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Phase III Randomized Trial of Induction Chemotherapy in Patients with N2/N3 Locally Advanced Head and Neck Cancer

Cohen, et al.

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A Phase III Randomized Trial of Docetaxel Based Induction Chemotherapy in Patients with N2/N3 Locally Advanced Head and Neck Cancer

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Trial center(s) and number of patients planned

20 centers (exact number to be determined), 400 patients planned

Trial period		**Phase of development**
Estimated date first patient enrolled	November 2004	III
Estimated date last patient enrolled	May 2009	

Endpoints:

Primary:

Overall survival

Secondary:

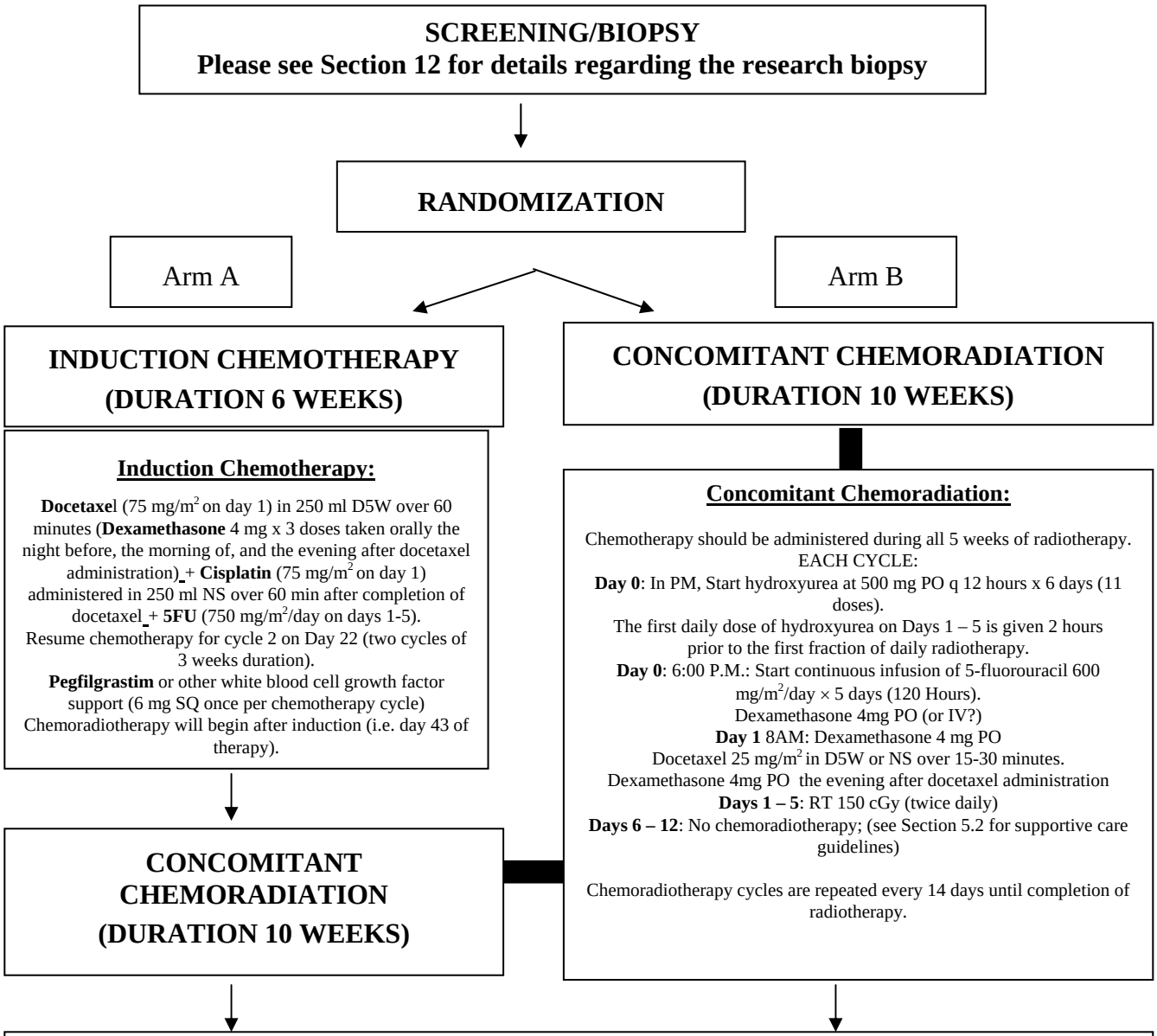
Distant failure free survival (DFFS)

Failure pattern

Progression-free survival

Quality of life

Trial Schema



Patients should be seen weekly after completing chemoradiotherapy for toxicity evaluation and management.

After the 30-day follow-up visits and evaluations, patients should undergo clinical, laboratory, and radiographic disease evaluation every 3 months in year 1, every 6 months in years 2-3, then every 12 months in years 4-5. Serum TSH should be measured annually.

Trial design

Phase III trial of induction therapy with docetaxel followed by chemoradiotherapy versus chemoradiotherapy alone in patients with nodal stage N2 or N3 head and neck cancer.

Background and rationale

Concurrent chemoradiotherapy has proven efficacy in locally advanced head and neck cancer with overall survival and local control improved compared to radiotherapy alone. Induction chemotherapy has been shown to reduce the distant failure rate. Survival and failure pattern based on TNM staging reveals a marked increase in distant failure in patients with N2 or N3 disease. Metastatic disease is incurable with most patients dying within 8 months. Therefore, patients with N2 or N3 disease should be most likely to benefit from induction chemotherapy.

