Mayo Clinic Radiation Oncology

MC1675: DART-HPV: A Phase III Evaluation of De-escalated Adjuvant Radiation Therapy for HPV-Associated Oropharynx Cancer

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√Study contributor(s) not responsible for patient care.

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Protocol Resources

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Patient eligibility*, test schedule, treatment delays/interruptions/adjustments, dose modifications, adverse events, protocol document, consent form, regulatory issues, forms completion and submission	Xxxxxxx, Study Coordinator Phone: E-mail:

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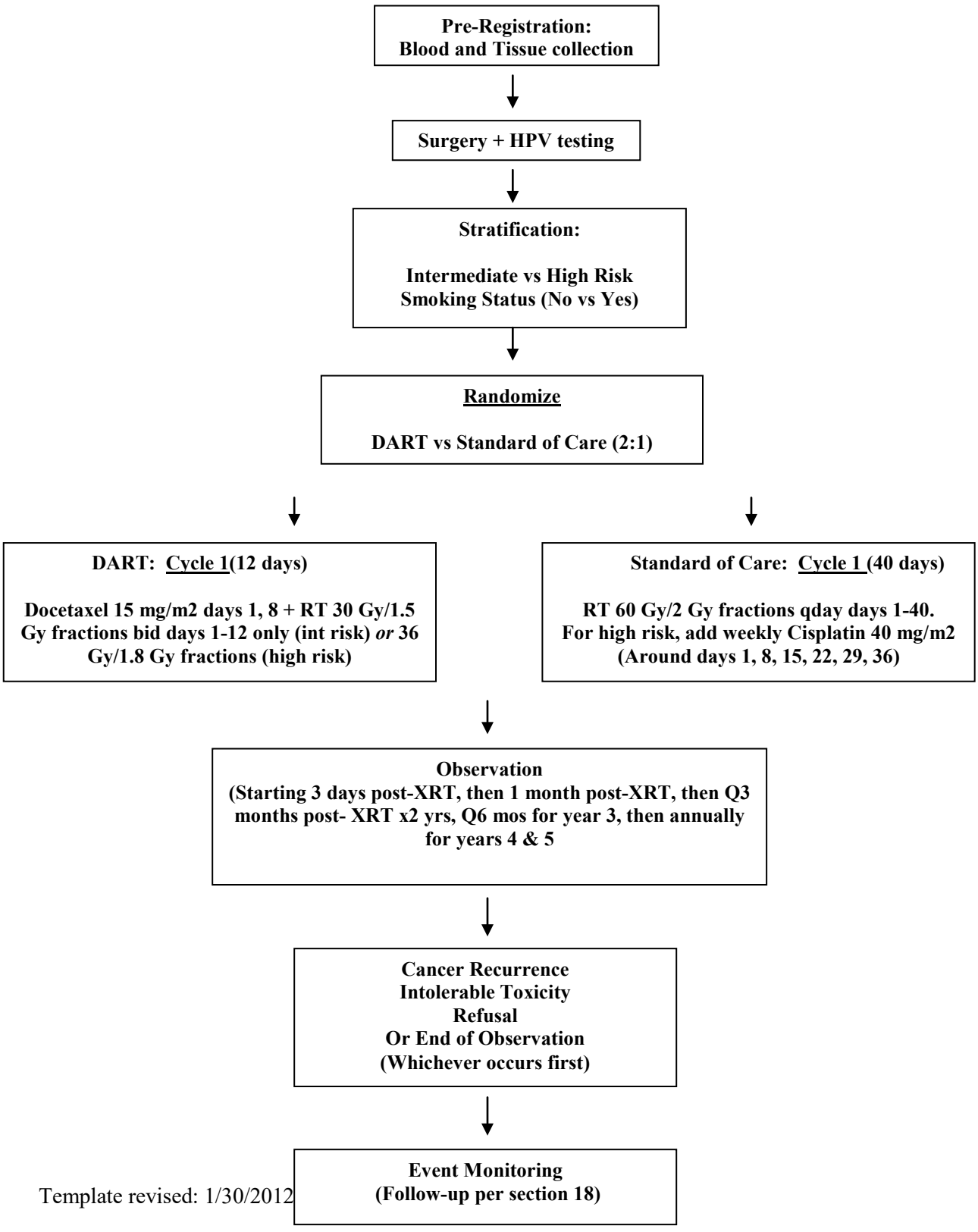
List of Abbreviations

LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience
CFR	Code of Federal Regulations
CRF	Case Report Form
DSMB	Data and Safety Monitoring Board
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IRB	Institutional Review Board
PHI	Protected Health Information
PI	Principal Investigator
SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure
DART	De-escalated Adjuvant Therapy
IMRT	Intensity modulated radiation therapy
HPV	Human papillomavirus

Schema


Pre-Registration:
Blood and Tissue collection
Surgery + HPV testing
Stratification:
Intermediate vs High Risk
Smoking Status (No vs Yes)
Randomize
DART vs Standard of Care (2:1)
DART: Cycle 1(12 days)
Docetaxel 15 mg/m2 days 1, 8 + RT 30 Gy/1.5 Gy fractions bid days 1-12 only (int risk) or 36 Gy/1.8 Gy fractions (high risk)
Standard of Care: Cycle 1 (40 days)
RT 60 Gy/2 Gy fractions qday days 1-40.
For high risk, add weekly Cisplatin 40 mg/m2 (Around days 1, 8, 15, 22, 29, 36)
Observation
(Starting 3 days post-XRT, then 1 month post-XRT, then Q3 months post- XRT x2 yrs, Q6 mos for year 3, then annually for years 4 & 5
Cancer Recurrence
Intolerable Toxicity
Refusal
Or End of Observation
(Whichever occurs first)
Event Monitoring
(Follow-up per section 18)

1.0 Background

1.1 The new epidemic in oropharynx cancer

Due to the success of public health initiatives in tobacco cessation, the overall rate of head and neck cancers (HNC) has steadily decreased in recent years (1). However, the number of cancers within the oropharynx (tonsils, base of tongue, or soft palate) has seen a dramatic and unexpected rise within the past two decades. From 1988 to 2004, there was a 225% population-level increase in HPV-related oropharynx cancers (HPV+ OPC) in the United States and the Centers of Disease Control project that oropharynx cancer cases will likely grow to 17,000 cases/year by 2030 (2). This rate of growth within a specific cancer type is unprecedented and has been described as an oncologic epidemic by many public health authorities (3).

1.2 Role of HPV in Oropharyngeal Cancers

Much of the rise in oropharynx cancer can be directly linked to the oncogenic role of the human papillomavirus (HPV). Oral cavity and oropharynx HPV infections are now widespread within the United States and upwards of 70% of the U.S. population are expected to have HPV exposure within their lifetime (4). While much of the population is able to clear an oral HPV infection, a subset of the population develops a persistent viral infection which eventually leads to oropharynx cancer over the course of many years. HPV+ OPC now comprises close to 80% of all oropharynx cancers while smoking and alcohol-related oropharynx cancers continue to decline (5). As a result, the demographics of an oropharynx patient has shifted from a more elderly population with significant smoking related co-morbidities to a younger, healthier population which is expected to live for many decades if they are cured of their cancer (6).

1.3 Long-term toxicities with standard therapies

Although HPV+ OPC patients can expect high rates of cure with standard therapies, these treatments are also associated with high rates of permanently disabling toxicities. The standard treatment for HPV+ OPC involves either seven weeks of daily radiation therapy (70 Gy) concurrent with cisplatin or surgery followed by six weeks of daily radiation therapy (60 Gy) with or without cisplatin depending upon post-surgical risk factors. Both definitive chemoradiation and surgery followed by adjuvant radiotherapy results in grade ≥3 toxicities rates of ~30% (9). The most common of these toxicities include dysphagia requiring a permanent feeding tube, severe xerostomia which limits food intake and increases dental issues, osteoradionecrosis of the mandible requiring surgery or hyperbaric oxygen treatments, or neck fibrosis which severely limits range of motion. Among patients who do not have grade ≥3 toxicities, grade 2 xerostomia, dysphagia, or neck fibrosis is nearly universal. The mechanism behind these toxicities is well-established. Post-treatment dysphagia and xerostomia are closely correlated with the total radiation dose received by the pharyngeal constrictors and salivary glands and extensive literature exists concerning the radiation dose constraints for these structures. For example, a mean dose ≥26 Gy to the parotid glands is closely linked to long-term xerostomia while mean doses of ≥50 Gy strongly increases the risk for permanent swallowing difficulties (10, 11). However, achieving these dose constraints with conventional treatment is problematic as standard definitive and post-operative radiation doses are 70 Gy and 60 Gy respectively. Even modern treatment techniques such as intensity modulated radiation therapy

(IMRT) and proton therapy may have difficulty in reducing this normal tissue radiation exposure as the structures in question often lie within the volume at risk for disease recurrence, hence are intentionally treated. Issues with long term toxicity are particularly germane in the HPV+ OPC population as these patients will likely be cured, are healthier, and are expected to live a long time post-treatment. This rapidly growing patient population will therefore live for decades with the severe accumulated side effects incurred from therapy.

1.4 Urgent need for novel treatment paradigms

Strategies for reducing treatment toxicity for HPV+ OPC patients have been identified as a research priority by a number of cooperative groups. Nevertheless, these efforts are incremental in treatment de-escalation and may not maximize the possible improvements in quality of life for these patients. Furthermore, an incremental dose de-escalation strategy may ultimately be more dangerous than an aggressive de-escalation strategy, as salvage options for locoregional recurrences remain limited after 50 Gy. An aggressive treatment de-escalation strategy is therefore required in order to maximize post-therapy quality of life while potentially leaving salvage options available.

1.5 Preliminary data supporting dose de-escalation

After observing the limitations with current research philosophies, the Head and Neck Disease Oriented Group at Mayo Clinic adopted a novel philosophy towards the issue of dose de-escalation. Rather than incrementally de-escalating therapy (i.e. reducing radiation from 60 to 50 Gy or changing the dose of cisplatin), we sought to aggressively de-escalate treatment using half the dose of total radiation (30-36 Gy) along with one-fifth the dose of a gentler chemotherapy (docetaxel 15 mg/m2 x 2).

The accrual goal for MC1273 was 80 patients in order to achieve 70 evaluable patients. Accrual was completed in April 2016, and all patients are currently evaluable. 35 patients have reached at least one year of follow-up while 14 patients have at least two years of follow-up. The current locoregional control rate for MC1273 is 100%. Three patients have developed distant metastases for a preliminary disease free survival rate of 96%, and no patients have died. Furthermore, no patients have required the placement of a PEG tube following adjuvant radiation and the grade ≥ 3 toxicity rate by six months post-therapy is 0%. Although full conclusions cannot be drawn until follow-up is complete, preliminary data suggest a high likelihood that MC1273 will exceed expectations for both disease control and quality of life preservation.

1.6 Inadequacy of pathologic risk factors

The need for adjuvant radiation and/or chemotherapy after surgical resection is traditionally based upon risk factors found during pathologic assessment. These factors include positive margins, extracapsular extension, lymphovascular space invasion, perineural invasion, tumor size, and nodal volume. Nevertheless, these pathologic risk factors are often poor predictors for locoregional recurrence. A review conducted on Mayo Clinic HPV+ OPC patients who had risk factors after surgery but no adjuvant care found that only 20% of patients had a locoregional relapse, and only 11% of patients with risk factors but without extracapsular extension had relapse after surgery alone (12). While these failure rates are still above traditional thresholds for

recommending adjuvant care, these data strongly suggest that pathologic review is insufficiently specific for detecting residual tumor burden.

1.7 Mate-pair sequencing for HPV-associated malignancies

The need for improved detection of post-surgical tumor burden motivated the development of mate-pair sequencing for detecting HPV-associated gene rearrangements (13). By focusing on gene rearrangements, mate-pair sequencing avoids the issue of variant calling errors associated with whole exome and whole genome techniques. Combined with currently available techniques for detecting circulating tumor DNA, mate-pair sequencing performed on the primary tumor specimen may allow for the detection of tumor specific genetic alterations which can be subsequently assayed in pre- and post-surgical serum samples (14-16).

2.0 Goals

2.1 Primary

2.11 To compare the rates and severity of late grade 3-5 toxicities and PEG tube dependence between de-escalated adjuvant radiation therapy (DART) and standard adjuvant therapy. *(For definitions concerning toxicity timing and attribution, see section 7.82).*

2.2 Secondary

2.21 To assess the cumulative incidence of local/regional failure at 2 years after study registration for patients treated with DART vs standard therapy..

