will be collected pre-treatment. The slide and block/punch must be submitted to be banked and should not be requested to be returned except for continuing patient care.

The following must be provided in order for the case to be evaluable for the Biospecimen Bank:

- One H&E stained slide (can be a duplicate cut H&E of the diagnostic slide block; does not have to be the diagnostic slide itself).
- A corresponding paraffin-embedded tissue block of the tumor (the block must match the H&E being submitted) or a 2 mm diameter core of tumor tissue, punched from the tissue block containing the tumor with a punch tool and submitted as a block with corresponding H&E or in a plastic tube labeled with the surgical pathology number and block id. **Note:** A kit with the punch, tube, and instructions can be obtained from the Biospecimen Bank. Block or core must be clearly labeled with the pathology identification number and block number that correspond to the Pathology Report.

  The submitted material must be from malignant tumor, not necrotic or fibrotic tissue. If the submitted material is reviewed and is not tumor, the site may be assessed a protocol violation.
- For sites unable to provide a block or punch, 1 H&E stained slide and 10 unstained slides are acceptable.
- A Pathology Report documenting that the submitted block or core contains tumor. The report must include the NRG Oncology protocol number and patient's case number. The patient's name and/or other identifying information should be removed from the report. The surgical pathology numbers and date of procedure information must NOT be removed from the report.
- A Specimen Transmittal (ST) Form clearly stating that tissue is being submitted for the NRG Oncology Biospecimen Bank; if for translational research, this should be stated on the form. The form must include the NRG Oncology protocol number and patient's case number.

10.3.2 Blood Collection

Whole blood will be collected pre-treatment, if the patient consents, **stored at -80°C and batch shipped with other plasma time points to the bank.** If a site misses this collection, the site may collect it at another time, but must note this on the Specimen Transmittal (ST) Form.

Plasma also will be collected for future translational science at the following 3 time points:

- During treatment: At week 4 of concurrent chemoradiation;
- Post-treatment: After completion of all adjuvant chemotherapy (approximately 4 months after completion of radiation treatment for those randomized to the observation arm);
- Post-treatment: At 12 months after completion of radiation treatment.

For U.S. and Canadian sites: Plasma samples for all patients who have consented to tissue banking should be shipped directly to the NRG Oncology Biospecimen Bank as described in Section 10.3.2.

For Asian sites: Unused plasma remaining after EBV DNA testing will be banked at the Asian laboratories until the end of the trial for all patients who have consented to tissue banking (see Section 10.3). These samples then will be shipped to the NRG Oncology Biospecimen Bank in a

large batch. For non-consenting or ineligible (EBV negative) patients, the remaining plasma will be discarded.

The following materials must be provided to the NRG Oncology Biospecimen Bank: A Specimen Transmittal (ST) Form documenting the date of collection of the biospecimen; the NRG Oncology protocol number, the patient's case number, time point of study, and method of storage, for example, stored at -80°C, must be included.

Storage Conditions: Store frozen specimens at -80°C (-70°C to -90°C) until ready to ship. If a -80°C Freezer is not available:

- Samples can be stored short term in a -20°C freezer (non-frost free preferred) for up to one week (U.S. sites ship out Monday-Wednesday only; Canadian sites: Monday-Tuesday only; Asian sites: Monday only).

OR:

- Samples can be stored in plenty of dry ice for up to one week, replenishing daily (U.S. sites ship out Monday-Wednesday only; Canadian sites: Monday-Tuesday only; Asian sites: Monday only).

OR:

- Samples can be stored in liquid nitrogen vapor phase (U.S. sites ship out Monday-Wednesday only; Canadian sites: Monday-Tuesday only; Asian sites: Monday only).

Please indicate on the ST Form the storage conditions used and time stored. Sites must complete the Form completely, including the consent box. Do not send any material from patients who did not consent to banking specimens.

10.3.3 Specimen Collection Summary for Optional Tissue Banking and Translational Research

Specimens taken from patient:	Collected when:	Submitted as:	Shipped:
Representative H&E stained slides of the primary tumor	Pre-treatment	H&E stained slide Pre-treatment	Slide shipped ambient to NRG Oncology Biospecimen Bank-San Francisco
A paraffin-embedded tissue block of the primary tumor taken before initiation of treatment or a 2 mm diameter core of tissue, punched from the tissue block with a punch tool	Pre-treatment	Paraffin-embedded tissue block or punch biopsy (must match the H&E slide being submitted)	Block or punch shipped ambient (or with cold packs during warm weather) to NRG Oncology Biospecimen Bank-San Francisco
PLASMA: 5-10 mL of anticoagulated whole blood in EDTA tube #1 (purple/ lavender top) and centrifuge	1. During treatment: At week 4 2. Post-treatment: At 4 mos. and at 12 mos. after completion of RT	Frozen plasma samples containing a minimum of 0.5 mL per aliquot in 1 mL cryovials (five)	Plasma sent frozen on dry ice via overnight carrier to 1 of the 3 Asian laboratories or for U.S. and Canadian sites, to the NRG Oncology Biospecimen Bank-San Francisco.
Whole blood for DNA: 5-10 mL of anticoagulated whole blood in EDTA tube #2 (purple/lavender top) and mix	Pre-treatment (within 1 week of registration), taken at same time as first EBV DNA plasma sample.	Whole blood samples containing 1 mL per aliquot in 1mL cryovials (three to five)	Whole blood sent frozen on dry ice via overnight carrier to 1 of the 3 Asian laboratories or for U.S. and Canadian sites, to the NRG Oncology Biospecimen Bank-San Francisco.

10.3.4 Submit tumor tissue and blood for banking and translational research as follows: **(3/4/15)**

Asian institutions: See the EBV DNA Testing Specimen Transmittal form on the NRG-HN001 page of the CTSU website, www.ctsu.org, for the contact information for each central clinical laboratory.

Tumor tissue and blood for banking and translational research will be kept at the Asian laboratories until the end of the trial for all patients who have consented to submit specimens. These samples then will be shipped to the NRG Oncology Biospecimen Bank in a large batch. For non-consenting or ineligible (EBV negative) patients, the remaining plasma will be discarded.

U.S. and Canadian institutions:
NRG Oncology Biospecimen Bank-San Francisco
University of California San Francisco
2340 Sutter Street, Room S341
San Francisco, CA 94115
U.S.A.
Questions: 415-476-7864/FAX 415-476-5271; NRGBB@ucsf.edu

Note: **Institutions will batch shipments and will e-mail a tracking number to the Asian laboratories or the Biospecimen Bank to indicate that a shipment is on the way.**

10.4 Reimbursement (3/4/15)
NCI funds for reimbursement for protocol-specified biospecimen materials will be distributed per the requirements/methods specified by the National Clinical Trials Network (NCTN). This information will be made available with the other registration materials in the Oncology Patient Enrollment Network (OPEN) portal system.

10.5 Confidentiality/Storage
(See the Patient Tissue Consent Frequently Asked Questions, http://www.rtog.org/Researchers/BiospecimenResource/BiospecimenResourceFAQs.aspx for further details.)

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

10.5.2 Specimens for tissue banking will be stored for an indefinite period of time. Specimens for translational science research will be retained until the study is terminated, unless the patient has consented to storage for future studies. If at any time the patient withdraws consent to store and use specimens, the material will be returned to the institution that submitted it.

11.0 PATIENT ASSESSMENTS

11.1 Study Parameters
See Appendix I for a summary of assessments and time frames. See the section below for details of evaluations and exceptions.

11.2 Details of Evaluations (23-Oct-2017)

11.2.1 Pretreatment Evaluation

- Evaluation of tumor extent with one of the following combinations required within 28 days prior to registration Note: If a treatment planning CT scan is used, it must be with ≤ 3 mm contiguous slices with contrast and be read by a radiologist.
    a) MRI of the nasopharynx and neck; or CT of the nasopharynx and neck with ≤ 3 mm contiguous slices with contrast and bone windows (to evaluate base of skull involvement).
    b) MRI of the nasopharynx and PET/CT (with contrast) of the neck or of the nasopharynx and neck.

Note: **Please refer to section 6.3.2 for MRI requirement for target delineation.**

- The bone scan is required if there is suspicion of bone metastases (a PET/CT scan can be substituted for the bone scan).
- Audiogram: Audiometric assessment must be done by a certified audiologist. Different audiologists for the baseline and post-treatment audiograms are permitted, if necessary, as long as the audiologists are certified and follow the same procedure. **Two slide sets are available, providing guidelines for audiometric assessment and participant instructions, which can be accessed on the HN001 protocol page of the NRG/RTOG website, www.rtog.org, and on the HN001 protocol page of CTSU's website, www.ctsu.org. In addition, participating sites can contact the Audiology Co-Chair, Dr. Anand, with any questions regarding audiometric assessment and/or bone conduction testing procedures.**

  The quality of PTA studies will be standardized to the maximum degree possible across participating sites. Audiometric testing does not depend on visual or other sensory functions, as it is entirely an auditory task. Cognitive requirements are minimal. Instructions for testing and grading will be recorded in English and Chinese by fluent speakers and distributed by compact disk or computer file to audiologists at participating sites. If a fluent speaker of the patient's native language is not available for test administration, a native-language patient-friendly recording will be played at a comfortable listening level for the patient. Patients will have the opportunity to ask questions and have them answered prior to testing.