Docetaxel is an active taxane in head and neck cancer patients. Phase II trials in head and neck cancer and non-small cell lung cancer have reported promising activity of docetaxel in these diseases as a single agent, in combination chemotherapy, and with concurrent radiotherapy. This trial seeks to establish the effect of docetaxel-based induction chemotherapy followed by concomitant chemoradiotherapy versus the same chemoradiotherapy in patients with N2 or N3 locally advanced head and neck cancer.

Patient population

- Patients with nodal stage 2 or 3 head and neck cancer (N2 or N3, AJCC 6th edition, Appendix 1)
- Patients with squamous cell carcinoma of unknown primary originating in the neck.

Measurable disease is not required, but all disease will be carefully evaluated using Response Evaluation Criteria in Solid Tumors (RECIST) criteria.

Inclusion criteria

- Histologically or cytologically confirmed diagnosis of squamous cell or poorly differentiated carcinomas of the head and neck (excluding lip), or lymphoepithelioma
- No prior chemotherapy or radiotherapy
- Prior surgical therapy will consist only of incisional or excisional biopsy, and organ sparing procedures such as debulking of airway-compromising tumors or neck dissection in a patient with an existing primary tumor
- Performance status of ≥ 70%
- Intact organ and bone marrow function
- Obtained informed consent

Treatment Plan:

Induction therapy: Two 21-day cycles of chemotherapy consisting of docetaxel (75 mg/m^2 on day 1), cisplatin (75 mg/m^2 on day 1), and 5-fluorouracil (750 mg/m^2/day on days 1-5). Pegfilgrastim or other white blood cell growth factor support (6 mg SQ once per chemotherapy cycle administered no sooner than 24 hrs post-chemotherapy).

Concurrent chemoradiotherapy: Five 14-day cycles of docetaxel (dose based on phase I trial 25 mg/m^2), 5FU (continuous infusion at 600 mg/m^2/day × 5 days), and hydroxyurea (500 mg PO BID day 0-5, 11 doses/cycle) with twice daily radiation (150 cGy per fraction).

No therapy on days 6-14. Supportive care should be administered as specified in Section 5.2.

All patients will undergo surgical evaluation after chemoradiation for possible neck dissection.

Duration of treatment

6 weeks induction chemotherapy
10 weeks chemoradiation

Number of patients expected to be enrolled each month

10-20

Statistical analysis

Patients will be randomized after eligibility is confirmed, stratified by clinical site, to induction plus chemoradiotherapy (CRT) or CRT alone. Overall survival will be calculated from the time of randomization to death from any cause. Survival rates will be estimated by the Kaplan-Meier method and compared between the two groups using the logrank test. Based on assumptions from prior studies a hazard ratio of approximately 1.6 is expected requiring a sample size of 400 patients (200 per treatment arm) to provide over 85% statistical power.

Table 1: Enrollment Phase

Item	Pre-therapy	CRF
Inclusion/exclusion criteria	X	01
Informed consent	X	01
Pregnancy test [1]	X	01
History and physical	X	02
Performance status	X	02
Concomitant medication[2]	X	02
Hematology[3]	X	02
Biochemistry[4]	X	02
Randomization	X	03
Head and neck PE, CT/MRI[5]	X	04
Quality of life assessment	X	13-15
Panendoscopy[6]	X	
Tumor map	X	
Dental assessment	X	
Swallowing assessment	X	
Chest CT	X	
Bone scan[7]	X	
Blood sample for DNA[8]	X	02
Blood sample for serum[9]	X	02
Blood Sample for mRNA	X	02

[1] Women of Childbearing potential

[2] Document use of concomitant medication

[3] CBC, differential, and platelet count will be done within 1 week of starting therapy

[4] Comprehensive metabolic profile will be done within 1 week of starting therapy. Should include TSH

[5] The same procedure should be done throughout therapy and follow-up

[6] Biopsy will be done within 6 weeks of starting therapy. A biopsy for research purposes should be collected at this time (see Section 11.2)

[7] If clinically indicated

[8] Lavender top tube, 10cc. This sample should be collected prior to therapy but can be collected at any time. See Section 12 for collection and shipment instructions

[9] Gold top tube, 7-10cc.

Table 2: Induction Phase. Numbers in subscript correspond to CRF form number.

	Cycle 1			Cycle 2			
	Week	**Week**	**Week**	**Week**	**Week**	**Week**	**Post-Induction[10]**
Item	**1**	**2**	**3**	**4**	**5**	**6**	
Docetaxel	X		$_{05}$	X		$_{05}$	
Cisplatin	X		$_{05}$	X		$_{05}$	
5FU	X		$_{05}$	X		$_{05}$	
History and physical	X			X			
Adverse event assessment	X_{09}	X_{09}	X_{09}	X_{09}	X_{09}	X_{09}	
Hematology[11]	X	X	X	X	X	X	
Biochemistry[12]	X	X	X	X	X	X	
Head and Neck PE, CT/MRI[13]							X_{04}
Chest CT							X_{04}
Quality of Life Assessment							X_{13-15}

[10] To be performed before CRT phase starts. Chemoradiotherapy will begin after induction (i.e. day 43 of therapy).
[11] CBC, differential, and platelet count once weekly
[12] Comprehensive metabolic profile once weekly
[13] The same procedure should be done throughout therapy and follow-up

Table 3: Chemoradiotherapy Phase. Numbers in subscript correspond to CRF form number.