2.22 To compare overall survival, disease-free survival, and distant failure associated with DART vs standard treatment.

2.12 To compare the overall QOL between DART and standard adjuvant therapy at 1-year post-treatment as measured by FACT H&N and EORTC H&N QLQ 35.

2.3 Correlative Research

2.31 To determine the genetic alterations of oropharynx tumor specimens and the detection rate of corresponding circulating DNA in the pre-surgical, post-surgical, and post-radiation blood of oropharynx cancer patients.

2.32 To investigate the usefulness of immunologic biomarkers in predicting progression free survival.

2.33 To establish a patient derived xenograft panel from representative oropharynx patients.

3.0 Patient Eligibility

3.1 Pre-Registration (optional)

3.11 Provide written informed consent

3.12 Submission of research blood draw and/or tumor sample.

3.2 Registration – Inclusion Criteria

3.21 Age ≥ 18 years.

3.22 Histological confirmation of HPV+ squamous cell carcinoma of the oropharynx. HPV positivity will be defined as positive staining for p16 on IHC.

3.23 Gross total surgical resection with curative intent of the primary tumor and at least unilateral neck dissection within 7 weeks of registration.

3.24 ECOG Performance Status (PS) 0 or 1 (Appendix I)

3.25 Absence of distant metastases on standard diagnostic work-up ≤ 16 weeks prior to registration. (Chest CT, CXR, or PET/CT.)

3.26 Must have one of the following risk factors:
- Lymph node > 3 cm
- 2 or more positive lymph nodes
- Perineural invasion
- Lymphovascular space invasion
- T3 or T4 primary disease
- Lymph node extracapsular extension

3.27 The following laboratory values obtained ≤ 35 days prior to registration.
- Absolute neutrophil count (ANC) ≥1500/mm^3
- Platelet count ≥100,000/mm^3
- Hemoglobin ≥8.0g/dL
- Creatinine ≤ 1.5 mg/dL or creatinine clearance ≥ 50 mL/min
- Total or direct bilirubin < 2 x institutional upper limit of normal (ULN)
- AST (SGOT) or ALT (SGPT) < 3 x institutional ULN

3.29a Negative pregnancy test done ≤7 days prior to registration, for women of childbearing potential only.

3.29b Ability to complete questionnaire(s) by themselves or with assistance.

3.29c Provide informed written consent.

3.29d Willingness to return to enrolling institution for follow-up (during the Active Monitoring Phase of the study).

3.3 Registration – Exclusion Criteria

3.31 Any of the following because this study involves an agent that has known genotoxic, mutagenic and teratogenic effects:
- Pregnant women
- Nursing women
- Men or women of childbearing potential who are unwilling to employ

adequate contraception

3.32 Co-morbid systemic illnesses or other severe concurrent disease which, in the judgment of the investigator, would make the patient inappropriate for entry into this study or interfere significantly with the proper assessment of safety and toxicity of the prescribed regimens.

3.33 Immunocompromised patients and patients known to be HIV positive.

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

3.35 Receiving any other investigational agent which would be considered as a treatment for the primary neoplasm.

3.36 Other active malignancy ≤ 5 years prior to registration. EXCEPTIONS: Non-melanotic skin cancer or carcinoma-in-situ of the cervix. NOTE: If there is a history or prior malignancy, they must not be receiving other specific treatment for their cancer.

3.37 Prior history of radiation therapy to the affected site.

3.38 History of connective tissue disorders such as rheumatoid arthritis, lupus, or Sjogren's disease.

3.39 Presence of any of the following risk factors after surgery:
- Any positive surgical margin.
- Adenopathy below the clavicles

3.40 Prior systemic chemotherapy.

3.41 History of allergic reaction to docetaxel

3.42 Receiving any medications or substances which in the opinion of the investigators would interfere with treatment. Examples could include strong inhibitors of CYP3A4 at oncologist discretion (see Appendix IV).

3.43 Severe pre-existing ototoxicity or neuropathy that would, in the opinion of the investigator, preclude the use of cisplatin chemotherapy.

4.0 Test Schedule

Assessments, tests and procedures	Pre-reg (prior to surgery)	Pre-Treatment		Active Monitoring	Observation		
		≤ 10 weeks prior to registration	≤ 2 weeks prior to registration	Weekly (+/- 3 days)	At 3 days post-XRT[19]	At 1 mo. post-XRT (+/- 14days)	Q3 months post- XRT x2 yrs q6 mos for year 3, then annually for years 4 & 5 (+/- 1 month)
Evaluation by Radiation Oncologist and/or Medical Oncologist		X[8]		X[10]	X[5]	X[5]	X[5]
ENT/Surgeon's exam		X[9]				X[5]	X[5]
CT with contrast, or CT/PET, and/or MRI of H & N[2]		X	X[14]	X[15]			X[15]
Chest x-ray (or chest CT or CT/PET)[2]		X		X[15]			X[5,6]
Pathology Assessment (Gross total resection ≤ 7 weeks		X[7]					
Biopsy				X[4, 15]			X[4, 15]
Performance status			X	X		X	X
CBC w/ diff			X	X[15]		X	X[15]
Total or Direct Bilirubin, AST (SGOT) or ALT (SGPI)			X	X[15]		X	X[15]
Serum creatinine			X	X[15]			
Na, K, glucose, Ca, Mg, albumin			X				
Serum pregnancy test (if applicable)[1]			X[1]				X[15]

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Assessments, tests and procedures (cont.)	Pre-reg (prior to surgery)	Pre-Treatment		Active Monitoring	Observation		
		≤ 10 weeks prior to registration ≤ 2 weeks	prior to registration	Weekly (+/- 3 days)	At 3 days post-XRT[19]	At 1 mo. post-XRT (+/- 14 days)	Q3 months post-XRT x2 yrs q6 mos for year 3, then annually for years 4 & 5
Dental evaluation		X[16]					
Assessment of swallowing function		X[18]				X	X[11]
Adverse event evaluation			X		X	X	X
Research Blood Specimens (section 14.0)[12 R]	X		X[13]				X[13]
QOL/Functional Assessments: QLQ H&N35; FACT-H&N;; EQ-5D; XeQOLS; DLQI[3]		X[17]			X[17]	X[17]	X[17]
Patient Assessment Form (completed by investigator) (see Appendix V)		X[17]			X	X	

1. For women of childbearing potential only. Must be done ≤7 days prior to registration.
2. Specify method (e.g., CT, MRI, or PET/CT, etc.) Same imaging modality throughout the study is encouraged.
3. Patient questionnaire booklets must be used; copies are not acceptable for this submission.
4. If suspicion of tumor recurrence.
5. An initial post-treatment evaluation by Radiation and/or Medical Oncology will be performed 3 days after completion of RT. A general history and physical by one of the following: a Radiation Oncologist, Medical Oncologist, an ENT, or a Head and Neck Surgeon must be done at 1 and 3 months post-XRT, then q3 months for 2 years, every 6 months for year 3, then annually for year 4 & 5. A laryngopharyngoscopy (mirror and/or fiberoptic and/or direct procedure) is recommended at these time points but is not required.
6. Chest imaging (at minimum a chest x-ray or chest CT or CT/PET of chest) is required once per year for a total of 5 image sets.
7. Gross total resection/surgical pathology must be completed ≤ 7 weeks prior to registration.

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8. A general history & physical by a Radiation Oncologist and/or Medical Oncologist must be done≤ 8 weeks prior to registration
9. An examination by an ENT or Head & Neck Surgeon must be done ≤ 8 weeks prior to registration. A laryngopharyngoscopy (mirror and/or fiberoptic and/or direct procedure) is recommended but not required
10. A general history & physical by a Radiation Oncologist and/or Medical Oncologist must be done weekly.
11. One year post XRT; two-year post XRT assessment is optional.

12. This blood collection will only be collected for patients that are enrolled at the Mayo Clinic Rochester.
13. This blood specimen only needs to be collected post-surgery but prior to radiation therapy treatment and then only at the 3 month post radiation therapy visit
14. Recommended within 8 wks prior to registration
15. As clinically indicated
16. To be completed within 3 months of starting treatment.
17. Questionnaires should be completed at the following time points: Baseline (prior to starting treatment) 3 days post treatment, and at 1, 3, 12, and 24 months post treatment.
18. If not able to get done completed prior to starting treatment, it should be completed within the first week of treatment.
19. Optional

R. Research Funded

5.0 Stratification Factors:

- Extracapsular Extension
  - No: Intermediate Risk
  - Yes: High Risk

- Smoking History
  - No: < 10 pack-year equivalents of tobacco product use AND ≥5 years abstinent of tobacco equivalent products.
  - Yes: ≥ 10 pack-year equivalents of tobacco product use OR <5 years abstinent of tobacco equivalent products.

6.0 Randomization/Registration

6.1 Randomization – After stratification, patients will be randomized between DART and standard therapy using a 2:1 randomization favoring DART. The treatment arms will be balanced based on the 2 stratification factors of interest: Risk (Intermediate vs. High Risk) and Smoking Status (No vs Yes). The balancing algorithm that we will use is a dynamic allocation procedure that is part of Medidata Rave, known as Balance.

6.2 Registration Procedures

Patient will be registered to the study when they have consented, met eligibility criteria, and have been logged into Research Participant Tracking (Ptrax).

7.0 Protocol Treatment

NOTE: FOR THIS STUDY, IMRT AND IGRT ARE MANDATORY

Dose Specifications DART

The prescribed radiotherapy dose will be 30-36 Gy in 1.5-1.8 Gy twice-daily fraction size (total of 20 fractions). Radiotherapy should strongly aim to begin on a Monday. If Monday therapy cannot be arranged due to Holidays or technical issues, treatment must start no later than Tuesday with chemotherapy arranged to begin on the same day. Treatments that begin on a Tuesday should be Tues – Sat b.i.d. both weeks with chemotherapy to start on Tuesday both weeks. The daily dose will be prescribed such that 100% of the PTV volume receives at least 30 Gy. PTV coverage has precedence over normal tissue constraints.

Cohort	Dose (Gy)	Number of Fractions	Fraction Size	Rx Length	Rx Days
Int. Risk	**30**	**20**	**1.5**	**Days 1-12**	**M-F**
High Risk	**36**	**20**	**1.8**	**Days 1-12**	

Dose Specifications Standard of care

The prescribed radiotherapy dose will be 60 Gy in 2 Gy daily fraction size (total of 30 fractions). Radiotherapy should aim to begin on a Monday. The daily dose will be prescribed such that 98% of the PTV volume receives at least 60 Gy.

Cohort	Dose (Gy)	Number of Fractions	Fraction Size	Rx Length	Rx Days
Int. and High Risk	**60**	**30**	**2**	**Days 1-40**	**M-F**

7.41 **Technical Factors**
Treatment Planning/Delivery: Megavoltage energy photon beam irradiation is required. Any treatment planning and delivery system that has been credentialed for head and neck IMRT is acceptable.

7.42 *Image Guidance for IGRT*: Daily image guidance of IMRT may be achieved using any one or more of the following techniques:

- Orthogonal kilovoltage (KV) images, e.g. ExacTrac;
- Linear-accelerator mounted kV and MV conebeam CT images;

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 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).

7.43 **Localization, Simulation, and Immobilization**

7.431 Patients must have an immobilization device (e.g., aquaplast mask) made prior to treatment planning CT scan.

7.432 The treatment planning CT scan can be performed with *IV* contrast so that the major vessels of the neck are easily visualized. The treatment planning CT scan must be performed with the immobilization device and in the treatment position. Slice thickness should be 0.3 cm.

7.5 Target and Normal Tissue Volume Definitions

7.51 *Definition of Target Volumes:*
Patients randomized to DART

7.510 CTV3600**:** This volume will receive 180 cGy per day b.i.d. and will only apply to patients who have +ECE (high risk cohort). This volume will be restricted to the prior location of the ECE-involved lymph node, expanded by 1 cm, and shaving off of bone and relevant normal anatomy. This volume may approach the skin but should not approach < 2mm. In the instance where the exact ECE-involved lymph node is unclear, CTV3600 will be defined as the nodal station from which the ECE-involved node originated. For questions, contact the Primary Investigator, Dr. Daniel J. Ma.

7.511 CTV3000: This volume will receive 150 cGy per day b.i.d. CTV3000 will include the primary tumor bed (based on preoperative imaging, preoperative physical exam/endoscopy, operative findings, pathologic findings) plus region(s) of grossly involved lymphadenopathy. This volume may approach the skin but should not approach < 2mm. It is recognized that after surgery, there can be considerable distortion of normal anatomy. If possible, map preoperative GTV(s) onto the postoperative radiation therapy planning CT scan, and add appropriate margins for microscopic spread (1.5-2 cm). CTV3000 also will generally include the bilateral necks. This usually means encompassing nodal levels 2, 3, and 4 for all cases. Nodal levels 1, 5a, and 5b are included in CTV3000 in selected circumstances. Ipsilateral neck

irradiation for the involved hemi-neck will only be allowed for a well-lateralized tonsillar cancer without any base of tongue involvement. For questions, contact the Principal Investigator, Dr. Daniel J. Ma.