  Participating sites will submit a form stating mean and maximum radiation doses to the left and right cochleae. This information will be recorded for each patient along with PTA results. Raw data will be submitted to NRG Oncology (see Section 12.1). Headquarters will forward the information submitted to the University of California, San Francisco Medical Center, which will produce the formal analyses supervised by Dr. Anand, the Audiology Co-Chair.

11.2.2 Evaluation During Treatment

- For cisplatin during chemoradiation: CBC/differential, sodium, potassium, creatinine, calcium, phosphate and magnesium should be done prior to every chemotherapy administration, with the time interval prior to treatment per institutional standards of care.
- For adjuvant chemotherapy, all arms except the no adjuvant treatment arm: CBC/differential and metabolic panel: sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, calcium, bilirubin, total protein, albumin, AST/ALT, alkaline phosphatase should be done prior to every chemotherapy administration, with time interval prior to treatment again according to institutional standards of care.
- CBC/differential should be done prior to every chemotherapy administration

11.2.3 Evaluation in Follow Up

- Chest x-ray: If a patient has a chest CT scan or PET/CT within the specified interval, then an additional chest x-ray is not necessary.
- A biopsy should be done for the following: Any suspicious mucosal lesion in the upper aerodigestive tract; pharyngeal pain referred to the ear; any firm node that persists longer than 4 weeks; epistaxis; chronic nasal congestion not thought to be due to radiation mucosal changes.
- For the MRI of nasopharynx and neck (if medically contraindicated, CT scan with contrast): If the site has done a PET/CT or CT of the neck, then only an MRI of the nasopharynx is necessary. MRI of the nasopharynx and neck can be done prior to the month 4 post RT at the treating physician's discretion. If the MRI is done prior to month 4 Post RT then a PET/CT would be acceptable at Month 4 Post RT.

11.3 Quality of Life (04May2017)

NOTE: Patients must be offered the opportunity to participate in the correlative components of the study, such as quality of life assessment.

Patient-Reported Outcome (PRO) assessments will include 3 cross-culturally validated, cancer-specific PRO tools: Functional Assessment of Cancer Therapy-Nasopharyngeal (FACT-NP), Hearing Handicap Inventory for the Elderly Screening Version (HHIE-S), and Functional Assessment of Cancer Therapy-Taxane (FACT-Taxane).

FACT-NP will be collected at 5 time points (including patients randomized to observation): pre-treatment baseline, after EBV re-testing, and at 4, 12, and 24 months after radiation therapy completion.

For the patients with detectable EBV DNA levels post-RT (phase II patients), HHIE-S and FACT-Taxane will be collected at 4 time points: after EBV re-testing and at 4, 12, and 24 months after radiation therapy completion.

Cost-effectiveness analysis will be incorporated into this trial using measurement of health-related QOL (HRQOL) from the EuroQol (EQ-5D) instrument. Time points of collection for the EQ-5D will be at the pre-treatment baseline, and at 12 and 24 months after radiation therapy completion.

11.3.1 Hearing Handicap Inventory for the Elderly Screening Version (HHIE-S)
The HHIE-S is a 10-item PRO, scored on a range of 0-40 that takes the patient less than 2 minutes to complete. Severe handicap is associated with a score of 25 or higher. HHIE-S is unique among PRO tools because its focus is less on the type or degree of actual hearing impairment with more emphasis on the impacts of hearing impairment in the social, functional, and emotional domains. It is available in Chinese and has been validated as a hearing QOL instrument in the international setting. NRG Oncology has obtained permission to use the HHIE-S for this study in English and Traditional Chinese (Hong Kong and Taiwan).

11.3.2 Functional Assessment of Cancer Therapy-Nasopharyngeal (FACT-NP)
FACT-NP is a fully scalable, cancer-specific PRO instrument containing 43 items, scored on a range of 0-172. The instrument has been psychometrically validated (Tong 2009) and has been used in Hong Kong to assess concerns specific to the nasopharyngeal cancer population. FACT-NP is available in both traditional and simplified Chinese versions, understandable to study participants in Hong Kong and Taiwan. Singaporeans will be offered the English-language version with an option if needed to complete the simplified Chinese version. FACT-NP is estimated to take 2-3 minutes per 10 items (Webster 2003) or approximately 12 minutes. NRG Oncology has obtained permission to use the FACT-NP for this study in English, Spanish, French, Traditional Chinese (Hong Kong and Taiwan), and Thai.

11.3.3 Functional Assessment of Cancer Therapy-Taxane (FACT-Taxane)
The FACT-Taxane is a 16-item chemotherapy-specific PRO subscale, scored on a range from 0 to 64, and it contains an 11-item neurotoxicity subset. It has been used in chemotherapy assessments and is available in cross-culturally validated translation. The patient can complete the assessment in approximately 3 minutes. It is also designed to be scored separately or in combination with the general subscales from FACT-NP. NRG Oncology has obtained permission to use the FACT-Taxane for this study in English, Spanish, French, Traditional Chinese (Hong Kong and Taiwan), Simplified Chinese (Singapore), Malay (Singapore), and Tamil (Singapore).

11.3.4 The EuroQol (EQ-5D) has been frequently used in cooperative group studies for cost-utility analysis. It is a 2-part questionnaire that the patient can complete in approximately 5 minutes. The EQ-5D is available in simplified and traditional Chinese language translation, and its use in measuring health state has been validated for populations in Taiwan and Hong Kong. The site research nurse or CRA should encourage the patient not to skip questions on the EQ-5D or take breaks during the completion of this questionnaire, as this will invalidate the assessment. If this occurs, sites will document it on the QOL cover page. NRG Oncology has obtained permission to

use the EQ-5D for this study in English, Spanish, French, Traditional Chinese (Hong Kong and Taiwan), Simplified Chinese (Singapore), Malay (Singapore), and Tamil (Singapore).

11.3.5 Optional Online Completion of QOL Assessments

Patients who consent to participate in the quality of life (QOL) component of this study have the option of completing QOL forms online from any location, including home, via VisionTree Optimal Care (VTOC). The baseline QOL forms must be completed in hardcopy at the time of enrollment, but all subsequent QOL forms can be completed by the patient online. Patients without e-mail or Internet access can participate in the QOL component of the study by completing hardcopy (paper) forms. Indeed, at any time, any patient may choose to fill out their QOL form using the hardcopy form. The QOL forms completed via VTOC are identical to the hardcopy forms; this technology does not add to or change the QOL assessments in this study.

Following completion of baseline QOL forms, if the patient wishes to complete any of the subsequent QOL assessments online, the patient must have an e-mail address that they consent to use for this purpose. Patients' e-mail addresses are necessary so that e-mail reminders may be sent to them to remind them to fill out QOL forms that are due. The patient's e-mail address also will be used for password-protected access to VisionTree Optimal Care (VTOC), Patients who are interested in participating but do not yet have an e-mail address can obtain one for free from a number of sources (e.g.,Yahoo!, Hotmail, or AOL). **Note: The site RA is responsible for setting up the patient's account on VTOC. The RA may do so by logging on the VTOC portal at the following link: https://rtog.optimalcare.com - medical team. RA login information will be provided by VTOC after the patient is randomized to the study. The patient's VTOC account must be set up within 14 days after randomization.**

VTOC will send patients e-mail reminders to complete QOL forms. The first reminder will be sent at the beginning of the window for completion of the form, with a second reminder sent halfway through the window, if the form has not yet been completed. A maximum of 3 reminders will be sent for each of the 4 QOL assessment time points (subsequent to the baseline assessments). After the patient has completed all forms, a dialogue box will appear thanking the patient for completing the QOL form(s), and the patient will no longer receive reminders for that time point.

Site Research Associates (RAs) will receive training in the use of VTOC via NRG Oncology webinars and educational sessions. The RA or study administrator will be informed via the VTOC "At a Glance" form management system when QOL forms have been completed or when the window for a particular form has closed. If the site RA receives a notice that forms have not been completed, she or he will contact the patient to remind the patient to fill out the QOL form or inquire why the forms have not been completed. The RA will complete the cover page for each form that was not completed (either via VTOC or in hardcopy) and will submit the cover page (see Section 12.1).

11.4 Measurement of Response/Outcomes Criteria

When evaluating local or regional control, it is important to assess using the same imaging scanner, ie, MRI 1.5T to 1.5T.