Item	Cycle 1[14]	Cycle 2	Cycle 3	Cycle 4	Cycle 5[15]	14 day follow-up	30-day follow-up
Docetaxel	X_{06}	X_{06}	X_{06}	X_{06}	X_{06}		
5 FU	X_{06}	X_{06}	X_{06}	X_{06}	X_{06}		
Hydroxyurea	X_{06}	X_{06}	X_{06}	X_{06}	X_{06}		
Radiotherapy[16,17]	X_{06}	X_{06}	X_{06}	X_{06}	$X_{06, 08}$		
History and physical	X	X	X	X	X	X	X
Adverse event[18]	X_{09}	X_{09}	X_{09}	X_{09}	X_{09}	X_{09}	X_{09}
Hematology[19]	X	X	X	X	X	X	X
Biochemistry[20]	X	X	X	X	X	X	X
Quality of life assessment					X_{13-15}		
Head and neck PE, CT/MRI[21]							X_{04}
Chest CT							X
Swallowing assessment							X
Dental assessment							X
Biopsy[22]/Surgery							X_{10}

[14] Each cycle is 2 weeks long

[15] Some patients may have only 4 cycles total

[16] Radiotherapy is given twice daily

[17] CRF 07 and CRF 09 should be filled out weekly during interruptions between cycles. Report worst grade toxicity during week of delay

[18] To be filled out at the end of each cycle. Worst grade toxicity over the entire cycle should be reported

[19] CBC, differential, and platelet count on days 0, 4, and 10 of each cycle

[20] Comprehensive metabolic profile on days 0, 4, and 10 of each cycle

[21] The same procedure should be done throughout therapy and follow-up

[22] Within 8 weeks of completing chemoradiotherapy

Table 4: Follow-Up Phase. Numbers in subscript correspond to CRF form number.

				1Yr		2Yr		3Yr	4Yr	5Yr
Item	**Mo. 3**	**Mo. 6**	**Mo. 9**	**Mo. 12**	**Mo. 18**	**Mo. 24**	**Mo. 30**	**Mo. 36**	**Mo. 48**	**Mo. 60**
History and physical	X_{11}	X_{11}	X_{11}	X_{11}	X_{11}	X_{11}	X_{11}	X_{11}	X_{11}	X_{11}
Outcome Assessment	X_{11}	X_{11}	X_{11}	X_{11}	X_{11}	X_{11}	X_{11}	X_{11}	X_{11}	X_{11}
Adverse event[23]	X_{11}	X_{11}	X_{11}	X_{11}	X_{11}	X_{11}	X_{11}	X_{11}	X_{11}	X_{11}
Hematology[24]	X_{11}	X_{11}	X_{11}	X_{11}	X_{11}	X_{11}	X_{11}	X_{11}	X_{11}	X_{11}
Biochemistry[25]	X_{11}	X_{11}	X_{11}	X_{11}	X_{11}	X_{11}	X_{11}	X_{11}	X_{11}	X_{11}
Head and neck PE, CT/MRI[26]	X_{04}	X_{04}	X_{04}	X_{04}	X_{04}	X_{04}	X_{04}	X_{04}	X_{04}	X_{04}
Chest CT	X_{04}	X_{04}	X_{04}	X_{04}	X_{04}	X_{04}	X_{04}	X_{04}	X_{04}	X_{04}
Swallowing Assessment[28]				X_{17}						
Quality of life assessment				$X_{13\text{-}15}$		$X_{13\text{-}15}$		$X_{13\text{-}15}$	$X_{13\text{-}15}$	$X_{13\text{-}15}$
Death Notification Form[27]										

[23] Worst grade toxicity since last follow-up visit

[24] CBC, differential, and platelet count

[25] Comprehensive metabolic profile. Serum TSH should be measured annually

[26] The same procedure should be done throughout therapy and follow-up

[27] CRF 12 (include death certificate and autopsy report [if available])

[28] For patients enrolled at the University of Chicago only

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1 INTRODUCTION

1.1 Background

1.1.1 Head and Neck Cancer

Approximately 40,000 new cases of head and neck cancer are diagnosed annually in the United States[1]. Of these patients, two-thirds present with locoregionally advanced disease (American Joint Committee on Cancer [AJCC] stage III or IV) and one-third with early stage disease (AJCC stage I or II). At presentation, 10% of patients may be found to have involvement of distant organs, most commonly the lung. In addition, 20% of patients will develop clinically detected distant metastases over the course of their disease. In autopsy series up to 50% of patients with head and neck cancer are found to have metastases[2, 3]. It is likely that with improvements in the rate of locoregional control, the risk of distant failure will become predominant, and that systemic therapy, if efficacious, will have a major impact on outcome. Approximately 95% of all head and neck malignancies are squamous cell carcinomas and this histological type is the focus of this review and study protocol. Also, it should be noted that even though head and neck malignancies are usually examined in one group, they represent a heterogeneous group of diseases, with variability in biologic behavior and natural history, prognosis, and considerations in management. Disease sites such as the hypopharynx and the base of tongue have a worse prognosis compared to the larynx or nasopharynx[4], and may require more aggressive treatment strategies.

1.1.2 Locoregionally Advanced Disease (AJCC Stages III and IV)

For patients with resectable locally advanced head and neck cancer (AJCC stage III or IV), surgery and postoperative radiation have been traditionally considered the mainstay of treatment, whereas radiation therapy alone has been offered to patients with unresectable tumors. It is important to recognize that the distinction between resectable and unresectable disease lacks clear definition. With the exception of a few widely accepted signs of unresectability, such as involvement of the carotid artery, in most cases the assessment is subjective and relates to the experience of the surgeon and the availability of reconstructive strategies. Despite aggressive locoregional treatment with surgical resection and postoperative radiotherapy, locoregionally advanced disease has a poor prognosis with 5-year survival of less than 30%[5]. The most common site of failure remains locoregional, whereas distant failure occurs in 20-30% of patients[6].