7.512 Planning Target Volumes (PTVs): In general, the PTV should not go outside of the skin surface; if it does exceed the skin surface, the application of bolus material over this portion of the PTV may be considered but is generally not recommended.

7.513 PTV Expansion with Daily IGRT: The minimum CTV-to-PTV expansion is 2.5 mm (a larger expansion may be necessary for a target volume subject to significant intra-fraction variability. In general, the CTV-to-PTV expansion (with IGRT) should not exceed 5 mm.

7.52 *Definition of Target Volumes:*

Patients randomized to Standard therapy

7.520 CTV6000: This volume will receive 200 cGy per day. CTV6000 will include the primary tumor bed (based on preoperative imaging, preoperative physical exam/endoscopy, operative findings, pathologic findings) plus region(s) of grossly involved lymphadenopathy. This volume may approach the skin but should not approach < 2mm. It is recognized that after surgery, there can be considerable distortion of normal anatomy. If possible, map preoperative GTV(s) onto the postoperative radiation therapy planning CT scan, and add appropriate margins for microscopic spread (1.5-2 cm). CTV6000 also will include the **involved** neck and/or dissected uninvolved neck at investigator discretion. This generally means encompassing nodal levels 2, 3, and 4 for all cases. Nodal levels 1, 5a, and 5b are included in CTV in selected circumstances. Ipsilateral neck irradiation for the involved hemi-neck will be allowed for a well-lateralized tonsillar cancer without any base of tongue involvement only. For questions, contact the Principal Investigator, [redacted]

7.521 CTV5400: This optional volume will receive 180 cGy per day. CTV5400 will include the **uninvolved** at-risk neck, generally the contralateral neck levels 2-4. Additional nodal levels may be included at investigator discretion for unusual case presentations. For questions, contact the Principal Investigator, [redacted]

7.522 Planning Target Volumes (PTVs): In general, the PTV should not go outside of the skin surface; if it does exceed the skin surface, the application of bolus material over this portion of the PTV may be considered but is generally not recommended.

7.523 PTV Expansion with Daily IGRT: The minimum CTV-to-PTV expansion is 2.5 mm (a larger expansion may be necessary for a target

volume subject to significant intra-fraction variability. In general, the CTV-to-PTV expansion (with IGRT) should not exceed 5 mm.

7.53 *Definition of Normal Tissues/Organs at Risk (OARs)*

7.531 Spinal Cord: The cord begins at the cranial-cervical junction (i.e., the top of the C1 vertebral body). Superior to this is brainstem and inferior to this is cord. The inferior border of the spinal cord is at approximately T3-4 (i.e., just below the lowest slice level that has PTV on it). The spinal cord shall be defined based on the treatment planning CT scan. In addition, however, a Planning Risk Volume (PRV) spinal cord shall be defined. The cord_prv = cord + 5 mm in each dimension. This is irrespective of whether or not IGRT is used.

7.532 Brainstem: The inferior most portion of the brainstem is at the cranial-cervical junction where it meets the spinal cord. For the purposes of this study, the superior most portion of the brainstem is approximately at the level of the top of the posterior clinoid. The brainstem shall be defined based on the treatment planning CT scan. In addition, however, a Planning Risk Volume (PRV) brainstem shall be defined. The brainstem_prv = brainstem + 3 mm in each dimension.

7.533 Lips and Oral Cavity: These should be contoured as 2 separate structures as the goal is to keep the lip dose much lower than the oral cavity dose. The definition of lips is self-explanatory. For non-oral cavity cancers, the oral cavity will be defined as a composite structure consisting of the anterior ½ to 2/3 of the oral tongue/floor of mouth, buccal mucosa, and palate. This should not overlap the PTVs.

7.534 Parotid Glands: Parotid glands will be defined based on the treatment planning CT scan. Parotid gland volume will not include any portion of any of the CTVs, although they can overlap the PTVs.

7.535 Constrictors: This will be defined as the posterior pharyngeal wall plus adjacent constrictor muscles. This extends from the superior constrictor region (the inferior pterygoid plates level) to the cricopharyngeal inlet (posterior cricoid cartilage level). This should not overlap the PTVs.

7.526 Esophagus: This will be defined as a tubular structure that starts at the bottom of constrictors and extends to the thoracic inlet.

7.527 Larynx: This will be defined as a “triangular prism shaped” volume that begins just inferior to the hyoid bone and extends to the cricoid cartilage inferiorly and extends from the anterior commissure to include the arytenoids. This includes the infrahyoid and suprahyoid epiglottis.

7.528 Mandible: This includes the entire boney structure of the mandible from the TMJ through the symphysis. It is recognized that for oropharynx cancers, this may overlap with PTVs.

7.6 Treatment Planning and Delivery

7.61 Management of the Low Neck/Supraclavicular Region (No Match)
No Match: The entire clinical target volume (CTV) [upper and lower neck and primary tumor bed] is irradiated with IMRT. There is no match line between upper and lower portions of the regions at risk. In this technique, limiting radiotherapy dose to organs at risk (OARs), e.g., the cervical esophagus, is entirely achieved by inverse treatment planning via IMRT algorithms.

7.62 IMRT Dose Prescription to PTVs
See Section 7.5 for definitions of CTVs and PTVs. For inverse planning IMRT, the goal is for 98% of the PTVs to receive ≥ 100% of prescription dose. It is recognized that portions of the PTV close to the skin may receive significantly less than prescription. This is acceptable as long as cold spots within PTV do not exist at a depth deeper than 5 mm beneath the skin.

7.63 IMRT Dose Constraints to Normal Structures
There are two goals for the dose constraints in this protocol. First, structures such as the parotid glands and the minor salivary glands within the oral cavity have a continuous, inverse relationship between dose and function. Thus the dose constraints for these structures reflect what should be achievable using IMRT techniques. Second, the dose received by critical structures such as the spinal cord and brainstem may limit the ability for re-irradiation if such treatment is required. Thus the dose constraints on these structures have been set conservatively to facilitate possible future interventions. PTV coverage has precedence over normal tissue constraints.

Dose constraints for all structures except spinal cord and brainstem are considered suggestions and subject to investigator clinical discretion.

For patients randomized to DART:

7.631 *Spinal Cord*: The cord_prv should not exceed 35 Gy to any volume in excess of 0.03 cc (approximately 3 mm x 3 mm x 3 mm). The spinal cord PRV should not exceed 30 Gy to any volume in excess of 0.01 cc. The goal for treatment planning will be a mean dose < 20 Gy.

7.632 *Brainstem*: The brainstem_prv should not exceed 35 Gy to any volume in excess of 0.03 cc (approximately 3 mm x 3 mm x 3 mm). The goal for treatment planning will be a mean dose < 20 Gy.

7.634 *Lips:* Reduce the dose as much as possible. The mean dose should be < 15 Gy.

7.635 *Oral Cavity:* Reduce the dose as much as possible. The mean dose should be < 20 Gy.

7.636 *Parotid Glands*: In most cases, it will be easier to spare one parotid than the other. The treatment planning goal will be for this individual parotid gland to receive a mean dose of < 10 Gy. Otherwise, the goal will be for the total mean parotid dose to be < 15 Gy.

7.637 *Submandibular Glands:* If either submandibular gland is outside of the target volume, the goal will be for a mean dose for that gland to be <20 Gy. Otherwise reduce the dose as much as possible.

7.637 *Constrictors*: Reduce the dose as much as possible. Target mean dose is <20 Gy.

7.638 *Esophagus*: Reduce the dose as much as possible. Target mean dose is <20 Gy.

7.639 *Larynx*: Reduce the dose as much as possible. Target mean dose is <15 Gy.

7.640 *Mandible:* Reduce the dose as much as possible. Keep 105% hotspot outside of mandible if possible.

For patients randomized to Standard Therapy:

7.641 *Spinal Cord*: The cord_prv must not exceed 45 Gy to any volume in excess of 0.03 cc (approximately 3 mm x 3 mm x 3 mm).

7.642 *Brainstem*: The brainstem_prv must not exceed 54 Gy to any volume in excess of 0.03 cc (approximately 3 mm x 3 mm x 3 mm).

7.643 *Lips:* Reduce the dose as much as possible. The mean dose should be < 20 Gy.

7.644 *Oral Cavity:* Reduce the dose as much as possible. The mean dose should be < 50 Gy.

7.645 *Parotid Glands*: In most cases, it will be easier to spare one parotid than the other. The treatment planning goal will be for this individual parotid gland to receive a mean dose of < 26 Gy. Otherwise, the goal will be for the total mean parotid dose to be < 39 Gy.

7.646 *Submandibular Glands:* If either submandibular gland is outside of the target volume, the goal will be for a mean dose for that gland to be <39 Gy. Otherwise reduce the dose as much as possible.

7.647 *Constrictors*: Reduce the dose as much as possible. Target mean dose is <50 Gy.

7.648 *Esophagus*: Reduce the dose as much as possible. Target mean dose is <34 Gy.

7.649 *Larynx*: Reduce the dose as much as possible. Target mean dose is < 35 Gy.

7.650 *Mandible:* Reduce the dose as much as possible. Keep 105% hotspot outside of mandible if possible.

Chemotherapy Treatment

Agent	Dose	Days administered	Pre-medication*
Docetaxel (DART)	15 mg/m^2 in 50-100 mL 0.9% NaCL (non-PVC container) IV infusion over 1 hour	1, 8 (Mondays)	1) Dexamethasone 10 mg in 100 mL 0.9% NaCL IV infusion over 15 minutes 2) Benadryl 50 mg in 100 ml 0.9% Sodium Chloride IV infusion over 15 minutes
Cisplatin (standard of care)	40 mg/m^2 IV weekly	Monday, Tuesday, or Wednesday	Per institutional protocol

*****For patients who have an infusion reaction despite pre-medication with dexamethasone and Benadryl, stop infusion and administer Pepcid 20 mg IV and an additional dose of Benadryl 50 mg IV. Once symptoms resolve and additional pre-medication has been given, resume infusion. If the infusion reaction occurs on day 1 of treatment (1st dose of docetaxel), administer all three medications with the 2nd cycle (dexamethasone, Benadryl, and Pepcid). If a patient is still symptomatic despite additional pre-medication, stop treatment and reschedule for the following day (day 2 or day 9), and send the patient home with high-dose steroid premedication.(dexamethasone 20 mg po the evening before the planned chemotherapy, and 20 mg po the morning of the planned chemotherapy). When the patient presents for the infusion, they should receive the following premedications: dexamethasone 20 mg IV, Pepcid 20 mg IV, Benadryl 50 mg IV, and Ativan 1 mg IV. If despite all of these efforts a patient still reacts, docetaxel should be permanently discontinued.

7.7 Compliance Criteria

Treatment breaks must be clearly indicated in the treatment record along with the reason(s) for the treatment break(s). Refer to Appendix II for full details.

7.81 **Adjuvant Therapy Adverse Events**

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4 will be utilized for grading all adverse events. All appropriate treatment areas should have access to a copy of the CTCAE, v. 4. A copy of the CTCAE, v. 4 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

Grade 3 therapy-induced mucositis and/or dysphagia are expected to develop in about one third of patients receiving standard of care. Nutritional evaluation prior to the initiation of therapy, to determine if prophylactic gastrostomy (PEG) tube placement is needed, is highly recommended. Placement of a feeding tube should be recorded on the appropriate case report form, 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, dysphagia, odynophagia, skin erythema, and desquamation within the treatment fields.

Less common long-term treatment adverse events include: hypothyroidism, loss of hearing, chronic swallowing dysfunction requiring permanent feeding tube, and cervical fibrosis.

Much less common radiation adverse events include: mandibular osteoradionecrosis (< 5% incidence with attention to dental recommendations), and cervical myelopathy (< 0.1% with restriction of spinal cord dose to ≤ 30 Gy).

Clinical experience on MC1273 demonstrated an unexpectedly high rate of thrush in patients receiving DART. Thrush prophylaxis is highly recommended for patients randomized to DART starting on Day 8 of therapy**. For full details of recommended symptomatic management for patients randomized to DART, please see Appendix VII**

7.82 **Definition of Adverse Event Timing and Attribution**

Early onset (acute) toxicities will be defined as toxicities which begin during the start of adjuvant therapy upwards to 90 days post radiation therapy.