11.4.1 Local or Regional Relapse

Relapse is defined as reappearance of tumor after complete response. If possible, relapse should be confirmed by biopsy.

11.4.2 Local or Regional Progression

Progression is defined as an estimated increase in the size of the tumor (product of the perpendicular diameters of the two largest dimensions) of greater than 25%, taking as reference the smallest value of all previous measurements or appearance of new areas of malignant disease.

11.4.3 Distant Metastasis

Clear evidence of distant metastases (lung, bone, brain, etc.); biopsy is recommended where possible. A solitary, spiculated lung mass/nodule is considered a second primary neoplasm unless proven otherwise in a patient with a smoking history.

11.4.4 Second Primary Neoplasm

Tumor reappearing within the initial and immediate adjoining anatomical region of the primary will be considered local recurrence. Multiple lung nodules/masses are considered distant metastases from the index cancer unless proven otherwise.

11.5 Criteria for Discontinuation of Protocol Treatment (04May2017)

- Progression of disease;
- A delay in protocol treatment, as specified in Sections 6.0 and/or 7.0;
- Unacceptable toxicity; see Section 7.9 for guidance regarding dose modifications or removal from protocol treatment;
- Patient declines to continue on study treatment.

If protocol treatment is discontinued, follow up and data collection will continue as specified in the protocol. **Note**: If the patient completes weekly cisplatin and IMRT or IMPT then is not randomized to further treatment (e.g. the patient progresses, refuses, etc.) the patient is treated off study as clinically indicated and is followed for 3 years. For the cases that are deemed ineligible prior to randomization, the site must complete step III registration to indicate that the patient goes off study. Ineligible patients must not be randomized to an arm. These patients are treated off study as clinically indicated and are followed for 3 years.

12.0 DATA COLLECTION

This study will utilize Medidata Rave® for remote data capture (RDC) of all data. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles in RSS. To access iMedidata/Rave, see Section 5.0.

Each person responsible for data entry must be on the NRG Oncology in order to receive access to Medidata Rave®.

Upon initial site registration approval for the study in RSS (Regulatory Support System), all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata (iMedidata-Notification@mdsol.com) to activate their account. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the “accept” link in the upper right-corner of the iMedidata page. Once an account is activated, eLearning modules will be available for Rave RDC instructions. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be listed in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave accounts will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU website under the Rave tab at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

12.1 Summary of Data Submission (04May2017)

Note: All data must be submitted in English.

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during the trial using Medidata Rave. Additionally, certain adverse events must be reported in an expedited manner for more timely monitoring of patient safety and care. The following sections provide information about expedited reporting. For this trial, the Protocol Specific Adverse Events and Other Adverse Events forms are used for routine AE reporting in Rave.

For reporting of secondary cancers or other report forms available in Rave:

Folder	Form/Item
Registration via the OPEN System	• ***Subject Enrollment Form***
Enrollment When pushed into RAVE there will be 6 forms representing registration	• ***Step Information*** • ***Treatment Assignment Form*** • ***Demography*** • ***Eligibility Checklist Form*** • ***Eligibility Checklist 2 Form*** • ***Eligibility Checklist 3 Form***
Pre-Treatment Plasma Collection	• ***Pre-treatment Plasma Collection-Must be completed prior to Step II registration.***
Pre-Treatment EBV DNA Results	• ***Only required to be completed prior to Step II Registration for patients who will be using existing EBV DNA results performed at a central laboratory (prior to Step I Registration)***
Baseline	• ***Work Up*** • ***Lab Results Baseline*** • ***Diagnostic Staging*** • ***Prior Treatment*** • ***Exclusion Criteria*** • ***Patient History Form*** *(formerly known as the A5)* • ***Protocol Specified AE Form*** • ***Audiogram Results***
Baseline RT	• ***Digital Data****-(Refer to section 12.2)*
End of RT	• ***RT Administration*** • ***RT Treatment-****if was radiation therapy given = 'yes'* • ***Protocol Specific RT Form*** • ***Cisplatin Concurrent*** • ***Supportive Care*** • ***Hospitalization*** • ***Follow-up Head and Neck*** • ***Protocol Specified AE Form*** • ***Other Adverse Event Forms****– if new or continuing adverse events = 'yes'* • ***Audiogram Results***
Concurrent Labs	• ***Lab Units week 1-6*** *(During Treatment Labs)* • ***Lab Results Follow Up Weeks 1-6*** *(During Treatment Labs)*
Note: Patients not randomized to an Arm will be followed every 4 months for years 1& 2 and every 6 months for year 3.	
Arm 1, 3 & 4 4, 8 and 12 Weeks Post RT **Arm 2**	• ***Supportive Care*** • ***Hospitalization*** • ***Follow-up Head and Neck***

4, 7, 10 & 13 weeks Post RT	• ***Protocol Specified AE Form*** • ***Other Adverse Event Forms****– if new or continuing adverse events = 'yes'*
Month 4 (ARM 1)	• ***Cisplatin Adjuvant*** • ***5-FU Adjuvant*** • ***Lab Units*** • ***Lab Results Follow-Up*** • ***Supportive Care*** • ***Hospitalization***
Month 4 (ARM 2)	• ***Gemcitabine Adjuvant*** • ***Paclitaxel Adjuvant*** • ***Lab Units*** • ***Lab Results Follow-Up*** • ***Supportive Care*** • ***Hospitalization***
Month 4 (ARM 3)	• ***Cisplatin Adjuvant*** • ***5-FU Adjuvant*** • ***Lab Units*** • ***Lab Results Follow-Up*** • ***Supportive Care*** • ***Hospitalization***
Adjuvant Labs	• ***Lab Units 1-8*** *(Prior to each dose)* • ***Lab Results Follow Up 1-8*** *(Prior to each dose)*
MONTH 4 (Post RT) MONTH 8 (Post RT) MONTH 12 (Post RT) MONTH 16 (Post RT) MONTH 20 (Post RT) MONTH 24 (Post RT) MONTH 30 (Post RT) MONTH 36 (Post RT) MONTH 42 (Post RT) MONTH 48 (Post RT) MONTH 54 (Post RT) MONTH 60 (Post RT) Year 6-15	• ***Patient Contacted*** • ***Follow-up-*** *if Patient able to be Contacted ='yes'* • ***Follow-up Head and Neck*** *-if Patient able to be Contacted ='yes'* • ***Disease Assessment-*** *if Documented clinical assessment = 'yes'* • ***New Primary Cancer-*** *If New Primary Cancer= 'yes'* • ***Non-Protocol Treatment-*** *if non-protocol cancer therapy= 'yes'* • ***Protocol Specified AE Form-*** *if Patient able to be Contacted ='yes'* • ***Other Adverse Events****– if new or continuing adverse events = 'yes'* • ***Primary Cause of Death- –*** *if Patient's Vital Status = 'dead'* • ***Audiogram Results (For Patients randomized to Arm 1, 2, 3 & 4 Month 12 visit only)***
Source Documentation Upload	• ***Source Documentation Upload-*** *used by site in the event that source documentation needs to be uploaded to HQ*
Quality of Life Coversheets will appear in the following folders if the patient has consented to the Quality of Life	• ***FACT-NP QOL Coversheet*** • ***FACT-NP**** • ***EQ-5D QOL Coversheet***

Component: **FACT-NP (Phase II & III: All Arms)** • Baseline • Week 4 Post RT • Month 4 • Month 12 • Month 24 **EQ-5D (Phase II & III: All Arms)** • Baseline • Month 12 • Month 24 **FACT-Taxane & HHIE-S (Phase II: Arm 1 & 2 only)** • Week 4 Post RT • Month 4 • Month 12 • Month 24 ***Note: Patients who have consented to QOL and are not randomized to an Arm will only have the baseline QOL.***	• ***EQ-5D**** • ***FACT-Taxane QOL Coversheet*** • ***FACT-Taxane****++ • ***HHIE-S QOL Coversheet*** • ***HHIE-S**** **These quality of life forms only appear if the corresponding cover page is submitted and 'Was the patient questionnaire completed' was answered as YES.* *++ If the entire FACT-NP (pages 1-3) is completed then only page 3 of the FACT-Taxane is required to be completed by the patient.*

12.2 Summary of Dosimetry Digital Data Submission (04May2017)
Note: Submit to TRIAD; see Section 5.2.

Item	**Due**
Preliminary Dosimetry Information	
Digital Data Submission – Treatment Plan submitted in DICOM format to TRIAD exported from treatment planning machine by Physicist	Within 1 week of start of RT
Digital data submission includes the following:	
• CT data, critical normal structures, all GTV, CTV, and PTV contours	
• Digital beam geometry for beam sets	
• Doses for concurrently treated beams	
• Digital DVH data for all required critical normal structures, GTV, CTV, and PTVs for total dose plan	
• All required structures MUST be labeled per the specifications in Section 6.4.4.	
• All digital RT data must be in DICOM format.	
• NRG-HN001 Datasheet, located on the NRG Oncology/RTOG website at www.ctsu.org, to be	

submitted via TRIAD with RT Digital Data listed above.	
Upon Submission of Digital Data to TRIAD	
Complete a Digital Data Submission Information form **(DDSI)** located: https://www.irocqa.org/Resources/TRIAD-for-RT-QA	

NOTE: ALL SIMULATION AND PORTAL FILMS AND/OR DIGITAL FILM IMAGES WILL BE KEPT BY THE INSTITUTION AND ONLY SUBMITTED IF REQUESTED.