The addition of chemotherapy to the overall treatment plan in patients with locoregionally advanced head and neck cancer has been studied intensively. Research strategies, generally, have included the use of induction (neoadjuvant) or adjuvant chemotherapy, as well as concomitant chemotherapy and radiation. The primary goal of such research is to improve local control and survival. Given the anatomic location of the disease and the frequently aggressive surgical approaches used, the use of less extensive surgery (and the preservation of organ function) is an important secondary

treatment goal. Concomitant chemoradiotherapy has led to improved disease-free and overall survival in randomized clinical trials and allows for organ preservation.

Three randomized trials have established the role of chemotherapy in organ preservation of the larynx[7, 8] and hypopharynx[9] demonstrating the ability of chemoradiotherapeutic approaches to maintain local control while avoiding radical surgery. A meta-analysis of 63 trials demonstrated an overall survival benefit to chemotherapy of 4% at 5 years[10]. Moreover, three separate randomized trials comparing chemoradiotherapy to radiotherapy alone have all concluded the superiority of the former approach[11-13]. Concurrent or neoadjuvant chemoradiotherapy therefore has become a standard of care for the treatment of locally advanced squamous cell carcinoma of the head and neck (SCCHN).

1.1.3 Concomitant Chemotherapy with Fluorouracil, Hydroxyurea and Radiotherapy (FHX) – the Chicago Oral Cancer Center Experience

In 1986, we initiated the clinical investigation of an intermittent schedule of chemoradiotherapy (one week on, one week off) based on the previous experience of Byfield et al. with single-agent 5-FU[14]. The recommended dose of 5-FU, 800 mg/m^2/day, was administered as a 5-day continuous infusion. The maximal tolerated dose of hydroxyurea was 1000 mg administered orally every 12 hours for a total of 11 doses beginning 6 to 12 hours prior to the 5-FU infusion with one daily dose preceding radiotherapy by 2 hours[15]. These doses resulted in moderate to severe mucositis and mild to moderate myelosuppression. Radiotherapy was administered once daily at 180 to 200 cGy. Five days of treatment were followed by a 9-day rest period to allow for recovery from toxicities (week on/week off). Response rates exceeded 90%. Only 3 of 19 patients without prior local therapy developed locoregional recurrence.

More recently, the FHX regimen was one of the arms of a 3-arm phase II randomized trial conducted by the RTOG (9703) in patients with stage III and IV head and neck cancer[16]. Regimens compared included cisplatin (10mg/m^2) and 5-FU (400mg/m^2) with 70 Gy/7 weeks of consecutive daily radiation (XCF), cisplatin (20mg/m^2) and paclitaxel (30mg/m^2) with 70 Gy/7 weeks consecutive daily therapy (XCT), or daily hydroxyurea (1 g PO twice daily [BID]) and 5-FU (800 mg/m^2) with 70 Gy/13 weeks radiation (alternating week schedule) (FHX). Toxicity and survival were not statistically different among the 3 arms. Estimated 1- and 2-year survival rates were 72% and 60% for XCF, 87% and 65% for FHX, and 80% and 67% for XCT, respectively. The survival rates on all three arms were superior to a historic control of radiotherapy and cisplatin (two year survival rate 46%). The pattern of failure showed a predominant locoregional failure pattern for all three arms. Therefore, conventional radiotherapy with concomitant chemotherapy given in consecutive weeks or a protracted course yielded acceptable patient toxicity and response rates. Thus, FHX is a feasible regimen in a national cooperative group setting with encouraging tumor control results. In the past decade, the FHX regimen has been the basis for the development of combined modality strategies by our group in an attempt to improve locoregional control and survival of previously untreated patients with locoregionally advanced head and neck cancer (Table)[17-19].

	Cisplatin-FHX[18]	Taxol-FHX (120h)[19]	Taxol-FHX (1h)[17]
N	76	64	90
*Progression-Free Survival**	72%	63%	62%
*Local Control	92%	86%	84%
*Systemic Control	83%	79%	79%
*Overall Survival	55%	64%	59%
Gr 3/4 Neutropenia	41/39	30/5	28/7
Gr 3/4 Thrombocytopenia	25/53	1/0	1/1
Gr 3/4 Mucositis	48/12	56/28	69/12

*3-year data

**Deaths from other causes were censored

Recent clinical trials for patients with locoregionally advanced disease in the Chicago Oral Cancer Center Network has used the T-FHX (paclitaxel added during FHX) regimen as previously defined[19]. Despite the high locoregional control and high survival rates, two problems were identified: distant failure emerged as the predominant site of failure and toxicities related to chemotherapy (specifically neuropathy and myelosuppression) often resulted in dose reduction and patient impairment.

To address the first goal, we added induction chemotherapy to precede concomitant chemoradiotherapy. The results of this trial involving 69 patients revealed response to induction chemotherapy to be PR 52% and CR 35%. Symptomatically, there was a significant reduction in mouth and throat pain. The most common grade 3 or 4 toxicity was neutropenia (36%) while 33% of patients experienced neuropathy. Best response following completion of T-FHX was CR in 83%. Toxicities of T-FHX consisted of grade 3 or 4 mucositis (74% and 2%), and dermatitis (47% and 14%). At a median follow up of 28 months, locoregional or systemic disease progression have each been noted in five patients. The overall three year progression-free survival (deaths due to causes other than cancer were censored) is 80% (95% confidence interval (CI): 71%-90%) and the two and three year overall survival rates are 77% (95% CI: 66%-87%) and 70%, (95% CI: 59%-82%), respectively. At 12 months, 5 patients were completely feeding-tube dependent[20].