Late onset (chronic) toxicities will be defined as toxicities which begin from 91 days to two years post radiation therapy. Early onset toxicities can also be considered late toxicities if they persist for at least one day beyond the 90 days used to define late onset toxicities. For example, a patient who requires PEG tube placement during radiation therapy but has the PEG tube persist at the 6-month post-treatment evaluation will be considered to have both an acute and chronic toxicity.

Attribution for toxicities will follow the guidelines outlined in section 10.22. For statistical purposes, only grade 3 or higher toxicities recorded as "possible", probable" or "definite" in relationship to adjuvant therapy will be used for the primary endpoint. For example, a patient who requires PEG placement after surgery, before the initiation of radiation therapy, and does not have worsening of swallowing outcomes on formal swallow evaluation after adjuvant therapy will be recorded as having a toxicity that is not probable or definite in attributable to adjuvant therapy for the purposes of the primary endpoint. These toxicities will nevertheless be recorded for safety and reporting purposes.

When ambiguity exists concerning the attribution of toxicities, an independent panel consisting of a radiation oncologist, ENT, and medical oncologist who were not involved in the patient's care will assess attribution.

8.0 Dose Modifications Based on Adverse Events

This study has no pre-specified radiation interruptions due to adverse events. If radiation needs to be interrupted, this will be approved by the Radiation chair [redacted] and documented.

8.1 Dose Levels (Based on Adverse Events in Tables 8.*2*)

For patients randomized to DART

Dose Level	DOCETAXEL (Day 1 or 8)
0*	15 mg/m2 IV
-1	10 mg/m2 IV
-2	5 mg/m2 IV

*Dose level 0 refers to the starting dose.
- If the patient requires one docetaxel delay (Day 1 or 8), start at Dose -1

For patients randomized to standard therapy, high risk cohort (+ECE)

For patients randomized to receive standard chemoradiotherapy, cisplatin at 40 mg/m2 will be given intravenously (IV) over 60 minutes weekly on a Monday, Tuesday, or Wednesday of each week. (6 doses for a total of 240 mg/m2). Cisplatin can be given prior to or after the patient's radiation on each day of chemotherapy delivery at the treating physician's discretion. Cisplatin administration outside of these specified time points during radiation is only allowed in the event of holidays or scheduling conflicts that do not permit drug and radiation delivery on the specific

date. Cisplatin is administered concurrent with radiation therapy. In the event that radiation therapy is held, no cisplatin will be administered.

Weekly cisplatin doses of may be reduced to 30 mg/m2 or held at the discretion of the treating Medical Oncologist for toxicity purposes. Possible indications for dose modification or withdrawal include an absolute neutrophil count (ANC) < 1000/mm3, platelet count < 75,000, development of grade 2 neurotoxicity or ototoxicity, or clinically relevant elevations of serum creatinine. Dose reduction will be performed at the discretion of the Medical Oncologist.

8.2

→ → ***Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified*** ← ←			
CTCAE System/Organ/ Class (SOC)	**ADVERSE EVENT**	**AGENT**	**ACTION****
BASED ON INTERVAL ADVERSE EVENT			
Investigations, Other, Blood/ Bone Marrow	ANC < 1500/mm3 **OR** PLT < 75,000/mm3	docetaxel	Hold docetaxel. Resume treatment at one decreased dose level when ANC ≥ 1500/mm3 and PLT ≥ 75,000.
Investigations, Other, Liver	AST or ALT > 1.5 x ULN when AP > 2.5 x ULN **OR** AST or ALT > 3 x ULN **OR** Total or Direct Bilirubin > 1.5 x ULN	docetaxel	Hold docetaxel. Resume treatment at one decreased dose level when AST/ALT ≤ 3 x ULN, AP < 2.5 x ULN, and Total or Direct Bilirubin ≤ 1.5 x ULN.
Neurology	Grade 3+ peripheral neuropathy	docetaxel	Discontinue docetaxel.
All other non-hematologic adverse events	Grade 2-4 (exclude nausea/vomiting that has not been pre-medicated)	docetaxel	Hold docetaxel. Resume treatment at one decreased dose level when resolved to grade 0-1 adverse event.

* Located at http:/ctep.cancer.gov/protocolDevelopment/electronic_applications.ctc.htm

** Use the following to describe actions in the Action column:

- Omit = Treatment is not given for this cycle
- Hold/Delay = Treatment can be made up as part of this cycle
- Discontinue = Treatment is totally stopped

Template revised: 1/30/2012

NOTE: If the patient experiences a significant adverse event requiring a dose reduction at the start of the next dose, then the dose will remain lowered for that entire cycle.

NOTE: Adverse events requiring a dose-reduction step for any or all drugs beyond the two dose-reduction steps (levels –1 and –2) will be at the discretion of the treating physician, if the decision is made for the patient to be kept on study. These dose reductions must be clearly recorded in reported clinical data.

9.0 Ancillary Treatment/Supportive Care

9.1 Antiemetics may be used at the discretion of the attending physician.

9.2 Blood products and growth factors should be utilized as clinically warranted and following institutional policies and recommendations. The use of growth factors should follow published guidelines of the American Society of Clinical Oncology (42) Update of Recommendations for the Use of Hematopoietic Colony-Stimulating Factors: Evidence-Based, Clinical Practice Guidelines. J Clin Oncol 18(20): 3558-3585, 2000.

9.3 Patients should receive full supportive care while on this study. This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications such as antidiarrheals, analgesics, and/or antiemetics received from the first day of study treatment administration until 30 days after the final dose will be recorded in the medical records.

9.4 Diarrhea: This could be managed conservatively with loperamide. The recommended dose of loperamide is 4 mg at first onset, followed by 2 mg every 2-4 hours until diarrhea free (maximum 16 mg/day).

In the event of grade 3 or 4 diarrhea, the following supportive measures are allowed: hydration, octreotide, and antidiarrheals.

If diarrhea is severe (requiring intravenous rehydration) and/or associated with fever or severe neutropenia (grade 3 or 4), broad-spectrum antibiotics may be prescribed. Patients with severe diarrhea or any diarrhea associated with severe nausea or vomiting may be hospitalized for intravenous hydration and correction of electrolyte imbalances.

9.5 For mucositis, esophagitis, and nutritional support: These may include analgesics, antiemetics, topical mouth rinses, skin creams/ointments, etc. The use of amifostine as a radioprotector is not allowed.

9.6 Premedication for chemotherapy will be given per institutional protocols.

9.7 Symptomatology for patients randomized to DART is unique to the regimen and may be unexpected for physicians without prior experience with this treatment schedule. **For recommended symptomatic management for patients randomized to DART, please refer to Appendix VII.**

10.0 Adverse Event (AE) Reporting and Monitoring

10.1 Definitions

Adverse Event- An untoward or undesirable experience associated with the use of a medical product (i.e. drug, device, biologic) in a patient or research subject.

Serious Adverse Event - Adverse events are classified as serious or non-serious. Serious problems/events can be well defined and include;

- death
- life threatening adverse experience
- hospitalization
- inpatient, new, or prolonged; disability/incapacity
- persistent or significant birth defect/anomaly

And/or per protocol may be problems/events that in the opinion of the sponsor-investigator may have adversely affected the rights, safety, or welfare of the subjects or others, or substantially compromised the research data.
All adverse events that do not meet any of the criteria for serious, should be regarded as **non-serious adverse events**.

Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSO) - Any unanticipated problem or adverse event that meets the following three criteria:

- Serious: Serious problems or events that results in significant harm, (which may be physical, psychological, financial, social, economic, or legal) or increased risk for the subject or others (including individuals who are not research subjects). These include: (1) death; (2) life threatening adverse experience; (3) hospitalization - inpatient, new, or prolonged; (4) disability/incapacity - persistent or significant; (5) birth defect/anomaly; (6) breach of confidentiality and (7) other problems, events, or new information (i.e. publications, DSMB reports, interim findings, product labeling change) that in the opinion of the local investigator may adversely affect the rights, safety, or welfare of the subjects or others, or substantially compromise the research data, **AND**
- Unanticipated: (i.e. unexpected) problems or events are those that are not already described as potential risks in the protocol, consent document, not listed in the Investigator's Brochure, or not part of an underlying disease. A problem or event is "unanticipated" when it was unforeseeable at the time of its occurrence. A problem or event is "unanticipated" when it occurs at an increased frequency or at an increased severity than expected, AND
- Related: A problem or event is "related" if it is possibly related to the research procedures.

Preexisting Condition- A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period. At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

10.2 Recording Adverse Events

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site: (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm)

10.21 Adverse event monitoring and reporting is a routine part of every clinical trial. First, identify and grade the severity of the event using the CTCAE version 4.0. Next, determine whether the event is expected or unexpected and if the adverse event is related to the medical treatment or procedure. With this information, determine whether the event must be reported as an expedited report (see Section 10.3).

10.22 Assessment of Attribution
When assessing whether an adverse event is related to a medical treatment or procedure, the following attribution categories are utilized:
Definite - The adverse event is clearly related to the agent(s).
Probable - The adverse event is likely related to the agent(s).
Possible - The adverse event may be related to the agent(s).
Unlikely - The adverse event is doubtfully related to the agent(s).
Unrelated - The adverse event is clearly NOT related to the agent(s).

Events determined to be possibly, probably or definitely attributed to a medical treatment suggest there is evidence to indicate a causal relationship between the drug and the adverse event.

10.3 Reporting of Serious Adverse Events and Unanticipated Problems

When an adverse event has been identified, the study team will take appropriated action necessary to protect the study participant and then complete the Study Adverse Event Worksheet and log. The sponsor-investigator will evaluate the event and determine the necessary follow-up and reporting required.

a. Serious Adverse Events will be reported as part of regular adverse event reporting mechanisms via the data capture system and logged for review reporting.

10.31 Investigator Reporting: Notifying the Mayo IRB:

The IRB requirements reflect the guidance documents released by the Office of Human Research Protections (OHRP), and the Food and Drug Administration (FDA) in early 2007 and are respectively entitled "Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events" and "Guidance for Clinical Investigators, Sponsors, and IRBs: Adverse Event Reporting – Improving Human Subject Protection."

10.311 According to Mayo IRB Policy any serious adverse event (SAE) which the Principal Investigator has determined to be a UPIRTSO must be reported to the Mayo IRB as soon as possible but no later than 5 working days after the investigator first learns of the problem/event.

10.312 Non-UPIRTSO – the investigator reports problems or events that do NOT meet criteria of an UPIRTSO in summary format at the time of the next continuing review. The investigator monitors the severity and frequency of subsequent non-UPIRTSOs.

Consider the following information to collect when developing any forms for documentation of adverse events.
Example
Information collected on the adverse event worksheet (and entered in the research database):

- Subject's name:
- Medical record number:
- Disease/histology (if applicable):
- The date the adverse event occurred:
- Description of the adverse event:
- Relationship of the adverse event to the research (drug, procedure, or intervention):
- If the adverse event was expected:
- The severity of the adverse event: (use a table to define severity scale 1-5)
- If any intervention was necessary:
- Resolution: (was the incident resolved spontaneously, or after discontinuing treatment)
- Date of Resolution:

The investigator will review all adverse event reports to determine if specific reports need to be made to the IRB and FDA. The investigator will sign and date the adverse event report when it is reviewed. For this protocol, only directly related SAEs/UPIRTSOs will be reported to the IRB.

10.4 Adverse events to be graded at each evaluation and pretreatment symptoms/conditions to be evaluated at baseline per the CTCAE v4.0 grading unless otherwise stated in the table below:

System Organ Class (SOC)	Adverse Event/Symptoms	Baseline	Each evaluation	Grading scale (if not CTCAE)
Gastrointestinal disorders	Dry mouth	X	X	CTCAE
	Dysphagia	X	X	CTCAE
	Mucositis oral	X	X	CTCAE
	Nausea	X	X	CTCAE
	Esophagitis	X	X	CTCAE
	Oral Pain	X	X	CTCAE
General disorders and administration site conditions	Fatigue	X	X	CTCAE
Musculoskeletal and connective tissue disorders	Superficial soft tissue fibrosis	X	X	CTCAE
Vascular disorders	Lymphedema	X	X	CTCAE

10.41 Submit via appropriate reporting mechanisms the following AEs experienced by a patient and not specified in Section 10.4:

10.4.11 Grade 2 AEs deemed possibly, probably, or definitely related to the study treatment or procedure.

10.4.12 Grade 3 and 4 AEs regardless of attribution to the study treatment or procedure.

10.4.13 Grade 5 AEs (Death)

10.4.131 Any death within 30 days of the patient's last study treatment or procedure regardless of attribution to the study treatment or procedure

10.4.132 Any death more than 30 days after the patients last study treatment or procedure that is felt to be at least possibly treatment related must also be submitted as a Grade 5 AE, with a CTCAE type and attribution assigned.