13.0 STATISTICAL CONSIDERATIONS

13.1 Detectable Plasma EBV DNA Cohort (Randomized Phase II) Component Primary Endpoint

13.1.1 Progression-free survival (PFS)

13.2 Undetectable Plasma EBV DNA Cohort (Phase III) Primary Endpoint

13.2.1 Overall survival (OS)

13.3 Randomized Phase II and Phase III Secondary Endpoints

13.3.1 Time to distant metastasis (DM);
13.3.2 Time to local progression;
13.3.3 Time to regional progression;
13.3.4 PFS (undetectable EBV group);
13.3.5 OS (detectable EBV group);
13.3.6 Acute grade 3-5 adverse events;
13.3.7 Late grade 3-5 adverse events;
13.3.8 Death during or within 30 days of end of protocol treatment;
13.3.9 Pure tone audiometry;
13.3.10 Quality of life (general and physical well-being);
13.3.11 Quality of life (hearing);
13.3.12 Quality of life (peripheral neuropathy);
13.3.13 Cost effectiveness.

13.4 Stratification

Patients will be stratified by N stage (N0-1 vs. N2-3); T stage (T1-2 vs. T3-4); and Zubrod performance status (0 vs. 1).

13.5 Sample Size with Power Justification

For the phase III non-inferiority trial of the low-risk group (undetectable EBV), we assume the 2 year OS is 91% (Chan 2002) with a 5% error rate, 80% power, and the null hypothesis is that the hazard ratio between the treatment arm and the control arm is greater than 1.5; the alternative hypothesis is that the hazard ratio equals to 1. A sample size of 600 analyzable patients accrued over 3 years is required. Allowing for 5% of patients to be retrospectively declared ineligible, the targeted accrual is 632 patients. Total study duration is expected to be 7.7 years. A possible decrease in the 5-year OS rate from 79% on the adjuvant arm to 70% or lower on the observation arm would be considered unacceptable.

For the phase II trial of the high-risk group (detectable EBV), we assume that the PFS is 40% (Chan 2002) at 1 year, with a 35% hazard reduction, 15% error, 85% power, and yearly accrual of 44 patients. The 1-year PFS difference is 40% vs. 55%. A sample size of 120 analyzable patients accrued over 2.7 years is required. Allowing for 5% of patients to be retrospectively declared ineligible, the targeted accrual is 126 patients. Total study duration is expected to be 4.2 years.

In the Hong Kong trial, 78% of consented patients were actually randomized [A. Chan, personal communication]. Therefore, it is projected that **a total of 924 patients** will need to be enrolled to

reach the required sample sizes for the 2 cohorts. The overall accrual rate is expected to be approximately 27 patients per month.

13.6 Analysis Plan

13.6.1 Statistical Methods

Analysis will include all eligible patients with follow up based on the treatment arm to which they were randomized, regardless of whether they started the assigned treatment. PFS and the OS rates will be estimated using the Kaplan-Meier method (1958) for each arm. Their distributions will be compared between treatment arms with a 1-sided log rank test (Mantel 1966). The cumulative incidence method will be used to estimate local, regional, and distant failure rates. The failure rates for the experimental treatment will be compared against the control using a failure-specific log-rank test. Multivariate analysis will be performed using the Cox proportional hazards model. An overall toxicity analysis will be done 2 ways: 1) The first method will be based upon only adverse events (AEs) attributed by investigator to be definitely, probably, or possibly related (if relationship is missing, it will be considered related) to protocol treatment; 2) The second method will be based upon all reported AEs regardless of attribution. Rates of specific acute toxicity profiles and late toxicity profiles will be estimated using a binomial distribution along with their associated 95% confidence intervals and will be compared using Fisher's exact test between the 2 treatment arms.

13.6.2 Routine Interim Analysis to Monitor Study Progress

Interim reports will be prepared twice each year until the final analysis has been accepted for presentation or publication. In general, these reports will contain information about the accrual rate with projected completion date for the accrual phase, exclusion rates and reasons, pretreatment characteristics of patients accrued, compliance rate of treatment delivered with respect to the protocol prescription, and the frequency and severity of adverse events.

13.6.3 Early Stopping Rules

We will monitor the unanalyzable rate for each cohort as follows:

1. We will look at this rate at 1 year. If the analyzable rate is lower than 65% or nontrivially lower than 78%, then the study chairs will review reasons that caused this and take corrective actions if possible. At year 2 if the observed rate is still lower than 65%, the trial will be considered unfeasible and the accrual will be stopped. If the unanalyzable rate is lower than 65% at 1 year, and this is due to reasons that cannot be corrected or improved, then the study accrual will be stopped.
2. We assume there will be 16% of the patients in the high risk group, if the observed rate is much higher or lower than 16%, the feasibility of one of the risk groups will be affected further. So, we will monitor this rate at 1 year, and we will amend the protocol for either or both of the above 2 reasons to ensure there will be 120 and 600 analyzable patients accrued to the high and low risk groups, respectively.

We will monitor for both the feasibility of administering planned treatment and the rate of grade 3 or higher oral mucositis in the experimental and control arms in the detectable EBV cohort.

For feasibility of administering planned treatment: Based on experiences from RTOG 0225, intergroup 0099, and Singapore and Hong Kong NPC-9901, we estimate the rate is 60% for 3 cycles of adjuvant therapy. If the rate of administering planned treatment (3 cycles of adjuvant therapy) in the experimental arm is less than that of the control arm by more than 35% we will close the high-risk cohort to accrual. With 10% two sided type I error and 80% power, we will need 30 patients per arm.

For the rate of oral mucositis: The rate for the control arm is estimated to be 15%. If the rate of grade 3 or higher oral mucositis (after each adjuvant cycle, q 3 weeks) in the experimental arm in the high risk cohort exceeds that of the control arm by 30%, we will close the study to accrual. With 10% two sided type I error and 79% power, we will need 32 patients per arm. If the control group rates are 5% or 21%, the statistical power will be 89% and 74% with 30% increase in oral mucositis.

13.6.4 Interim Analysis for the DMC

The NRG Oncology Data Monitoring Committee (DMC) will review the study twice a year with respect to patient accrual and morbidity. The DMC also will review the study on an "as needed" basis. In addition, this study will be monitored by the Clinical Data Update System (CDUS) version 3.0. An abbreviated report containing cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31, and October 31.

Detectable EBV Cohort

The interim analysis for efficacy and futility will be performed when there are 51 events for PFS, and the results will be reported to the NRG Oncology DMC. If the P value from the log rank test is less than 0.0418 according to O'Brien-Fleming type spending function, then we stop for efficacy and if it is greater than 0.5308, then we would recommend stopping for futility. The futility stopping boundary is derived using the Rho family of spending function with a parameter of 1.5. Final analysis will be after 102 PFS events are reported.

Undetectable EBV Cohort

Overall survival monitoring for both efficacy and futility will be performed when there are 38, 76, 114 deaths occurred; a total of 151 deaths is required for the final analysis. A Haybittle-Peto boundary will be utilized for efficacy. For futility, the statistical monitoring boundary will be based on testing the alternative hypothesis at a one-sided alpha of 0.0075, 0.025, and 0.025 at each interim analysis (the approximate stopping boundaries are 2.20, 1.57, 1.44 on the hazard ratio scale for each interim analysis), as recommended by Freidlin, Korn, and Gray (2010). Futility analysis will be performed together with each of the efficacy interim analyses. For efficacy, the statistical monitoring boundary will be based on testing the null hypothesis at one-sided alpha level of 0.001 (the approximate stopping boundaries are 0.5484, 0.7363, 0.839, 1.1464 on the hazard ratio scale).

13.6.5 Analysis for Reporting the Treatment Results

The usual components of this analysis are:

- Tabulation of all cases entered and any excluded from analysis with reasons for exclusion;
- Patient accrual rate;
- Institutional accrual;
- Distribution of important baseline prognostic variables;
- Frequency and severity of adverse events;
- Observed results with respect to the endpoints described in Section 6.1.

13.6.6 Final Analysis

Detectable EBV Cohort

Final analysis will occur when 102 events for PFS have been reported. A one-sided log rank test will be used to compare the PFS at a significance level of 0.1379.