The second goal was addressed by substituting docetaxel for paclitaxel in both the induction and concomitant portions of the regimen. Recent evidence has suggested that docetaxel has activity and is better tolerated than paclitaxel in SCCHN[21]. Furthermore, docetaxel has been evaluated as induction therapy in combination with 5-fluorouracil (5FU) and cisplatin (TPF) in a number of phase II trials revealing feasibility of

administration and encouraging activity. Depending on the number of cycles given as induction therapy, response rates have ranged between 70-100% with complete response rates as high as 50%[22-24].

This level of activity led to a recently reported phase III trial conducted by the European Organization for Research and Treatment of Cancer (EORTC) comparing 4 cycles of induction chemotherapy consisting of 5FU and cisplatin, with (TPF) or without (PF) docetaxel[25]. With growth factor support, the toxicity of TPF was manageable and comparable to PF without delay in initiation of local therapy. Moreover, the investigators reported an improvement in response rate, progression free survival, and overall survival suggesting that TPF is a reasonable standard induction regimen in patients with locally advanced SCCHN.

Docetaxel has been employed as part of a concurrent chemoradiotherapy regimen in a number of different treatment schemata usually given on a weekly schedule. Tolerable doses of docetaxel as the sole chemotherapeutic agent with standard fractionation radiotherapy have ranged from 20-30 mg/m^2/week[26-29]. Dose limiting toxicities have been within the radiation field consisting of mucositis, esophagitis, and dermatitis depending on the disease site. Phase II trials have confirmed the tolerability and efficacy of this combination[30].

Docetaxel has also been administered with platinum agents and concurrent radiotherapy again on a weekly schedule. Given with either cisplatin or carboplatin, 20-25 mg/m^2/week of docetaxel is tolerable with similar toxicities[26].

A phase I trial at the University of Chicago administered docetaxel with induction chemotherapy followed by concomitant chemoradiotherapy. This study established a tolerable dose of docetaxel/5FU/hydroxyurea/hyperfractionated RT (DFHX) as concomitant chemoradiotherapy. Thus the dose of docetaxel used in the present study is 25 mg/m^2 during concomitant therapy (see Section 6).

1.1.4 Quality of Life (QOL)

Quality of Life – Background

It is now widely recognized that SCCHN and its treatment may significantly affect patients' functioning in basic areas such as eating, speaking and socializing, all of which may, in turn, have a profound influence on overall quality of life[31-35]. Particularly in advanced disease, treatment is aggressive and confers significant acute toxicity and functional impairment. Perhaps of even greater concern, however, is the potential late effects, which may interfere, long term, with specific functions as well as overall quality of life[36-38].

One of the goals of chemoradiotherapy is to minimize acute toxicity, improve long term function and overall QOL while maintaining high rates of local and distant control. Previous studies have shown that, in contrast to traditional surgical treatment, chemoradiotherapy regimens result in little disfigurement or change in appearance, and

minimal, if any, speech disturbance[39, 40]. However, these regimens are accompanied by considerable acute morbidity with a parallel decline in at least some QOL dimensions. Most patients recover from acute toxicities but some problems (e.g., dry mouth, diet restriction) can persist years after treatment[41]. Thus, while traditional efficacy endpoints are undeniably critical considerations, assessment of the patient's QOL and performance is important to comprehensive evaluation of the success of these intensive regimens.

The University of Chicago Oral Cancer Center has compiled a battery of validated measures for practical and efficient assessment of key functional, performance and quality of life domains germane to SCCHN. These instruments include:

1. The Performance Status Scale for Head and Neck Cancer Patients (PSS-HN) a clinician rated tool composed of three scales measuring diet, speech and eating in public.

2. The Functional Assessment of Cancer Therapy Head and Neck (FACT-H&N), a patient completed QOL measure providing individual domain scores, head and neck specific subscale score as well as a global QOL score.

3. Items from the Radiotherapy Questionnaire developed at McMaster University, a patient rated scale of the troublesomeness of specific radiation related side effects.

Inclusion of this battery has proven to be feasible in a multi-institutional setting and the instruments have been shown to be sensitive to change over time.

Results from prior trials revealed that the most persistent long-term impairment associated with concurrent chemoradiotherapy was a restriction in the types of foods patients could eat, with 20% unable to take anything by mouth. Patients with oropharyngeal primary tumors were found to have the most restricted diets[40, 41]. It is clear that continued evaluation of QOL/performance endpoints is warranted.

1.2 Study Rationale and Proposal

1.2.1 Pattern of failure

A retrospective analysis of FHX trials conducted from 1993 to 1998 including 210 patients has revealed a distinct failure pattern based on TNM staging. That is, patients with T_4 tumors tended to fail locally while those with N_2 or N_3 disease failed distantly (30%), usually in the lungs[42]. Distant failure in these patients is devastating, as there is no opportunity for salvage with either surgery or re-irradiation, making the potentially lowered distant failure rate associated with introduction of neoadjuvant (induction) therapy especially significant.

1.2.2 Induction chemotherapy

The addition of neoadjuvant chemotherapy has never been validated in a randomized trial in this patient population and in the context of subsequent chemoradiotherapy. Previous trials have been criticized for being underpowered, employing inferior chemotherapy regimens, delaying definitive local therapy, or not defining the timing and role of surgery[43, 44]. A recent large meta-analysis examining 63 trials concluded that there appeared to be a benefit to neoadjuvant chemotherapy although modest (2%) and not statistically significant (p=0.10). However, when the analysis included only trials with what would be considered acceptable chemotherapy regimens, a statistically significant benefit to induction chemotherapy emerged[10]. Moreover, a review of randomized trials utilizing induction or adjuvant chemotherapy has shown a reduction in distant failure rates[44].