10.5 Monitoring and Auditing

The investigator will permit study-related monitoring, audits, and inspections by the IRB, the sponsor, and government regulatory agencies, of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable compliance offices

10.51 Medical Monitoring
It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see section 10.5 "Monitoring and Auditing"). Medical monitoring will include a regular assessment of the number and type of serious adverse events. "Any serious adverse events will be followed up by the sentinel event reporting procedure"

10.52 Internal Data and Safety Monitoring Board

As an interventional study, this study will be reviewed in conjunction with the Mayo Clinic Cancer Center DSMB processes. The study will also be reviewed by the Radiation Oncology Research Executive Board on a yearly basis to assess accrual, adverse events, and any endpoint problems. Any safety issues requiring protocol changes will be communicated through protocol amendments.

The trial will be reviewed by the Cancer Center Auditing area on a bi-annual or yearly basis dependent on random study selection to assess accrual, adverse events, and any endpoint problems. Any safety issues requiring protocol changes will be communicated through protocol amendments.

11.0 Treatment Evaluation

11.1 Patients will be evaluated at baseline, 3 days post XRT, 1 month post-XRT, then every 3 months for 2 years post-XRT followed by every 6 months during year 3, then annually for years 4 & 5. Once patients go off treatment or observation for recurrence, they will be followed per the Section 18.0 criteria.

11.2 At the time of reevaluation, patients will be classified in the following manner:

11.21 No evidence of disease (NED).

11.22 Recurrence of disease (REC). Recurrence must be confirmed by imaging and/or biopsy, with supporting materials submitted per Section 18.0. If recurrence occurs, the report documenting recurrence is to be submitted per Section 18.0.

11.221 The site of recurrence (or failure) will also be collected and classified as local vs. regional vs. distant recurrence. The specific site of failure will also be collected as well.

11.222 Secondary Treatment. The date of the first retreatment and extent of retreatment post-recurrence (i.e. secondary resection or re-irradiation for primary disease), will be collected. Pathology, if available, and operative reports are required to be submitted per Section 18.0.

12.0 Descriptive Factors

- Primary tumor site: Tonsil vs. Tongue Base vs. Soft palate vs. Pharyngeal Wall vs. Other. (Can choose multiple)
- Neck Radiation: Bilateral vs. Unilateral.
- T Stage: 1 vs. 2 vs. 3 vs. 4a vs. 4b
- N Stage: 0 vs. 1 vs. 2a vs. 2b vs. 2c vs. 3.
- HPV-positivity by HPV-ISH: Yes vs. No
- Smoking history in pack-years.

13.0 Treatment/Follow–up Decision at Evaluation of Patient

13.1 Patients who have a recurrence while receiving therapy or during observation will go to the event-monitoring phase and be followed per Section 18.0.

13.2 Patients who go off protocol treatment or observation for reasons other than recurrence will go to the event-monitoring phase and be followed per Section 18.0.

13.3 Patients that complete all adjuvant treatment will then be followed during the observation phase at 3 days post-XRT, 1 month post-XRT, followed by every 3 months post-XRT for 2 years, followed by every 6 months for year 3, then annually for years 4 & 5.

13.4 A patient is deemed *ineligible* if after registration, it is determined that at the time of registration, the patient did not satisfy each and every eligibility criteria for study entry. The patient may continue treatment off-protocol at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered. The patient will go directly to the event-monitoring phase of the study (or off study, if applicable).

- If the patient received treatment, all data up until the point of confirmation of ineligibility must be submitted. Event monitoring will be required per Section 18.0 of the protocol.
- If the patient never received treatment, on-study material must be submitted.

13.5 A patient is deemed a *major violation*, if protocol requirements regarding treatment in cycle 1 of the initial therapy are severely violated that evaluability for primary end point is questionable. All data up until the point of confirmation of a major violation must be submitted. The patient will go directly to the event-monitoring phase of the study. The patient may continue treatment off-protocol at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered. Event monitoring will be required per Section 18.0 of the protocol.

13.6 A patient is deemed a *cancel* if he/she is removed from the study for any reason before any study treatment is given. On-study material and the End of Active Treatment/Cancel Notification Form must be submitted. No further data submission is necessary.

14.0 Body Fluid or Biospecimens

14.1 Summary Table of Research Blood and Body Fluid Specimens to be Collected for this Protocol

NOTE: This blood collection system will only be collected for Mayo Clinic Rochester patients.

Correlative Study (Section for more information)	Mandatory or Optional	Blood or Body Fluid being Collected	Type of Collection Tube (color of tube top)	Volume to collect per tube (#of tubes to be collected)	Pre-registration (Pre-surgery)	Pre-Treatment	Three Month Post XRT	Process at site? (Yes or No)	Temperature Conditions for Storage/ Shipping
cfDNA	Optional	Whole Blood	Streck	Two 10 mL whole blood samples in Streck Cell Free DNA BCT tubes	X	X	X	Yes	Frozen BAP Lab
Immunogenic markers	Optional	Serum	Red-top, no anti-coagulant	One 10 mL serum in red-top tube	X	X	X	Yes	Frozen BAP Lab
Immunogenic markers	Optional	Peripheral blood lymphocytes and plasma	10 mL EDTA vacuatiner	One 10 mL EDTA	X	X	X	Yes	Frozen BAP Lab

14.2 Collection and Processing

14.21 Specimens will be collected at the following time points

- Prior to surgery as a pre-registration collection
- Post-surgery prior to radiation therapy
- 3 months post radiation therapy

14.22 Two 10 mL blood samples will be collected in Streck Cell Free DNA BCT tubes. The tubes should be gently inverted 7 to 10 times to thoroughly mix the samples. These samples will be processed within 7 days of collection for cfDNA extraction using the Qiagen QIAmp Circulating Nucleic Acid kit according to manufacturer's specifications. Evaluation for prespecified gene mutations will be performed using digital droplet PCR with the RainDrop platform (raindancetech.com). All of these samples must be labeled for immediate processing. The Streck Cell Free DNA BCT tubes will be provided for this study.

14.23 Draw one 10 mL vacutainer (no anti-coagulant). Allow to coagulate at room temperature for 20 minutes. Separate by centrifugation at approximately 1200 G x 20 minutes. Aliquot serum into four cryovials and discard residual cells. Samples to be frozen.

14.24 Draw one 10 mL potassium EDTA (purple top) vacutainer, invert gently 4-5 times. Upon receipt at BAP, tubes will be processed to isolate plasma and buffy coat peripheral blood lymphocytes. Samples must be processed immediately upon receipt.

14.3 Shipping and Handling

14.31 Shipping Specimens

The Streck tubes for cfDNA should be kept at 6°C (42.8°F) to an ambient temperature of 37°C (98°F) during shipping. Ship cfDNA sample and CTC samples together to:

[redacted]

Samples for the cfDNA studies should be collected and shipped Monday – Thursday. However, if the study participant can only be seen on Fridays, please contact the Biospecimen Resource Manager [redacted]

14.4 Background and Methodology

14.41 Circulating Cell Free DNA (cfDNA): Several studies indicate that circulating cell free DNA (cfDNA) includes representation of key genetic alterations related to cancer progression or resistance to systemic therapy; these alterations include mutations of tumor suppressor genes (e.g., *TP53*) and oncogenes (e.g., *PIK3CA*, *KRAS* and *BRAF*). Commercially available platforms exist with a predefined set of genes and point mutations of interest for use across multiple malignancies. A more

flexible system for individualized monitoring is needed. Mayo Clinic Rochester has developed an internal assay for this purpose.

14.42 Immunogenic markers: Given the immunogenic nature of HPV infections, we will investigate whether tumor antigen specific cellular immunity can serve as biomarkers for disease progression. Peripheral blood lymphocytes, cytokines, and chemokines from post-surgery, pretreatment, and post treatment samples will be correlated with disease recurrence, DFS, and OS.

15.0 Drug Information

15.1 Docetaxel (Taxotere®, TATER) Commercial Supply

15.11 **Background**: Antineoplastic Agent, Antimicrotubular, Taxane derivative. Docetaxel promotes the assembly of microtubules from tubulin dimers, and inhibits the depolymerization of tubulin which stabilizes microtubules in the cell. This results in inhibition of DNA, RNA, and protein synthesis. Most activity occurs during the M phase of the cell cycle.

15.12 **Formulation**: **Note:** Docetaxel is now available as a one-vial formulation in two concentrations: 10 mg/mL and 20 mg/mL. The older formulation included 2 vials which consisted of a concentrated docetaxel vial and a diluent vial, resulting in a reconstituted concentration of 10 mg/mL. Admixture errors could occur due to the concentration difference between the new formulations of 10 mg/mL and 20 mg/mL and the old formulation (10 mg/mL). Do not use the two-vial formulation with the one-vial formulation for the same admixture product.

15.13 Drug procurement:

Preparation, storage, and stability: Storage conditions: Store the packaged docetaxel between 2 and 25°C (36 and 77°F). Retain in the original package to protect from bright light. Freezing does not adversely affect the product.

One-vial formulation: Note: One-vial formulation is available in two concentrations: 10 mg/mL and 20 mg/mL. Further reconstitution with diluent is not required. Further dilute for infusion in 250-500 mL of NS or D_5W in a non-DEHP container (e.g., glass, polypropylene, polyolefin) to a final concentration of 0.3-0.74 mg/mL. Gently rotate to mix thoroughly. Solutions prepared from the one-vial formulation and diluted for infusion should be used within 4 hours of preparation (infusion should be completed within 4 hours).

Two-vial formulation: Vials should be diluted with 13% (w/w) ethanol/water (provided with the drug) to a final concentration of 10 mg/mL. Do not shake. Further dilute for infusion in 250-500 mL of NS or D_5W in a non-DEHP container (e.g., glass, polypropylene, polyolefin) to a final concentration of 0.3-0.74 mg/mL. Gently rotate to mix thoroughly. Diluted solutions of the two-vial formulation are stable in the vial for 8 hours at room temperature or under refrigeration. Solutions prepared with the two-vial formulation and diluted for infusion in D_5W or NS are stable for up to 4 weeks (Thiesen, 1999) at room temperature of 15ºC to 25ºC (59ºF to 77ºF) in

polyolefin containers; however, the manufacturer recommends use within 4 hours (infusion should be completed within 4 hours).

15.14 **Administration:** Administer IV infusion over 1-hour through non-absorbing polyethylene lined (non-DEHP) tubing; in-line filter is not necessary. **Note:** Premedication with dexamethasone is required (see Section 7.0)

15.15 **Pharmacokinetic information**: Docetaxel exhibits linear pharmacokinetics at the recommended dosage range.
Distribution: Extensive extravascular distribution and/or tissue binding; $V_{d:}$ 80-90 L/m2, V_{dss}: 113 L (mean steady state)
Protein binding: ~94% to 97%
Metabolism: Hepatic; oxidation via CYP3A4 to metabolites
Half-life elimination: Terminal: ~11 hours
Excretion: Feces (~75%, <8% as unchanged drug); Urine (<5%)

15.16 **Potential Drug Interactions**:
Cytochrome P450 Effect: Substrate (major) of CYP3A4; **Inhibits** CYP3A4 (weak).
Increased Effect/Toxicity: CYP3A4 inhibitors may increase the levels/effects of docetaxel. Concomitant use of docetaxel with a potent CYP3A4 inhibitor should be avoided. If systemic administration of a potent CYP3A4 inhibitor cannot be avoided, a 50% reduction in docetaxel dose should be considered along with close monitoring for docetaxel toxicity. Refer to the package insert or LexiComp[1] for example inhibitors. When administered as sequential infusions, observational studies indicate a potential for increased toxicity when platinum derivatives (carboplatin, cisplatin) are administered before taxane derivatives (docetaxel, paclitaxel). Taxane derivatives may enhance the adverse/toxic effect of anthracyclines.
Decreased Effect: CYP3A4 inducers may decrease the levels/effects of paclitaxel. Refer to the package insert or LexiComp[1] for example inducers.
Ethanol/Herb/Nutraceutical Interactions: Avoid ethanol (due to GI irritation). Avoid St John's wort (may decrease docetaxel levels).

15.17 **Known potential adverse events:** Consult the package insert for the most current and complete information. Percentages reported for docetaxel Monotherapy; frequency may vary depending on diagnosis, dose, liver function, prior treatment, and premedication. The incidence of adverse events was usually higher in patients with elevated liver function tests.