Undetectable EBV Cohort

Final analysis will occur when 151 deaths have been reported. The confidence interval approach will be used for the final analysis of OS; if the upper bound is below 1.5, then the experimental arm is noninferior to standard arm. And if the lower bound is above 1 then it is inferior.

13.7 Statistical Design for Translational Science

13.7.1 Blood and Tissue Collection

The projected timeline for the parent study is 7 years. The predictive and prognostic potential for these biomarkers may become scientifically obsolete or the assay technology may evolve over time making the technology outlined in the current protocol obsolete. As such, NO marker assays will be conducted (i.e. ERCC1 and p53) on the collected specimens other than those required for patient treatment stratification (i.e. EBV). When sufficient information is available from the parent study, a full correlative study protocol for the marker studies detailing the scientific hypothesis, research plan, assay methods for each biomarker, and a complete statistical section (with adequate power justification and analysis plan) will be submitted and subjected to CTEP review in accordance with the National Clinical Trials Network (NCTN) policies. The proposed biomarkers above will serve as place-holders to facilitate local institutional IRB approval.

13.8 Statistical Design for Quality of Life (QOL)

It is not known prior to completion of initial chemoradiation therapy whether patients will enter the phase II or phase III trial. After collection of plasma in step 1 of the study, all patients with detectable levels of EBV DNA will receive the same treatment (concurrent cisplatin and radiation) during step 2 of the study. Depending on their post-radiation EBV DNA results, patients then are offered entry into either the phase II or phase III study.

Enrollment into the QOL studies will be according to 2 separate sets:

1) A set number of patients (450) will complete the FACT-NP at the pretreatment baseline and will continue to be followed with FACT-NP after EBV re-testing, at 4 months post-RT, and at 1 and 2 years from end of RT whether or not they enter the phase II or phase III study. Once the data has been collected from these 450 patients, then patients will no longer complete the FACT-NP.
2) All 126 phase II patients (including some who completed the FACT-NP) will be asked to complete the HHIE-S and FACT-Taxane instruments after EBV re-testing, at 4 months post-RT, and at 1 and 2 years from end of RT. It is anticipated that 15% (67) of the 450 patients completing the FACT-NP will participate in the phase II study. Thus, enrollment across the entire trial into any QOL component will total 509 patients (450 baseline patients + [126 total phase II patients – estimate of 67 patients who started QOL with the FACT-NP at baseline]), but it is impossible to exceed a maximum of 576 (for a near-impossible scenario of absolutely no overlap between the 126 phase II patients and 450 phase III patients).

FACT-NP will be formally used to judge the predictive value of general and physical well-being subscale scores to predict survival and distant metastases; in addition, exploratory correlations will be done to pre- and post-treatment EBV titer levels, and changes in PRO scores will be correlated to clearance or non-clearance of EBV titers. Descriptive statistics derived from FACT-NP will be used to enrich the understanding of QOL as it pertains to the 2 phase III arms of observation versus additional adjuvant chemotherapy.

In the phase II trial, quality of life is not a co-primary endpoint but will be used to inform the decision between regimens, especially if there is not a large survival difference between the 2 arms. Neuropathic PRO scores will be used as a decision making tool in formulating the design of a subsequent trial. Formal comparisons will be determined based on comparison of the neuropathic PRO scores between the experimental and standard arms.

Decision algorithms to incorporate QOL results are as follows for the phase II trial, in which the experimental arm is gemcitabine/paclitaxel compared to the standard of cisplatin/5FU:

PFS	Hearing and Peripheral Neuropathy Related QOL Results	Decision
Experimental arm is better, significant (> 15%)	Both similar between arms with effect size < 0.50	Experimental arm moves to phase III – endpoint of superior OS
Experimental arm is better, significant (> 15%)	Both similar between arms with effect size ≥ 0.50	Experimental arm moves to phase III – endpoint of superior OS; QOL endpoints used as secondary endpoints to inform decision making
Experimental arm is better, significant (> 0% but <15%)	Difference in hearing and/or peripheral neuropathy QOL with effect size < 0.50	Experimental arm moves to phase III – endpoint of superior OS; QOL endpoints used as secondary endpoints

		to inform decision making
Experimental arm is better, significant (> 0% but < 15%)	Difference in hearing and/or peripheral neuropathy QOL with effect size ≥ 0.50	Experimental arm moves to phase III – endpoint of superior OS; QOL endpoints used as secondary endpoints to inform decision making
Experimental arm is better, not significant (> 0% but <15%)	Both similar between arms with effect size < 0.50	No phase III; evaluation of survival metrics, general and physical well-being QOL, and CTCAE- graded toxicities will be analyzed to inform choice of preferred arm or future design; cost effectiveness considerations used if highly relevant to choice of preferred arm
Experimental arm is better, not significant (> 0% but < 15%)	Difference in hearing and/or peripheral neuropathy QOL with effect size ≥ 0.50	Experimental arm moves to phase III – endpoint of superior QOL
Experimental arm is worse, not significant (> 15%, < 0%)	Regardless	No phase III; evaluation of survival metrics, QOL metrics, and CTCAE- graded toxicities will be analyzed to inform choice of preferred arm or future design; cost effectiveness considerations used if highly relevant to choice of preferred arm
Harm due to experimental arm, significant (< 15%)	Regardless	No phase III

13.8.1 General and Physical Well-Being QOL

We anticipate collecting data from 450 patients for this hypothesis starting at the pretreatment baseline, in order to obtain a range of patients who have cleared or not cleared EBV DNA from the blood by the end of RT. The estimate is that approximately 85% of these patients will enter the phase III trial and 15% will enter the phase II trial. Regardless of which trial they enter, these 450 patients will be followed with FACT-NP at the time points of pretreatment baseline, after EBV re-testing , 4 months post-RT, and at 1 and 2 years from the end of RT in order to investigate the following specific hypotheses:

1) Higher general and physical well-being QOL scores across all time points will predict for improved survival;
2) General and physical well-being QOL scores will be improved in patients who cleared EBV compared to those who did not.

To investigate the prognostic effect of general and physical well-being QOL among the 450 patients across the 2 trials, we consider below the sample size and power combining all randomized and eligible patients. Of the 450 patients, we anticipate 297 patients to be randomized and eligible for the phase III trial, 53 randomized and eligible for the phase II trial, with 81 patients not be randomized and 19 patients randomized but ineligible. In this analysis, the variable of interest would be QOL as a continuous variable. With 119 events for OS and 74 events for DM at the end of the phase III trial for both studies (based on exponential distributions), we calculate the statistical power as follows: the statistical power can be calculated by the

method of Hsieh (2000). The table below shows statistical power to detect hazard ratios of 1.01, 1.05, 1.10, 1.15 and 1.20. The 2-sided significance level was set at 0.05. As seen in the tables, for OS, there will be > 92% power to detect a hazard ratio of 1.15 or greater. The power will be greater than 88% for DM if we want to detect a hazard ratio of 1.10 or larger (variance ≥ 15 assumed).

Statistical power to detect various hazard ratios, continuous variable (OS 104 [0% attrition] or 62 [40% attrition] events, 2-sided 0.05)

	Hazard Ratio				
Variance	1.01	1.05	1.10	1.15	1.20
5	0.04	0.22	0.64	0.92	0.99
10	0.05	0.39	0.90	0.99	0.99
15	0.6	0.54	0.98	0.99	0.99
20	0.07	0.66	0.99	0.99	0.99
25	0.07	0.75	0.99	0.99	1.00

Univariable and multivariable analysis will be performed using the Cox proportional hazards model for OS and distant metastasis. Potential covariates evaluated for the multivariate models would be assigned treatment, age, gender, race, Zubrod performance status, T-stage, N-stage, primary site, and smoking history, as well as QOL as a continuous variable. In addition, exploratory analysis will be performed to determine if there is any outcome difference between QOL and treatment arms. A Cox regression model will be used with the following covariates: 1) assigned treatments; 2) QOL; and 3) assigned treatments by QOL interaction. The covariate for interaction will provide an estimate as to whether the treatment effects are similar between the groups of patients. Pearson correlation will be estimated between general and physical well-being. QOL measures and change from baseline will be correlated to EBV DNA quantitative measurements and compared between EBV detectable and undetectable groups. With a 2-sided alpha of 0.05 and 450 patients (211 analyzable with 40% attrition rate), we will have 88% power to detect an effect size/difference of 0.5 (Mean/SD), the power is 73% with a less likely attrition rate of 60% at 1 year.

13.8.2 Hearing-Related PRO Measurements and Peripheral Neuropathy-Related QOL

In the 126 phase II patients, the HHIE-S will be collected after EBV re-testing, at 4 months post-RT, and at 1 and 2 years from the end of RT to test the following specific hearing-related hypothesis: There will be improvement in HHIE-S scores at ≥ 4 months resulting from the substitution of adjuvant cisplatin/5-FU chemotherapy with gemcitabine/paclitaxel.