Another critical issue is the efficacy of local therapy since SCCHN is traditionally a disease of local failure. The addition of induction therapy is unlikely to reveal a benefit with respect to survival unless definitive and effective local therapy is administered with long-term local control rates of 80%. This level of local control has been achieved in repeated phase II trials with T-FHX[17, 19].

This trial seeks to establish induction chemotherapy in patients that historically have a propensity to metastatic spread (N_2 or N_3). In order to demonstrate a survival benefit, local therapy will need to be aggressive and effective in reducing local failure rates. Induction therapy, meanwhile, needs to be active, well tolerated, and easily administered in a timely manner. The trial will therefore apply a tested regimen of induction docetaxel, cisplatin, and 5FU followed by concomitant docetaxel, 5FU, hydroxyurea, and twice-daily radiation in patients with N_2 or N_3 disease.

1.2.3 Study Objectives

The primary objective is to determine the effect on overall survival when induction chemotherapy is administered prior to chemoradiotherapy in patients with N_2 or N_3 disease.

Secondary objectives are to determine the effect of induction chemotherapy when administered prior to chemoradiotherapy on distant failure-free survival (DFFS), failure pattern, progression free survival and quality of life.

1.2.4 Quality of Life Objectives

The proposed regimen aims to improve survival and minimize distant metastases while minimizing performance and QoL deficits. Thus, QoL and performance are important treatment endpoints. The objective is to describe these dimensions prospectively, pretreatment, through treatment, to long-term follow-up. Specific aims are to

- Document patient's experience of treatment effects
- Evaluate changes in QoL and performance as a function of induction chemotherapy alone
- Determine extensiveness and persistence of QoL and function-related treatment effects
- Describe the pattern, timing and extent of recovery of function and QoL

1.2.4.1 Quality of Life Assessment

1.2.4.1.1 Schedule

QOL/Performance will be assessed pretreatment, post induction/pre-CRT (for the induction arm), on treatment (last cycle) and then at 12 months post treatment and annually thereafter until year 5.

1.2.4.1.2 Assessment Instruments

Quality of life and performance measures to be used in this protocol include:

1) Performance Status Scale for Head and Neck Cancer Patients (PSS-HN)

2) Functional Assessment of Cancer Therapy - Head and Neck Version 4 (FACT-H&N)

3) Selected questions from the McMaster University Head and Neck Radiotherapy Questionnaire

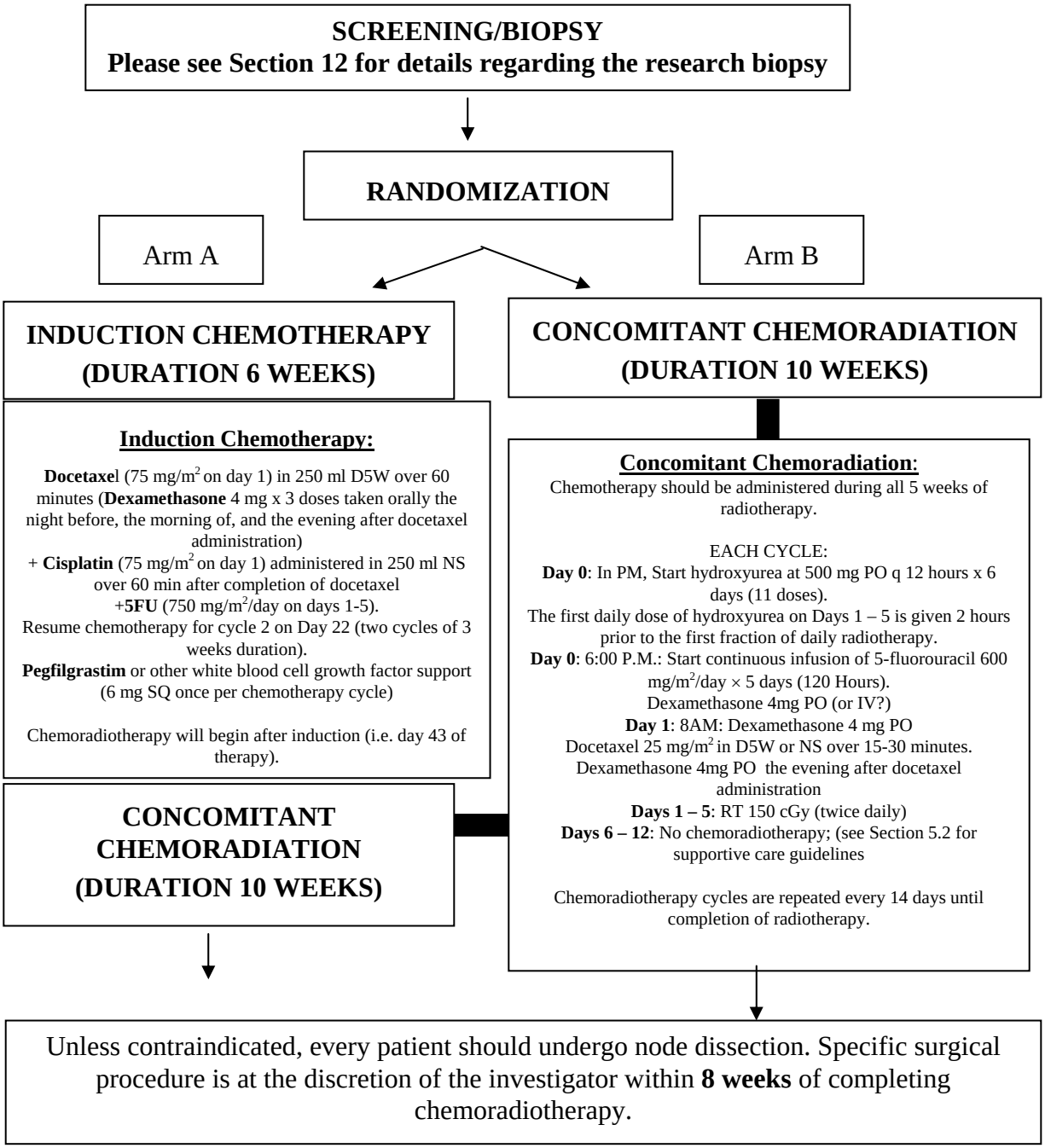
Performance Status Scale for Head and Neck Cancer (PSS-HN) The PSS-HN is a clinician rated instrument consisting of three subscales: Normalcy of Diet, Eating in Public, and Understandability of Speech. It has been demonstrated to be reliable and valid in head and neck cancer patients.