Common known potential toxicities, > 10%:
Cardiovascular: Fluid retention
Central nervous system: Neurosensory events including neuropathy, fever, neuromotor events.
Dermatologic: Alopecia, cutaneous events, nail disorder
Gastrointestinal: Stomatitis, diarrhea, nausea, vomiting
Hematologic: Neutropenia, leukopenia, anemia, thrombocytopenia, febrile neutropenia
Hepatic: Transaminases increased

Neuromuscular & skeletal: Weakness, myalgia
Respiratory: Pulmonary events
Miscellaneous: Infection, hypersensitivity

Less common known potential toxicities, 1% - 10%:
Cardiovascular: Left ventricular ejection fraction decreased, hypotension
Dermatologic: Rash/erythema
Gastrointestinal: Taste perversion
Hepatic: Bilirubin increased, alkaline phosphatase increased
Local: Infusion-site reactions including hyperpigmentation, inflammation, redness, dryness, phlebitis, extravasation, swelling of the vein
Neuromuscular and skeletal: Arthralgia
Ocular: Epiphora associated with canalicular stenosis

Rare known potential toxicities, <1% (Limited to important or life-threatening):
Acute myeloid leukemia, acute respiratory distress syndrome, anaphylactic shock, angina, ascites, atrial fibrillation, atrial flutter, bleeding episodes, bronchospasm, cardiac tamponade, chest pain, chest tightness, colitis, conjunctivitis, constipation, cutaneous lupus erythematosus, deep vein thrombosis, dehydration, disseminated intravascular coagulation, drug fever, duodenal ulcer, Dyspnea, dysrhythmia, ECG abnormalities, erythema multiforme, esophagitis, gastrointestinal hemorrhage, gastrointestinal obstruction, gastrointestinal perforation, hand and foot syndrome, hearing loss, heart failure, hepatitis, hypertension, ileus, intestinal pneumonia, ischemic colitis, lacrimal duct obstruction, loss of consciousness (transient), MI, multiorgan failure, Myelodysplastic syndrome, neutropenic enterocolitis, ototoxicity, pleural effusion, pruritus, pulmonary edema, pulmonary embolism, pulmonary fibrosis, radiation pneumonitis, radiation recall, renal insufficiency, seizure, sepsis, sinus tachycardia, Stevens-Johnson syndrome, syncope, toxic epidermal necrolysis, tachycardia, thrombophlebitis, unstable angina, visual disturbances (transient)

15.18 Nursing guidelines -

15.181 Monitor CBC closely, as neutropenia, and thrombocytopenia are common and may be life threatening, and dose limiting. Instruct patient to report any signs or symptoms of infection, any unusual bruising, or bleeding.

15.182 Administer antiemetics as ordered. Evaluate for their effectiveness.

15.183 Monitor for signs/symptoms of hypersensitivity reactions that may include chills, rigors, dyspnea, bronchospasms, etc. Stop infusion immediately and administer proper emergency treatment.

15.184 Because of the risk of anaphylaxis and development of edema, instruct patient that is imperative to take steroid premedications as ordered.

15.185 Instruct patient on proper oral care, as mucositis may occur.

15.186 Advise patient about alopecia.

15.187 Monitor liver function tests.

15.188 Drug is a vesicant. Monitor infusion site frequently for signs of irritation or infiltration. Drug extravasation causes acute streaking, burning pain, and discoloration at the site. Skin may be reddened for several weeks and occasionally blister and/or peel. Reactions are usually reversible over time. Because of this central venous access may be necessary. Discuss with MD if patient has poor peripheral venous access. If docetaxel concentrate or diluted solution comes into contact with skin, wash with soapy water immediately. If it comes into contact with mucosa, wash with warm water immediately.

15.189a Instruct patient to report any signs of peripheral neuropathy to the health care team (pain, numbness, tingling).

15.189b Monitor for signs and symptoms of fluid retention, weight gain, ascites and CHF.

15.189c Instruct patient about possible facial flushing, rash, and skin and nail changes. Monitor for signs and symptoms of hand/foot syndrome. However premedication with steroids can minimize this side effect. Discuss with MD possible ways to manage itching and skin changes that may occur up to a week after docetaxel administration. Advise patients that nails may crack, peel, or fall off all together. This may be a chronic toxicity. Instruct patient to keep nails clean, short and to avoid wearing nail polish or artificial nails.

15.189d In case of overdose, patient should be hospitalized and vital signs monitored. Patient should receive therapeutic G-CSF ASAP after discovery of the overdose.

15.2 **Cisplatinum (Cisplatin®) Commercial Supply.** Refer to the package insert for detailed pharmacologic and safety information.

15.2.1 **Formulation**: Each vial contains 10 mg of DDP, 19 mg of sodium chloride, 100 mg of mannitol,and hydrochloric acid for pH adjustment. One vial is reconstituted with 10 ml of sterile water. The pH range will be 3.5 to 4.5. Cisplatin injection also is available from the manufacturer in aqueous solution, each ml containing 1 mg cisplatin and 9 mg NaCl and HCL or NaOH to adjust pH.

15.2.2 **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.

15.2.3 **Administration**: After administering appropriate antiemetics, cisplatin will be infused over 1-2 hours or according to institutional guidelines along with vigorous hydration.

15.2.4 **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.

15.2.5 **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.

15.2.6 **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.

15.3 **Neck radiation**

15.31 Nursing guidelines

15.211 Assess for increased fatigue. Instruct patient in energy saving lifestyle.

15.213 Monitor for nutritional status. Advise patient accordingly.

15.214 Assess for skin reaction.

15.215 Assess for possible mouth/throat soreness, dry mouth, thick secretions, nausea, and treat as necessary.

16.0 Statistical Considerations and Methodology

This study will have two stratification factors (intermediate vs high risk and no vs yes smoking history) which will be used for randomization. In addition to the primary statistical analysis, pre-planned sub-group analyses for each stratification factor comparing DART to standard adjuvant therapy will be independently evaluated for all the endpoints described below.

16.1 **Overview:** This phase III study will compare DART with standard adjuvant therapy. Standard therapy for this disease yields a 2-year cumulative incidence of local/regional failure of approximately 10%, but it also has high rates of grade 3 or worse adverse events. Given the high rates of severe or worse adverse events (AEs), it is of high interest to find a

chemo/RT combination that can still yield low rates of local/regional failure with reduced AE rates. Preliminary data from our phase II study, MC1273, suggests that local/regional control with dose de-escalated adjuvant radiation therapy (DART) is at least equivalent to historical control rates and rates of grade 3 or higher AEs are substantially better. We seek to conclusively demonstrate the superiority of DART over standard therapy in terms of chronic AEs. Based upon historical Mayo data, the rate of chronic grade 3 or higher AEs after standard treatment attributable to radiation therapy is 25%. Based upon preliminary MC1273 data, the rate of chronic grade 3 or higher late AEs ($\geq$ 3 months) after DART attributable to radiation therapy is around 2%.

16.2 **Late AE Primary Endpoint:** 186 eligible patients (124 DART vs. 62 standard treatment) will be randomized in a 2:1 fashion, unless the study is stopped early. With this sample size, we have 90% power to detect a reduction in the grade 3+ late AE rate ($\geq$ 3 months) from around 25% to 7%, with a 2-sided significance level of 0.05. The hypothesis is that the DART treatment will reduce the grade 3 or higher AE rate significantly as compared to standard treatment. Final analysis would need p-value <= 0.05 to reject Ho hypothesis and conclude that active treatment had significant reduction in grade 3 or higher AE rate. Since the difference in accumulated chronic toxicity rates between DART and standard therapy is expected to be highest at two years following adjuvant therapy, we will assess AEs out to 2 years.

16.3 **Total Sample Size:** This study will randomize 186 eligible patients (124 DART vs. 62 standard). To account for possible dropouts, cancellations, and ineligibles, we plan to randomize 214 total patients (148 vs. 74) and screen 256 patients. The combined Head and Neck services of Mayo Clinic Rochester and Arizona saw approximately 200 patients eligible for this study in 2015. Assuming even a modest accrual rate, we anticipate being able to finish accrual in three years. Total follow-up for this study will be five years after completion of therapy. Total study duration will therefore be for eight years.

16.4 Secondary Endpoints:

- To assess the cumulative incidence of local/regional failure at 2 years after study registration. All patients meeting the eligibility criteria who have signed a consent form, and begun treatment will be considered evaluable for the 2-year cumulative incidence rate.
    - The 2-year cumulative incidence of local/regional failure will be estimated by the competing risk method (Gooley, et al.), where the competing risks are distant failures and deaths from other causes (i.e. deaths from distant failure or non-Oropharynx Cancer).

    - Local/Regional Failure Analysis for First 10 Smokers Randomized to DART:
      Our pilot study (MC1273) only included non-smokers for treatment with DART. Though published reports suggest that locol/regional control rates between smokers and non-smokers are equivalent following radiation therapy, the application of DART to a HPV-associated smoking population will nonetheless be novel. The first 10 smokers who are randomized to DART will be evaluated for local/regional control. If three or more of these ten patients have a local or regional failure by the 6-month post-radiation time-point, the radiation dose for this group may be modified. Accrual will continue while we wait for these first 10 smokers to be followed for a

minimum of six months. As long as the radiation dose remains the same, these first 10 smokers will be included in the final analysis as well.

- Interim Analysis at around the halfway point (after first 99 patients enrolled):
  At nearly the halfway point for accrual (99 patients), we plan to conduct an interim analysis for the Local/Regional Failure rate in the DART patients. At 6-months post-treatment, we will estimate the local/regional control rate and if the confidence interval contains 95% for DART treatment, we will continue to full accrual. The current standard of care has a local/regional control rate of around 95% at 6-months. With 99 patients, we'd expect 66 to be DART treated. Of those, we hope that at least 55 will be eligible for analysis. With 55 DART treated patients, we'd need to observe an LRC rate of at least 86% (95% CI: 77-95%) to continue to full accrual.

- To compare overall survival, disease-free survival, and distant failure associated with DART vs standard treatment. All patients meeting the eligibility criteria who have signed a consent form, and begun treatment will be considered evaluable for these endpoints.

  - Overall survival: Overall Survival (OS) is defined as the time from randomization to death from any cause. OS will be estimated using the Kaplan-Meier method, where the log-rank test will be used to compare the 2 treatment arms.

  - Disease-free survival: Disease-free survival (DFS) is defined as the time from randomization to the first of either disease recurrence or death from any cause. DFS will be estimated using the Kaplan-Meier method, where the log-rank test will be used to compare the 2 treatment arms.

  - Distant Failure Rates: The 2-year cumulative incidence of distant failure will be estimated by the competing risk method (Gooley, et al.), where the competing risks are local/regional failures and deaths from other causes (i.e. deaths from local/regional failure or non-Oropharynx Cancer).

- Quality of Life (QOL): The patient QOL will be measured and compared between the treatment arms using the following tools: 1) XeQOLS form, 2) Eq-5D, 3) FACT H & N (Version 4), 4) Dermatology Life Quality Index; and QLQ H&N35 (see QOL Booklet). These QOL measures will be assessed at baseline, 1 month post-XRT and 3, 12 and 24 months post-XRT. These QOL scores will be compared between arms to detect patterns and substantial changes over time. In addition, differences between post-baseline and baseline QOL scores will be compared between arms using a 2-sample t-test or the nonparametric equivalent to see if the QOL differs between treatment arms.
  - NOTE: All survey responses will be reviewed by the study coordinator at the time of completion. If participants self-report negative social-emotional symptoms of depression while completing the initial or follow-up survey, a member of the study staff will share the responses with a member of the participants care team who will determine whether the individual should be referred for additional support.

- Swallowing Studies: Swallowing will be scored (yes, no) for aspiration, penetration, velopharyngeal incompetence, epiglottic everson, tongue base retraction, and pharyngeal swallow response using the metric outlined by Eisbruch et al. (Eisbruch A, Teresa L, Bradford CR, et al.) Swallowing assessments will be completed at baseline, along with 1and

12 months after the completion of protocol XRT. The swallowing questions will be explored descriptively to detect patterns and substantial changes over time between arms.

16.5 Translational studies:

- To determine the genetic alterations of oropharynx tumor specimens and the detection rate of corresponding tumor DNA in the pre-surgical, post-surgical, and post-radiation blood of oropharynx cancer patients.
- To investigate the usefulness of immunologic biomarkers in predicting progression free survival.
- To establish a patient derived xenograft panel from representative oropharynx patients.