For peripheral neuropathy-related QOL, the hypothesis for the 126 patients in the phase II component is: FACT-Taxane scores at ≥ 4 months will show no worsened peripheral neuropathy effects resulting from the substitution of adjuvant cisplatin/5-FU chemotherapy with gemcitabine/paclitaxel.

For the comparison of HHIE-S and FACT-Taxane scores, the power is 85% with the overall sample size from the phase II trial, 2-sided alpha of 0.1 and effect size of 0.5. If we plan to detect an effect size of 0.6 with 40% attrition rate and the same alpha, the statistical power will be 80%, and the power is 74% if the attrition rate is 50% at 1 year. According to the Bonferroni method, if adjusting for 2 comparisons, the overall error rate would be 0.20 for these 2 comparisons.

QOL analysis including overall score and change from baseline will be summarized using mean and standard deviation at each time point for each arm. Overall and nasopharyngeal-specific QOL, hearing QOL (FACT-NP hearing domain, HHIE-S scores), peripheral neuropathy QOL over the short and long term and PTA scores will be compared using a two sample independent t test and paired t test if the comparison is within the experimental arm between different time points. If data normality assumptions are not met, the Wilcoxon rank sum test will be used to test the

hypothesis. Mean change from baseline will be tested using an omnibus F test, followed by individual comparisons of change scores at different time points within each treatment group. The same analysis will be conducted for between-group comparisons at each time point. In addition to comparing the change scores, overall trends in these scores will be modeled using the general linear mixed-effect model. Other potential covariates evaluated for the multivariate models would be assigned treatment, age, gender, race, Zubrod performance status, T-stage, N-stage, primary site, and smoking history, mean radiation dose to cochlea, baseline hearing status, and conductive involvement depending on the outcome variable. A logistic regression model will be used to summarize the number of missing data and to test if the dropout process is missing completely at random. Analyses of complete cases and cases with imputations will be considered as a sensitivity analysis. A pattern mixture or selection model may be used to assess treatment effect to see if it is dropout dependent. Binary and categorical endpoints (such as PTA) will be compared using Fisher's exact test and/or chi-squared tests at each time point. A longitudinal model for categorical outcomes based on the general estimating equation approach may be considered for comparing categorical outcomes across time. Effects of prevalence rate change from baseline will be estimated based on linear or generalized linear mixed models using QOL and hearing thresholds shifts as independent variables while adjusting for other covariates as listed above. Correlation between FACT-NP toxicity, functional assessments, and biomarker levels will be calculated using Spearman's correlation coefficient and the corresponding p values will be reported. Correlation between categorical measures will be summarized by odds ratios, chi-square tests, and associated measures. Adjusted correlation may be derived from ANCOVA models or derived directly using nonparametric ANOVA models if normality assumption is violated. In addition, we will compare peripheral neuropathy-related QOL between the 2 arms in the phase II trial. Kappa statistics will be used to summarize inter-rater reliability for PTA.

13.8.3 Pure Tone Audiometry (PTA) Scores in Relation to QOL

PTA is required in this trial as a necessary medical evaluation to be used in the clinical assessment of toxicity, and thus, all patients receiving treatment will have PTA at pretreatment baseline (for eligibility purposes), at the end of RT and at approximately 1 year (+/- 4 months) from the end of RT. However, comparison of the correlation of PTA to FACT-NP versus HHIE-S will be done in the phase II population (126 patients) in which both instruments are to be administered. For PTA, the single hypothesis is: Loss of high frequency hearing on PTA in the post-RT time period will be more readily detected by HHIE-S rather than FACT-NP (among patients in the phase II trial who will be tested with both instruments, estimated at 15% of 450 patients or 67 patients).

The correlation between HHIE-S, FACT-NP, and PTA will be calculated. Correlation between categorical measures will be summarized by odds ratios, chi-square tests, and associated measures. Adjusted correlation may be derived from ANCOVA models or derived directly using nonparametric ANOVA models if normality assumption is violated. We also will conduct exploratory analyses on hearing-related QOL in the phase II trial, and correlate these with PTA. Correlations between HHIE-S PRO scores and PTA and FACT-NP hearing, and PTA will be compared as dependent statistics

13.8.4 Health-Related Quality of Life (HRQOL) and Cost-Effectiveness Analysis

EuroQol HRQOL will be converted into QALYs. Costs will be estimated and selectively validated by retrospective comparison to institutional reporting. Markov decision modeling will be developed based on cycling health states and rates of complications up to 2 years. Incremental cost effectiveness ratios will be compared to determine the probability of cost effectiveness of various interventions, with sensitivity analyses to identify model weaknesses. The expected value of perfect information will be determined to delimit the upper boundary for cost-effective future investment in this area of research.

13.9 Gender and Minorities (3/4/15)

Projected Distribution of Gender and Minorities

Detectable plasma EBV DNA Post-Treatment

	Gender		
Ethnic Category	**Females**	**Males**	**Total**
Hispanic or Latino	0	1	1
Not Hispanic or Latino	32	93	125
Ethnic Category: Total of all subjects	32	94	**126**
	Gender		
Racial Category	**Females**	**Males**	**Total**
American Indian or Alaskan Native	0	0	0
Asian	28	89	117
Black or African American	1	1	2
Native Hawaiian or other Pacific Islander	1	1	2
White	2	3	5
Racial Category: Total of all subjects	32	94	**126**

Undetectable plasma EBV DNA Post-Treatment

	Gender		
Ethnic Category	**Females**	**Males**	**Total**
Hispanic or Latino	0	2	2
Not Hispanic or Latino	158	472	630
Ethnic Category: Total of all subjects	158	474	**632**
	Gender		
Racial Category	**Females**	**Males**	**Total**
American Indian or Alaskan Native	0	0	0
Asian	149	449	598
Black or African American	1	6	7
Native Hawaiian or other Pacific Islander	1	1	2
White	7	18	25
Racial Category: Total of all subjects	158	474	**632**

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APPENDIX I, STUDY PARAMETER TABLE: PRE-TREATMENT ASSESSMENTS (23-Oct-2017)

*See Section 11.2 for details and exceptions

Assessments	Prior to Step 1 Registration (calendar days)	Prior to Treatment (calendar days)
Collection of plasma for EBV DNA analysis: Required or documentation of previous testing within 28 days at a credentialed central lab	When patient is registered to Step 1	
History/physical exam by Med Onc or Clinical Oncologist and/or Rad Onc: Must include endoscopic eval, current medications, weight, and weight loss in the past 6 months	21	
Imaging: • *MRI or CT scan with contrast) of nasopharynx and neck (with contrast) • *MRI (with contrast) of nasopharynx and PET/CT (with contrast) of the neck	28	
CT scan with contrast of chest and abdomen (required), and pelvis (optional), or total body PET/CT scan (non-contrast is acceptable)	28	
*Bone scan	28 (see Section 11.2 for details)	
Zubrod Performance Status	21	
CBC/differential and platelets	21	
Bilirubin, AST/ALT, Alk Phos	21	
Serum creatinine or calc. creatinine clearance	21	
Serum pregnancy test, as applicable	14	
Audiogram		180; see Section 11.2.1 for details
Dental evaluation		Recommended, not required: 180
Nutritional evaluation		Recommended, not required: Pre-treatment
For patients who consent to participate in collection of tumor tissue or blood for translational research		X
For all patients who consent to participate in QOL assessments: FACT-NP and EQ-5D		X

APPENDIX I, STUDY PARAMETER TABLE: ASSESSMENTS DURING TREATMENT (04May2017)

*See Section 11.2 for details and exceptions

Assessments	**Concurrent Cisplatin and RT Weekly During Treatment**	**Adjuvant Chemotherapy** See Section 11.2.2 for details on flexibility of timing and specific tests that are mandated vs. suggested. Parameters below represent ideal intervals.
History/Physical exam	X	On Friday for patient treated on Monday Within 24 hrs. prior to each treatment
Weight	X	Prior to each cycle
Zubrod Performance Status	X	Prior to each cycle
CBC/differential and platelets	X	Within institutional SOC interval prior to each dose (day 1 for PF, days 1, 8 for GT)
Metabolic panel	X Metabolic panel: potassium, creatinine, calcium, phosphate and magnesium should be done prior to every chemotherapy administration, within the time interval prior to treatment per institutional standards of care	Metabolic panel: sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, calcium, bilirubin, total protein, albumin, AST/ALT, alkaline phosphatase should be done prior to every chemotherapy administration, within time interval according to institutional standards of care (day 1 for PF, days 1, 8 for GT)
Adverse event evaluation	X	For patients receiving chemotherapy: Prior to each dose For patients being observed: Every 28 days
Audiogram	At completion of RT (+/- 2 weeks)	
For phase II or phase III patients who consent to participate in QOL assessments and who completed the FACT-NP at pretreatment baseline: FACT-NP	After EBV re-testing is complete (at the time of Step 3 registration)	
For all phase II patients who consent to participate in QOL assessments: HHIE-S, FACT-Taxane	After EBV re-testing is complete (at the time of Step 3 registration)	
For patients who consent to participate in collection of blood for translational research	At week 4 of concurrent cisplatin and RT	