Functional Assessment of Cancer Therapy-Head and Neck Version 4 (FACT-H&N) The FACT-H&N is a multidimensional, self-report QoL instrument specifically designed for use with head and neck cancer patients. The core scale (FACT-G) consists of 27 core items assessing patient well being in four areas: Physical, Social/Family, Emotional, and Functional. The Core scale is supplemented with site-specific modules, of which the head and neck version (12 items) will be employed here.

McMaster Radiotherapy Questionnaire. This patient self-report instrument (can be clinician administered) quantifies patients' perception of the frequency and severity (troublesomeness) of radiation related side effects.

In addition basic demographic information including such parameters as age, ethnicity, education, marital status as well smoking and alcohol history, will be collected.

TRIAL SCHEMA



Patients should be seen weekly after completing chemoradiotherapy for toxicity evaluation and management.
After the 30-day follow-up visits and evaluations, patients should undergo clinical, laboratory, and radiographic disease evaluation every 3 months in year 1, every 6 months in years 2-3, then every 12 months in years 4-5. Serum TSH should be measured annually.

Version: 8/11/04, 9/10/04, 11/04/04, 12/13/04, 4/25/05, 7/12/05, 2/6/06, 2/16/06, 11/3/06, 5/30/07

2 INCLUSION CRITERIA

1. Histologically or cytologically confirmed diagnosis of squamous cell or poorly differentiated carcinomas of the head and neck (excluding lip), or lymphoepithelioma of the nasopharynx

2. Age 18 years or older

3. Patients with AJCC (6^{th} edition, 2002; Appendix 1) N_2 or N_3 disease, including patients with cervical lymph node metastasis of an unknown primary (i.e., TxN2 or TxN3). The unequivocal demonstration of distant metastasis (M_1) confers ineligibility.

4. Prior to entry in the study, the resectability and alternative treatment options for each patient will be determined by a team composed of a head and neck surgeon, a radiation oncologist, and a medical oncologist. Stage determination, optimal local treatment, and its timing according to this protocol will be determined at this evaluation.

5. Unidimensionally measurable disease (based on RECIST) is desirable but not strictly required. Individuals who are disease free at baseline after excisional biopsy or node dissection will be considered not evaluable for response assessment but are eligible.

6. No prior chemotherapy or radiotherapy

7. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 (Karnofsky $\geq$ 70%)

8. Existing peripheral neuropathy $\leq$ grade 1

9. Patients must have normal organ and marrow function as defined below

Hemoglobin	$\geq$ 8.0 g/dl
absolute neutrophil count (ANC)	$\geq$ 1,500/μl
platelets	$\geq$ 100,000/μl
total bilirubin	within normal institutional limits

AST **and** ALT **and** Alkaline Phosphatase must be within the range allowing for eligibility.

In determining eligibility the more abnormal of the two values (AST or ALT) should be used.

	AST or ALT:			
ALK PHOS:	**≤ ULN**	**>1x but ≤1.5x**	**>1.5x but ≤5x**	**>5x ULN**
≤ ULN	Eligible	Eligible	Eligible	Ineligible
>1x but ≤2.5x	Eligible	Eligible	Ineligible	Ineligible
>2.5x but ≤5x	Eligible	Ineligible	Ineligible	Ineligible
>5x ULN	Ineligible	Ineligible	Ineligible	Ineligible

creatinine	within normal institutional limits
albumin	> 2.9 g/dl

10. Informed consent must be obtained from all patients prior to beginning therapy. Patients should have the ability to understand and the willingness to sign a written informed consent document.

3 EXCLUSION CRITERIA

1. Demonstration of metastatic disease (i.e. M_1 disease).

2. Patients with a history of severe hypersensitivity reaction to docetaxel or other drugs formulated with polysorbate 80. History of allergic reactions attributed to compounds of similar chemical or biologic composition to cisplatin, 5 FU, or hydroxyurea

3. Other coexisting malignancies or malignancies diagnosed within the previous 3 years with the exception of basal cell carcinoma, cervical cancer in situ, and other treated malignancies with no evidence of disease for at least 3 years.

4. Prior surgical therapy other than incisional or excisional biopsy and organ-sparing procedures such as debulking of airway-compromising tumors or neck dissection in a patient

with an unknown primary tumor. Any non-biopsy procedure must have taken place less than 3 months from initiating protocol treatment.

5. Incomplete healing from previous surgery

6. Pregnancy or breast feeding (men and women of child-bearing potential are eligible but must consent to using effective contraception during therapy and for at least 3 months after completing therapy)

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

8. Patients with clinically significant pulmonary dysfunction, cardiomyopathy, or any history of clinically significant CHF are excluded. The exclusion of patients with active coronary artery disease will be at the discretion of the attending physician.