16.6 Data & Safety Monitoring:

16.61 The principal investigator(s) and the study statistician will review the study at least twice a year to identify accrual, adverse event, and any endpoint problems that might be developing. The trial is monitored continually by the study team who are notified of every grade 4 and 5 event in real time. The Mayo Clinic Cancer Center (MCCC) Data Safety Monitoring Board (DSMB) is responsible for reviewing accrual and safety data for this trial at least twice a year, based on reports provided by the MCCC Statistical Office. Any safety issues requiring protocol changes are communicated through protocol amendments.

16.62 Adverse Event Stopping Rules: The stopping rules specified below are based on knowledge available at study development. We note that the Adverse Event Stopping Rule may be adjusted in the event of either (1) the study re-opening to accrual or (2) at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatment(s) under investigation. The study team may choose to suspend accrual because of unexpected adverse event profiles that have not crossed the specified rule below.

Based on data from previous studies, we expect about 20-25% of patients to experience Grade 3 or higher non-hematologic adverse events within 1 month post-treatment. Accrual will be temporarily suspended to this study if at any time we observe adverse events that satisfy any of the following criteria for each treatment arm separately:

- If at any time 8 or more patients in the first 20 treated patients experience a Grade 3 or 4 non-hematologic adverse event (at least possibly related to treatment).
- If at any time 2 or more Grade 5 events occur in the first 20 treated patients (at least possibly related to treatment).
- If after the first 20 patients have been treated:
    - 40% or more of all patients experience a Grade 3 or 4 non-hematologic adverse event (at least possibly related to treatment).

- 10% or more of all patients experience a Grade 5 adverse event (at least possibly related to treatment).

We note that we will review all Grade 5 adverse events on a case-by-case basis as well (regardless of attribution), and may suspend accrual after just one Grade 5 event, if we feel it is necessary for patient safety.

16.7 Results Reporting on ClinicalTrials.gov: At study activation, this study will have been registered within the "ClincialTrails.gov" website. The Primary and Secondary Endpoints (i.e., "Outcome Measures") along with other required information for this study will be reported on ClinicalTrials.gov. For purposes of timing of the Results Reporting, the initial estimated completion date for the Primary Endpoint of this study is 60 months after the study opens to accrual. The definition of "Primary Endpoint Completion Date" (PECD) for this study is when the last patient registered has been followed for at least 2 years for the AE primary endpoint.

16.8 Inclusion of Women and Minorities

16.81 This study will be available to all eligible patients, regardless of race, gender, or ethnic origin.

16.82 There is no information currently available regarding differential effects of this regimen in subsets defined by race, gender, or ethnicity, and there is no reason to expect such differences to exist. Therefore, although the planned analysis will, as always, look for differences in treatment effect based on racial and gender groupings, the sample size is not increased in order to provide additional power for subset analyses.

16.83 The geographical region served by the Mayo Clinic, has a population which includes approximately 15% minorities. We expect about 15% of patients will be classified as minorities by race and about 50% of patients will be women. Expected sizes of racial by gender subsets are shown in the following table:

Accrual Estimates by Gender/Ethnicity/Race for All Phase II and III Studies

Accrual Targets			
Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	5	5	10
Not Hispanic or Latino	106	106	212
Ethnic Category: Total of all subjects*	111	111	222

Template revised: 1/30/2012

Racial Category			
American Indian or Alaskan Native	2	1	3
Asian	7	7	14
Black or African American	7	7	14
Native Hawaiian or other Pacific Islander	1	1	2
White	94	95	189
Racial Category: Total of all subjects	111	111	222

Ethnic Categories:

Hispanic or Latino – a person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. The term "Spanish origin" can also be used in addition to "Hispanic or Latino."

Not Hispanic or Latino

Racial Categories:

American Indian or Alaskan Native – a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.

Asian – a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)

Black or African American – a person having origins in any of the black racial groups of Africa. Terms such as "Haitian" or "Negro" can be used in addition to "Black or African American."

Native Hawaiian or other Pacific Islander – a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

White – a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

17.0 Pathology Considerations/Tissue Biospecimens

17.1 Summary Table of Research Tissue Specimens to be Collected for this Protocol

Correlative Study (Section for more information)	Mandatory or Optional	Type of Tissue to Collect	Block, Slides, Core, etc. (# of each to submit)	Prior to Radiation Treatment	At time of Failure (if applicable)	Process at site? (Yes or No)	Temperature Conditions for Storage/ Shipping
Tumor Genetic Analyses	Optional	FFPE\fresh frozen	2 to 6 curls	X	X	Yes	Ambient (FFPE), -80 (fresh frozen)
Patient-derived xenograft panel	Optional	Fresh	2-6 mg	X	X	Yes	Ambient

17.2 Diagnostic Slides from Original and /or Recurrent Tissue

Either 2-6 FFPE tissues curls, samples from fresh frozen tumor, and/or fresh tumor specimen will be collected from original tumor biopsy, tumor removed during surgery, or recurrent tumor specimens. This tissue will be used for determining tumor-specific genetic alterations and/or for establishing a patient-derived xenograft panel.

17.3 Correlative Tissue Collection

17.31 Tissue Kits will not be provided for this protocol.

17.32 Frozen Tissue

17.321 Frozen tissue will be collected at time of primary surgery and also at time of surgery for recurrent disease if applicable.

17.322 Samples will be directed to [redacted] on dry ice. An email notification should be sent [redacted] so that tissue sample can be picked up. Samples will then be stored in a -150ºF at:

[redacted]

17.33 Fresh Tissue

17.331 Fresh tissue will be collected at time of primary surgery and also at time of surgery for recurrent disease if applicable.

17.332 Samples should be directed to [redacted], and should be placed into DMEM in 50 ml tubes.

[redacted]

17.4 Methodology

17.4.1 Mutational Analyses: Genetic alterations from tumor specimens will be sequenced using formalin-fixed paraffin-embedded or fresh frozen samples to determine prognostic and/or predictive biomarkers. Techniques utilized may include mate-pair sequencing, whole exome sequencing, whole genome sequencing, whole transcriptome sequencing, or focused exome sequencing.

17.4.2 Patient Derived Xenograft (PDX): PDX models for representational oropharynx tumors from smokers, non-smokers, and recurrent disease may be established for upwards to 50 samples using techniques outlined by Stein et al (PLoS One, 2014 Jun 26;9(6):e100995.)

18.0 Records and Data Collection Procedures

18.1 Submission Timetable

Pre-Registration Material(s)

Case Report Form (CRF)	**Active-Monitoring Phase** (Compliance with Test Schedule Section 4.0)
Pre-Registration Screening Failure Form	Complete only if patient is NOT registered after he/she is pre-registered
Research Blood Submission	≤30 days after pre-registration

Initial Material(s) -

CRF	**Active-Monitoring Phase** (Compliance with Test Schedule Section 4.0)
Pre-Registration Eligibility checklist	≤2 weeks after registration
Baseline Adverse Events Form	
OP and Path Reports (see Section 17.0)	
Baseline Swallowing Function Assessment Form	≤2 weeks after registration but prior to treatment
Pathology Assessment Form	≤7 weeks prior to treatment
End of Active Treatment/Cancel Notification Form	Submit ≤2 weeks after registration if withdrawal/refusal occurs prior to beginning protocol therapy
Patient Questionnaire Booklet	≤2 weeks after registration but prior to treatment- Patient questionnaire booklet **must** be used; copies are not acceptable for this submission.
Patient Questionnaire Booklet Compliance Form	This form must be completed **only** if the patient Questionnaire Booklet contains absolutely **NO** patient provided assessment information.
Patient Assessment Form	≤2 weeks after registration
Research Blood Submission	≤2 weeks after registration

Test Schedule Material(s)

CRF	**Active-Monitoring Phase** (Compliance with Test Schedule Section 4.0)		
	At each evaluation during treatment	At end of treatment	Observation
Evaluation/Treatment Form	X	X	
Adverse Events Form	X	X	X
Disease Status Form[4]	X	X	X
End of Active Treatment/Cancel Notification Form		X	
Evaluation/Observation Form			X
Swallowing Function Assessment Form			X[3]

CRF	Active-Monitoring Phase (Compliance with Test Schedule Section 4.0)		
	At each evaluation during treatment	At end of treatment	Observation
Patient Questionnaire Booklet			X[1]
Patient Questionnaire Booklet Compliance Form			X[2]
Patient Assessment Form			X[5]
Notification Form – Grade 4 or 5 Non-AER Reportable Events/Hospitalization Form	At each occurrence (see Section 10.0)		
ADR/AER	At each occurrence (see Section 10.0)		
Research Blood Submission			X[6]

1. At 14 days post-XRT, and 1, 3, 12, and 24 months from the end of radiation treatment. Patient questionnaire booklet **must** be used; copies are not acceptable for this submission.
2. This form must be completed ONLY if the patient questionnaire contains absolutely NO patient provided assessment information.
3. One month post treatment, and one year post treatment (see section 4.0)
4. As needed to report NED or disease recurrence.
5. At 14 days post-XRT, and 1, 3, 12 and 24 months post-XRT.
6. This will only occur 3 months post-XRT

CRF	Event Monitoring Phase[1]				
	q. 6 months until recurrence	At recurrence	After recurrence q. 6 mos.	Death	New Primary
Event Monitoring Form	X[2]	X[2]	X	X	At each occurrence

Follow-up Material(s)

1. If a patient is still alive 5 years after registration, no further follow-up is required.
2. Submit copy of documentation of response or progression to the MCCC Operations Office, Attention: QAS for MC1273.

18.8 Data Handling and Record Keeping

18.81 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why

- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

(This information is contained within the Mayo IRB Informed Consent Template Section 14)

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (long term survival status that the subject is alive) at the end of their scheduled study period.

18.82 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial. Source documents are kept in a secure location that is locked and requires approved access.

18.83 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. Do not erase or use "white-out" for errors. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it. If the reason for the correction is not clear or needs additional explanation, neatly include the details to justify the correction. *Note what the data management system is that houses the CRFs.*

18.84 Data Management

All data will be entered into electronic case report forms (eCRF's) through the Medidata Rave system. Case report forms will be automatically rolled out based on a predetermined, and visit based schedule to improve study staff workflow and data quality. Data will be exported nightly to a secure FTP for analysis and reporting.

18.85 Data Quality Assurance and Clarification Process

Each eCRF will contain edit checks and custom functions to ensure the highest possible data quality. Only necessary eCRF's will be available for data entry to reduce the possibility of erroneous entry.

The edit checks and custom functions on the eCRF's will trigger queries requesting the attention of appropriate study staff. The fields will be marked in pink to allow study staff to quickly identify the data fields that require attention or actions. Additionally, secure email notifications will be sent for adverse event tracking and monitoring.

18.86 Records Retention
The investigator will maintain records and essential documents related to the conduct of the study. These will include subject case histories and regulatory documents.

The investigator will retain the specified records and reports for;
1. [redacted]

19.0 Study Finances

This study is funded through Mayo Clinic Institutional funds.

19.1 Costs charged to patient: Routine clinical care

19.2 Tests to be research funded: Research blood draws, Sample Collection.

19.3 Patient expenses which will be reimbursed:

Adjuvant therapy with DART under our pilot study (MC1273) proved to be extremely popular among both patients and outside hospital physicians. Many patients referred to the Mayo Clinic from distant facilities specifically for the purpose of participating in DART on study. Furthermore, many patients who would have been logistically unable to stay in Rochester for 6 weeks under standard therapy have been willing to stay for a shortened two-week therapy course. In our clinical experience, however, when patients who refer from the outside have been unable to participate in DART due to exclusion criteria, many have been unable to remain for the standard six weeks of therapy. As the six-week treatment course is available closer to home, many returned to their home institutions for therapy. This situation was further compounded by the fact that radiation side effects requiring supportive care usually begin around the three week time point. The additional supportive requirements for patients undergoing standard treatment translated into additional costs and expenses for a caretaker as well. Although patients generally wish to stay at Mayo for the excellence of clinical care, the additional time, inconvenience and expense required from a prolonged therapy course were more than many families could logistically endure.

Since the current trial will be a randomized trial between DART (two weeks) and standard adjuvant treatment (six weeks), the logistical difficulties underlying a six week therapy course pose a particular challenge to the standard course arm. While out-of-town patients have historically demonstrated willingness to logistically support a two week treatment, many out-of-town patients have also been historically unable to support a six-week treatment course. If this pattern continues on the current trial, we would expect that our six-week treatment arm will be overly enriched with wealthy patients who are able to afford staying in Rochester for an extended period. Not only would this be unequitable for patients with lesser means, this self-selection would undermine the randomization process and disrupt the demographics of the study.