APPENDIX I, STUDY PARAMETER TABLE: ASSESSMENTS IN FOLLOW UP (04May2017)

*See Section 11.2 for details and exceptions

Assessments	From end of RT: q4 mos. x 2 yrs.; q6 mos. x 3 years; then annually, unless otherwise indicated (also see Section 11.5)
History/Physical exam	X
Weight	X
Zubrod Performance Status	X
Adverse Event evaluation	X
Chest x-ray	Annually for 5 years from end of RT, unless other imaging is done instead; see Section 11.2.
TSH evaluation	Annually from end of RT
*MRI of nasopharynx and neck (if medically contraindicated, CT scan with contrast) OR MRI of nasopharynx and PET/CT of the neck	At 4 months and 1 year from end of RT
PET/CT or CT with contrast of chest, abdomen and/or pelvis	At 1 year from end of RT
Audiogram	At 1 year (+/- 4 months) from end of RT
Biopsy	X*
For phase II or phase III patients who consent to participate in QOL assessments and who completed the FACT-NP at pretreatment baseline: FACT-NP	At 4, 12, and 24 months from end of RT
For all phase II patients who consent to participate in QOL assessments: HHIE-S, FACT-Taxane	At 4, 12, and 24 months from end of RT
For all patients who consent to participate in QOL assessments: EQ-5D	At 12 and 24 months from end of RT
For patients who consent to participate in collection of blood for translational research	At 4 and 12 months from end of RT

APPENDIX II: ZUBROD PERFORMANCE SCALE

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

APPENDIX III: AJCC STAGING SYSTEM

Edge, SB, ed. *AJCC Cancer Staging Manual*. 7th ed. New York, NY: Springer; 2010.

PHARYNX

Nasopharynx	
T1	Tumor confined to the nasopharynx, or tumor extends to oropharynx and/or nasal cavity without parapharyngeal extension*
T2	Tumor with parapharyngeal extension*
T3	Tumor involves bony structures of skull base and/or paranasal sinuses
T4	Tumor with intracranial extension and/or involvement of cranial nerves, hypopharynx, orbit, or with extension to the infratemporal fossa/masticator space

REGIONAL LYMPH NODES (N) Nasopharynx	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Unilateral metastasis in cervical lymph node(s), ≤6 cm in greatest dimension, above the supraclavicular fossa, and/or unilateral or bilateral, retropharyngeal lymph nodes, ≤6 cm in greatest dimension.[1]
N2	Bilateral metastasis in cervical lymph node(s), ≤6 cm in greatest dimension, above the supraclavicular fossa.[2]
N3	Metastasis in a lymph node, more than 6 cm in greatest dimension and/or to supraclavicular fossa.[1]
N3a	>6 cm in dimension.
N3b	Extension to the supraclavicular fossa.[d]

[1]Midline nodes are considered ipsilateral nodes.

[2]Supraclavicular zone or fossa is relevant to the staging of nasopharyngeal carcinoma and is the triangular region originally described by Ho. It is defined by three points: (1) the superior margin of the sternal end of the clavicle, (2) the superior margin of the lateral end of the clavicle, (3) the point where the neck meets the shoulder. Note that this would include caudal portions of levels IV and VB. All cases with lymph nodes (whole or part) in the fossa are considered N3b.

STAGE GROUPING Nasopharynx	
Stage 0	T*is*, N0, M0
Stage I	T1, N0, M0
Stage II	T1, N1, M0 T2, N0-1, M0
Stage III	T1, N2, M0 T2, N2, M0 T3, N0-2, M0
Stage IVA	T4, N0-2, M0
Stage IVB	Any T, N3, M0 Any T, Any N, M1

APPENDIX IV: BIOSPECIMEN COLLECTION (04May2017)

FFPE Specimen Plug Kit Collection

Courier Address (FedEx, UPS, etc.): <u>For Frozen or Trackable FFPE Specimens</u>
NRG Oncology Biospecimen Bank-San Francisco
University of California San Francisco
2340 Sutter Street, Room S341
San Francisco, CA 94115
U.S.A.

- ❑ Include all NRG Oncology paperwork in pocket of biohazard bag.
- ❑ Check that the Specimen Transmittal (ST) Form has the consent boxes checked off.
- ❑ Check that all samples are labeled with the NRG Oncology study and case number, and include date of collection as well as collection time point (e.g., pretreatment, post-treatment).

- ❑ **<u>FFPE Specimens:</u> See Section 10.0 for study-specific instructions.**
  - o Slides should be shipped in a plastic slide holder/slide box. Place a small wad of padding in top of the container. If you can hear the slides shaking it is likely that they will break during shipping.
  - o FFPE Blocks can be wrapped with paper towel, or placed in a cardboard box with padding. **NEVER** wrap blocks with bubble wrap. Place padding in top of container so that if you shake the container the blocks are not shaking. If you can hear the blocks shaking, it is likely that they will break during shipping.
  - o Slides, Blocks, or Plugs can be shipped ambient or with a cold by Courier to the Street Address (94115). **Do NOT ship on Dry Ice**.

- ❑ **<u>Frozen Specimens:</u> See Section 10.0 for study-specific instructions.**
  - o Institutions will batch shipments and will e-mail a tracking number the Biospecimen Bank to indicate that a shipment is on the way.
  - o Place specimens and absorbent shipping material in Styrofoam cooler filled with dry ice (at least 7 lbs. for North American sites and 20 lbs. for Asian sites). There should be plenty of dry ice under and above the specimens. If the volume of specimens is greater than the volume of dry ice then ship in a larger Styrofoam box, or two separate boxes. Any Styrofoam box can be used, as long as it is big enough.
  - o Specimens received thawed due to insufficient dry ice or shipping delays will be discarded and the site will be notified.
  - o Send frozen specimens via overnight courier to the address above. Specimens should be shipped as follows to prevent thawing due to delivery delays: U.S. sites ship out Monday-Wednesday only; Canadian sites: Monday-Tuesday only; Asian sites: Monday only. Saturday or holiday deliveries cannot be accepted. Samples can be stored frozen at -80° C until ready to ship.

- ❑ **For Questions regarding collection/shipping please contact the NRG Oncology Biospecimen Bank by e-mail: NRGBB@ucsf.edu or phone: 415-476-7864 or Fax: 415-476-5271.**

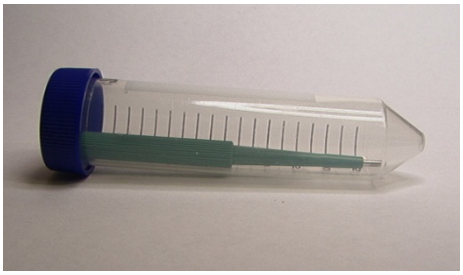
FFPE SPECIMEN PLUG KIT INSTRUCTIONS

This Kit allows sub-sampling of an FFPE block for submission to the NRG Oncology Biospecimen Bank. The plug kit contains a shipping tube and a punch tool.

Step 1
If the block is stored cold, allow it to equilibrate for 30 minutes at room temperature. Place the punch tool on the paraffin block over the selected tumor area. (Ask a pathologist to select area with tumor.) Push the punch into the paraffin block. Twist the punch tool once around to separate the plug from the block. Then pull the punch tool out of the block. The punch should be filled with tissue sample.

Step 2
Label the punch tool with the proper specimen and block ID. DON'T remove specimen from the punch.

Use a separate punch tool for every specimen. Call or e-mail us if you have any questions or need additional specimen plug kits.



Step 3
Once punch tool is labeled, the site can embed the punch or place in shipping tube and mail to address below. Please do not mix specimens in the same tube.

We will remove core specimen from the punch, embed in a paraffin block, and label with specimen and block ID.

***NOTE:** If your facility is uncomfortable obtaining the plug but wants to retain the tissue block, please send the entire block to the NRG Oncology Biospecimen Bank and we will sample a plug from the block and return the remaining block to your facility. Please indicate on the submission form the request to perform the plug procedure and return of the block and include an airbill with a return request form from the bank.

Ship specimen plug kit, specimen in punch tool, and all paperwork to the address below. For Questions regarding collection/shipping or to order an FFPE Specimen Plug Kit, please contact the NRG Oncology Biospecimen Bank by e-mail: NRGBB@ucsf.edu or call 415-476-7864/Fax 415-476-5271.

NRG-HN001 BLOOD COLLECTION KIT INSTRUCTIONS

This Kit is for study specific collection, processing, storage, and shipping of plasma for EBV DNA or plasma and whole blood for banking *(as specified by the NRG-HN001 protocol)*:

Kit contents: Sites must supply their own blood draw tubes for the translational banking samples.

- Two Purple Top EDTA tubes, specifically for EBV plasma (A)
- Six cold packs: Freeze these at -20°C immediately, so the packs are frozen when you are ready to ship the plasma for EBV DNA
- Two Ziploc bags for EBV DNA plasma cold packs
- Two Styrofoam/cardboard boxes for the cold EBV DNA plasma shipments
- Four (4) 3.5 ml Sarstedt cryovials (cat# 60.549.001) for EBV plasma (two [2] for each time-point)
- Twenty (20) 1 ml cryovials for banking
- Biohazard bags (6) and Absorbent shipping material (6)
- Styrofoam container (inner) and Cardboard shipping (outer) box
- UN1845 DRY Ice Sticker and UN3373 Biological Substance Category B Stickers
- EBV and Banking Specimen Transmittal (ST) Forms and Kit Instructions

PREPARATION AND PROCESSING OF PLASMA AND WHOLE BLOOD:

(A) Plasma (If requested): Purple Top EDTA tube #1

- ❑ **For EBV testing**: Label two 3.5 ml Sarstedt cryovials with NRG Oncology study HN001 and four-digit case number (use leading zeros), collection date, time, and time point, and clearly mark cryovials "EBV plasma". For example: HN001-0046, EBV plasma, 1/7/17.

  Note: The information on the ST form must match the vials. Failure to properly label the samples may result in the CLIA lab being unable to perform the required testing.

  Acceptable:
  Plasma vial: NRG-HN001 Case X
  ST form: NRG-HN001 Case X

  Unacceptable:
  Plasma vial: NRG-HN001 Case X
  ST form: NRG-HN001 Case 0000X

- ❑ **For Banking**: Label five (5) 1 ml Corning cryovials as necessary for the plasma collected. Label them with the NRG Oncology study and case number, collection date, time, and time point, and clearly mark cryovials "banking plasma".

Process:

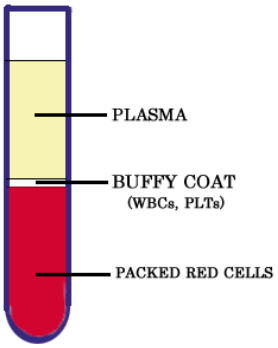
1. After collection, invert tube(s) multiple times to ensure adequate mixing of EDTA.
2. Centrifuge specimen(s) within one hour of collection in a standard clinical centrifuge at ~2500 RPM for 10 minutes at 4°C (preferred). If sites are unable to process samples at 4°C then spinning at room temperature is acceptable if done within 2 hours of draw but must be noted on the ST Form.
3. If the interval between specimen collection and processing is anticipated to be more than one hour, keep specimen on ice until centrifuging is performed.
4. Carefully pipette and aliquot 2.0 ml plasma into two 3.5 ml Sarstedt tubes for EBV or a minimum of 0.5 ml plasma in up to five (5) 1 ml cryovials as are necessary for the plasma collected for banking labeled with NRG Oncology study and case numbers, collection date/time, time point collected and clearly mark specimen as "EBV plasma" or "banking plasma". Avoid pipetting up the buffy coat layer.
5. Place cryovials into biohazard bag
   - For mandatory EBV DNA plasma samples: Ship frozen immediately by overnight courier with 2-3 frozen packs sealed in a Ziplock bag to appropriate laboratory (see Section 10.2 and photos below); **Note**: Due to possible degradation of plasma EBV

DNA, centers should ship frozen plasma samples on the day of collection whenever possible. For patients who are consented late in the day and for which shipment is not possible on the day of collection, sites can freeze the samples at -80°C and ship the following day (Monday-Wednesday) or wait until Monday to ship with 4-6 frozen cold packs inside a Ziplock bag and tight-fitting Styrofoam box with outer cardboard box. Utek 1C silver cold packs or frozen Polar packs are recommended. DO NOT use Utek -23C silver cold packs, as these can thaw more rapidly.

- For plasma for banking (if patient consents), immediately freeze at -70 to 90° C.

6. Store frozen plasma at -80°C for banking until ready to batch ship on dry ice.
7. See below for storage conditions.

(continued on next page)



(B) <u>Whole Blood for DNA (if requested): Purple Top EDTA tube #2</u>

- ❑ Label as many 1ml Corning cryovials (3 to 5) as necessary for the whole blood collected. Label them with the NRG Oncology study and case number, collection date/time, and time point, and clearly mark cryovials "blood".

<u>Process</u>:

1. After collection, invert tube(s) multiple times to ensure adequate mixing of EDTA. Blood can also be mixed for 5 minutes on a mixer at room temperature.
2. Carefully pipette and aliquot 1.0 ml blood into as many cryovials as are necessary for the blood collected (3 to 5) labeled with NRG Oncology study and case numbers, collection date/time, time point collected and clearly mark specimen as "blood".
3. Place cryovials into biohazard bag and either
    - Freeze immediately at -70 to -80° Celsius and batch ship at a later date with banking plasma samples.
4. Store blood samples frozen until ready to ship on dry ice.
5. See below for storage conditions.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED and include collection time point on ST Form.

<u>Freezing and Storage</u>:

- ☐ Freeze Blood samples in a -80°C Freezer or on Dry Ice or snap freeze in liquid nitrogen.
- ❑ Store at –80°C (-70°C to -90°C) until ready to ship. If a - 80°C Freezer is not available:
    - Samples can be stored short term in a -20° C freezer (non-frost free preferred) for up to one week (U.S. sites ship out Monday-Wednesday only; Canadian sites: Monday-Tuesday only; Asian sites: Monday only).

    <u>OR</u>:
    - Samples can be stored in plenty of dry ice for up to one week, replenishing daily (Ship out Monday-Wednesday only; Asian sites: Monday only).

    <u>OR</u>:
    - Samples can be stored in liquid nitrogen vapor phase (U.S. sites ship out Monday-Wednesday only; Canadian sites: Monday-Tuesday only; Asian sites: Monday only).

- ❑ Please indicate on Specimen Transmittal (ST) Form the storage conditions used and time stored.

(continued on next page)

Shipping/Mailing of Plasma Samples for EBV DNA Measurement: See Section 10.2 for address of appropriate laboratory. Do NOT ship to the NRG Oncology Biospecimen Bank.

- **For mandatory EBV DNA plasma samples**: Ship frozen by overnight courier with 2-3 frozen ice packs, sealed in a large Ziploc bag to appropriate laboratory as soon as possible (see Section 10.2 and photos below)
- **Note**: Due to possible degradation of plasma EBV DNA, centers should ship plasma samples on the day of collection whenever possible. For patients who are consented late in the day and for which shipment is not possible on the day of collection, sites can freeze the samples at -80°C and ship the following day (Monday-Wednesday) or wait until Monday to ship with 4-6 frozen cold packs inside a Ziplock bag and tight-fitting Styrofoam box with outer cardboard box. Utek 1C silver cold packs or frozen Polar packs are recommended. DO NOT use Utek -23C silver cold packs, as these can thaw more rapidly.

Shipping of Plasma for EBV DNA with Frozen Cold Packs:

Shipping/Mailing of Samples for Banking:

- ❑ Ship specimens for banking on dry Ice overnight **Monday-Wednesday (Asian sites: Monday only)** to prevent thawing due to delivery delays. Saturday and holiday deliveries cannot be accepted.
- ❑ Include all NRG Oncology paperwork in a sealed plastic bag and tape to the outside top of the Styrofoam box.
- ❑ Wrap frozen specimens of same type (i.e., all plasma together and whole bloods together) in absorbent shipping material and place each specimen type in a separate biohazard bag. Place specimen bags into the Styrofoam cooler and fill with plenty of dry ice (7-10 lbs/3.5kg minimum). ***Add padding to avoid the dry ice from breaking the tubes.***
- ❑ Place Styrofoam coolers into outer cardboard box, and attach shipping label and UN3373 and UN1895 stickers to outer cardboard box.
- ❑ *Multiple cases may be shipped in the same cooler, but make sure each one is clearly labeled and separated in a separate bag and that there is enough room for plenty of dry ice.* ***Add padding to avoid the dry ice from breaking the tubes.***
- ❑ **For questions regarding collection, shipping or to order a Blood Collection Kit, please e-mail NRGBB@ucsf.edu or call (415)476-7864.**

Shipping Address for Banking Samples from U.S. and Canadian Sites Only:

Courier Address (FedEx, UPS, etc.): For all Frozen Specimens
NRG Oncology Biospecimen Bank-San Francisco
University of California San Francisco
2340 Sutter Street, Room S341
San Francisco, CA 94115
For questions, call 415-476-7864 or e-mail: NRGBB@ucsf.edu