In order to support patients for the additional expenses and inconvenience associated with an additional four weeks of care, we will reimburse each subject randomized to the six-week course of treatment for additional meals and incidental travel expenses related to the extended period of stay at Rochester. Lodging will be available through the Hope Lodge and will not require coverage. Reimbursement will be based upon receipts and upwards to $1000 per subject.

20.0 Publication Plan

The principal investigators hold primary responsibility for publication of the results of this study and approval from the principal investigators must be obtained before any information can be used or passed on to a third party.

21.0 References

1. R. L. Siegel, K. D. Miller, A. Jemal, Cancer statistics, 2015. *CA Cancer J Clin* **65**, 5 (Jan-Feb, 2015).
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Appendices

Appendix I

ECOG PERFORMANCE STATUS

Grade	
0	Fully active, able to carry on all pre-disease activities without restriction (Karnofsky 90-100).
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work (Karnofsky 70-80).
2	Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50 percent of waking hours (Karnofsky 50-60).
3	Capable of only limited self-care, confined to bed or chair 50 percent or more of waking hours (Karnofsky 30-40).
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair (Karnofsky 10-20).
5	Dead

Appendix II

Guidelines for the use of IMRT

1. For all patients, as outlined in Section 7.0, the prescription isodose must cover 98% of the PTV volume for standard therapy and 100% of the PTV volume for DART. If the minimum dose falls below these parameters, an unacceptable deviation will be assigned. The maximum dose for the PTV should not exceed 115%. If the maximum doses exceed these parameters, an unacceptable deviation will be assigned.

2. Radiation breaks, if necessary, should not exceed one treatment day on DART or two days on standard therapy. Radiation breaks should be allowed only for resolution of severe acute toxicity and/or for intercurrent illness and not for social or logistical reasons. Any radiation break(s) exceeding one treatment day for reasons other than toxicity/illness/technical issues will be considered a major protocol deviation.

Appendix III

Radiation Therapy Quality Control Guidelines

1. Tumor Volume Coverage
   a. No deviation -- coverage + ≤ 1 cm of specified.
   b. Minor deviation -- coverage + > 1 to 2 cm of specified or failure to cover tumor volume + ≥ 1/2 specified margin.
   c. Major deviation -- > 2 cm of specified or no CT and/or MRI scans available to assess treatment volume appropriateness (if not initially available should be requested) or failure to cover the target (tumor or tumor + edema) as defined in the protocol.

2. Isodoses - initial volume isodose plots are required on a minimum of three contours; one at central axis (CA), one superior to CA (2 cm below the superior field edge) and one inferior to CA (2 cm above the inferior field edge). Boost volume isodose plot required at CA.
   a. No deviation -- isodoses submitted as required, and inhomogeneity across the target volume shall be no greater than ± 5%.
   *b. Minor deviation -- isodose information incomplete or inhomogeneity across the target volume > 5 but ≤ 10%.
   *c. Major deviation -- no isodoses submitted or inhomogeneity across the target volume > 10%.

   * Deviations would occur only if isodose information is incomplete or not submitted after there has been a request to submit complete isodose information.

3. Normal Tissues
   Normal structures are only to be included within the radiation field in as much as this is necessary to treat the primary tumor volume. A minor deviation will result when normal structures are unnecessarily included, but this is not felt to result in unacceptable toxicity that would interfere with the scientific aims of the protocol. A major deviation will result when normal structures are unnecessarily included in the radiation therapy field and such inclusion is felt likely to result in a major increase in toxicity which would potentially compromise the scientific goals of the study.

4. Other parameters: (dose per fraction, total dose, overall treatment time and portal films).
   a. No deviation -- +/- < 5% of protocol specification.
   b. Minor deviation -- +/- > 5% to 10% of protocol specification.
   c. Major deviation -- +/- > 10% of protocol specification or incomplete data (i.e. no portal or sim films, etc.) available for review (after additional request has been made).

5. Any individual minor deviation will result in an overall score of minor deviation; any major deviation will result in an overall score of a major deviation. Multiple minor deviations will not add up to a major deviation.

Appendix IV

Known inducers & inhibitors of isoenzyme CYP3A4

Inducers	
Carbamazepine Dexamethasone Ethosuximide Glucocorticoids Griseofulvin Nafcillin Nelfinavir Nevirapine Oxcarbazepine Phenobarbital Phenylbutazone	Phenytoin Primidone Progesterone Rifabutin Rifampin Rofecoxib (mild) St John's wort Sulfadimidine Sulfinpyrazone Troglitazone
Inhibitors	
Amiodarone Anastrozole Azithromycin Cannabinoids Cimetidine Clarithromycin Clotrimazole Cyclosporine Danazol Delavirdine Dexamethasone Diethyldithiocarbamate Diltiazem Dirithromycin Disulfiram Entacapone (high dose) Erythromycin Ethinyl estradiol Fluconazole (weak) Fluoxetine Fluvoxamine Gestodene Grapefruit juice lndinavir lsoniazid ltraconazole	Ketoconazole Metronidazole Mibefradil Miconazole (moderate) Nefazodone Nelfinavir Nevirapine Norfloxacin Norfluoxetine Omeprazole (weak) Oxiconazole Paroxetine (weak) Propoxyphene Quinidine Quinine Quinupristin and dalfopristin Ranitidine Ritonavir Saquinavir Sertindole Sertraline Troglitazone Troleandomycin Valproic acid (weak) Verapamil Zafirlukast Zileuton

Appendix V

Patient Assessment Form

INSTRUCTIONS:
This form is completed by the investigator (rater) and submitted at each time point specified by the protocol, whether or not any of the patient assessment items (Q's 6,7,8) are answered.

SUGGESTIONS FOR ADMINISTRATION:
These performance scales must be rated by health professionals such as physicians, nurses, nutritionists, etc. Ratings are determined through use of an unstructured interview format.

1 SCHEDULED DATA POINT (CHECK ONE)(1)

- ☐ 1 = Pre-treatment assessment
- ☐ 2 = At completion of radiotherapy
- ☐ 3 = Four weeks followup
- ☐ 4 = ___other followup (specify calendar date or followup interval, e.g., 3 months, 2 years, etc.)(2)
- ☐ 5 = Other, specify_____(3)

2 IF NO PATIENT ASSESSMENT, SPECIFY REASON (CHECK ONE)(4)

- ☐ 0 = Not applicable, questionnaire was completed
- ☐ 1 = Patient was too ill
- ☐ 2 = Patient unable to be contacted
- ☐ 3 = Questionnaire not completed due to institutional error
- ☐ 4 = Patient refused, including attempts by telephone interview, specify reason for refusal _____(5)
- ☐ 5 = Patient refused, telephone interview not attempted, specify reason for refusal _____(6)
- ☐ 6 = Other reason, specify _____(7)

3 WAS INFORMATION OBTAINED BY TELEPHONE INTERVIEW

(CHECK ONE)(8)

- ☐ 1 = No
- ☐ 2 = Yes

4 _____-_____-_____DATE OF EVALUATION(9)

5 RATER'S NAME_____(10)

6 NORMALCY OF DIET (CHECK ONE) **RATING**(11)
Begin by asking the patient what kind of foods are difficult for him/her to eat. Based on patient's response, choose an item at the low end of the scale. Move up the scale giving examples of foods in each category and ask patient if s/he can eat those food items. The patient's score is the highest number to which an affirmative response is received.

- ☐ 100 = Full diet (no restrictions)
- ☐ 90 = Peanuts
- ☐ 80 = All meat
- ☐ 70 = Carrots, celery
- ☐ 60 = Dry bread and crackers
- ☐ 50 = Soft, chewable foods (e.g., macaroni, canned/soft fruits, cooked vegetables, fish, hamburger, small pieces of meat)
- ☐ 40 = Soft foods requiring no chewing (e.g., mashed potatoes, apple sauce, pudding)
- ☐ 30 = Pureed foods (in blender)
- ☐ 20 = Warm liquids
- ☐ 10 = Cold liquids
- ☐ 0 = Non-oral feeding (tube fed)

7 PUBLIC EATING (CHECK ONE) **RATING**(12)
Score the Public Eating scale by asking the patient where s/he eats, with whom s/he eats and whether s/he alters his/her diet according to where s/he is eating. Choose the score beside the description that best fits the patient.

- ☐ 100 = No restriction of place, food or companion (eats out at any opportunity)
- ☐ 75 = No restriction of place, but restricts diet when in public (eats anywhere, but may limit intake to less "messy" foods, e.g., liquids)
- ☐ 50 = Eats only in presence of selected persons in selected places
- ☐ 25 = Eats only at home in presence of selected persons
- ☐ 0 = Always eats alone

8 UNDERSTANDABILITY OF SPEECH (CHECK ONE) **RATING**(13)
This scale is scored based on the interviewer's ability to understand the patient during conversation (in this case, based on conversation regarding the Normalcy of Diet and Public eating scale. Choose the score beside the description that best fits the patient.

- ☐ 100 = Always understandable
- ☐ 75 = Understandable most of the time; occasional repetition necessary
- ☐ 50 = Usually understandable; face-to-face contact necessary
- ☐ 25 = Difficult to understand
- ☐ 0 = Never understandable; may use written communication

COMMENTS(14)_____
_____

Template revised: 1/30/2012

Appendix VI

QOL
Patient Information Sheet

You have been given a booklet to complete for this study. The booklet contains some questions about your 'quality of life' as a patient receiving treatment for cancer. Your answers will help us to better understand how the treatment you are receiving is affecting the way you feel.

1. This booklet contains the EORTC-QLQ H&N 35 form, the FACT H & N (Version 4), the XeQOLS form, the Dermatology Life Quality Index form, and the EQ-5D form.

2. Directions on how to complete each set of questions are written at the top of each set.

3. You will be given the nurse's name and telephone number. You can call them any time with any concerns or questions.

4. It is very important that you return the booklet with us, whether you finish the study or not.

Please complete and return to the study staff as soon as possible.

Thank you for taking the time to help us.

EORTC QLQ - H&N35

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

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

Please go on to the next page

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

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

FACT-H&N (Version 4)

Below is a list of statements that other people with your illness have said are important. **By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days**.

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

SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
I feel close to my friends	0	1	2	3	4
I get emotional support from my family	0	1	2	3	4
I get support from my friends	0	1	2	3	4
My family has accepted my illness	0	1	2	3	4
I am satisfied with family communication about my illness	0	1	2	3	4
I feel close to you partner (or the person who is my main support)	0	1	2	3	4
Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please check this box ☐ and go to the next section.					
I am satisfied with my sex life	0	1	2	3	4

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

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

<u>FUNCTIONAL WELL-BEING</u>	Not at all	A little bit	Some-what	Quite a bit	Very much
I am able to work (including work in home)	0	1	2	3	4
My work (include work in home) is fulfilling	0	1	2	3	4
I am able to enjoy life	0	1	2	3	4
I have accepted my illness	0	1	2	3	4
I am sleeping well	0	1	2	3	4
I am enjoying the things I usually do for fun	0	1	2	3	4
I am content with the quality of my life right now	0	1	2	3	4

Appendix VII

Recommended Symptomatic Management for Patients Randomized to DART

The DART regimen pioneered in MC1273 utilizes a novel radiation schedule for head and neck patients and has a side effect profile which may be unexpected to providers who have not previously utilized this regimen. The following symptomatic regimen has been found to be effective for handling treatment related side effects specific to DART. Patients undergoing standard therapy may follow the symptomatic regimen that the treating radiation oncologist is most comfortable with.

In our pilot study, an unexpectedly high rate of thrush developed in the immediate post-radiation period for patients undergoing DART without fungal prophylaxis. Furthermore, most patients undergoing DART are essentially pain free during their two week therapy course, but rapidly develop a fairly brisk mucositis lasting for about one week starting the day after completion of therapy.

□ **Fungal prophylaxis starting Day 8** (beginning of second week) of DART. Fluconazole 100 mg po qday x 15 days is the recommended regimen though Nystatin may be utilized if contraindications to fluconazole exist. Nystatin should be utilized at least 5 times / day x 15 days.

□ **Prophylactic narcotic pain medication.** Most patients will be essentially pain free upwards to the day of completion of therapy. However, a brisk mucositis generally emerges rapidly on the afternoon of the day after treatment completion. For this reason, it is recommended that all patients begin a prophylactic Fentanyl patch, 12 mcg, on the morning following the completion of therapy (generally Saturday morning.) Liquid oxycodone should also be available for breakthrough pain relief. Stool softeners and laxatives should also be used concurrently.

□ **IV Fluids.** Even with prophylactic pain medication, most patients have approximately three days of poor oral intake because of the rapid onset of odynophagia / oral pain. We recommend having IV fluid orders on hand for the first five days following the completion of therapy.