9. Uncontrolled active infection unless curable with treatment of their cancer.

4 CRITERIA FOR DISCONTINUATION/WITHDRAWAL OF INFORMED CONSENT

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

- Objective progression of disease
- Unacceptable adverse events
- Protocol non-compliance
- Study closure,
- Patient decision to withdraw from the study, or
- In the judgment of the investigator, further treatment would not be in the best interest of the patient.

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

All trial treatment-related toxicities and SAEs must be followed up until resolution.

All patients who have new or worsening CTC grade 3 or 4 laboratory values at the time of withdrawal must have additional testing performed, and the results must be recorded in the patients' medical records. In these cases, the investigators must record their opinions in the patients' medical records. Laboratory abnormalities should not be reported as adverse events unless a criterion for an SAE is fulfilled, the laboratory abnormality causes the patient to

discontinue from the study, or the investigator insists the abnormality should be reported as an AE.

After withdrawal from treatment, patients must continue to be followed per study protocol for assessment of outcomes and toxicity unless the patient withdraws consent and/or drops out of the study entirely.

5 TREATMENT PLAN

5.1 Agent Administration

Induction chemotherapy and maintenance therapy will be administered on an outpatient basis and chemoradiotherapy will be administered on an inpatient basis. Expected AEs and appropriate dose modifications for docetaxel, cisplatin, 5-FU, hydroxyurea, and radiation are described in sections 6 and 7. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

5.1.1 Pre-therapy Checklist (See table 1 for all testing requirements)

- Inclusion/exclusion criteria
- Informed consent
- Dental consultation
- Speech and swallow consultation
- Panendoscopy with biopsy and tumor map (please see section 12 regarding the research biopsy)
- Radiographic studies (CT or MRI of the head and neck, CT chest, bone scan [if indicated], within four weeks of starting therapy)
  N.B.: a bone scan is not required prior to therapy unless the investigator feels there is a clinical indication or suspicion of bone metastases.
- Complete blood count (CBC), complete metabolic profile (within one week prior to starting therapy).

5.1.2 Induction Therapy

Cisplatin, 5FU, and docetaxel combination will be administered for two cycles of 3 weeks duration each. Chemoradiotherapy will begin after induction (i.e. day 43 of therapy). Dose delays and dose modifications should take place as in section 7. **In no case should the two cycles of induction chemotherapy be given over a period exceeding eight (8) weeks.**

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

Dexamethasone 4 mg x 3 doses taken orally the night before, the morning of, and the evening after docetaxel treatment will be administered.

Docetaxel: 75 mg/m^2 in 250 ml of D5W over 60minutes (on Day 1).

Cisplatin: Start after completion of docetaxel on Day 1, 75 mg/m^2 in 250 ml of NS over 60 minutes

5FU: 750 mg/m^2/day on days 1-5 (3750mg/m^2, 120 hours total)

Resume chemotherapy for cycle 2 on Day 22.

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

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

Hydration: Administer in 1000 ml of NS with 20 mmol KCl over 120 minutes before and after administration of cisplatin. Measures should be taken to insure the patient is well hydrated prior to receiving cisplatin, including insuring that urinary output should is at least 100 mL per hour before initiation of cisplatin infusion. The addition of magnesium sulfate or mannitol to hydration is left to the discretion of the treating physician.

For each cycle: White blood cell growth factors in the first cycle of induction chemotherapy should be administered according to regional/national standards of care. White blood cell growth factors will be administered prophylactically during the second cycle if the following conditions are met during the first cycle:

- patients with a prior episode of febrile neutropenia or infection
- delayed recovery of absolute neutrophil count at day 21
- grade 4 neutropenia (ANC < 0.5 x 109/L) which persists for > 7 days

Pegfilgrastim (Neulasta, 6mg SQ once per chemotherapy cycle administered no sooner than 24 hours post-chemotherapy). Any other white blood cell growth factor support (e.g. filgrastim or sargramostim) can also be used.

Administer ciprofloxacin (or equivalent) 500mg BID from day 5-15 of each cycle.

5.1.3 Concomitant Chemoradiotherapy

Chemotherapy should be administered during all 5 weeks of radiotherapy. If less than 3 days of radiation therapy (RT) are required during Week 5, chemotherapy may be omitted.

Day 0		
	P.M.:	start hydroxyurea at 500 mg PO q 12 hours × 6 days (11 doses). The first daily dose of hydroxyurea on Days 1 – 5 is given 2 hours prior to the first fraction of daily radiotherapy.
		dexamethasone 4 mg PO (first dose)
	6:00 P.M.:	start continuous infusion of 5-FU at 600 mg/m^2/day × 5 days (120 hours).
Day 1 – 5		dexamethasone 4 mg PO in am & pm Day 1
		Start docetaxel 25 mg/m^2 after first RT fraction on day 1 of each cycle. Docetaxel should be administered in 100 ml D5W over 15-30 minutes.
		Radiation therapy is administered twice daily at 150 cGy per fraction.
Days 6 – 13:		No chemoradiotherapy. **Patients should be seen once on an outpatient basis during these non-treatment days to monitor for toxicity.**
For each cycle:		Administer 5 μg/kg subcutaneously (SQ) of G-CSF (filgrastim) daily, beginning on Day 6 through Day 12 at a minimum of 24 hours after completion of 5-FU in patients who develop grade 3 neutropenia or who have neutropenia ≥ grade 2 on Day 0 of any cycle. In these patients, G-CSF should be utilized in all subsequent cycles. G-CSF can be utilized prophylactically from the start of chemoradiotherapy in all cycles at the discretion of the treating physician.

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

5.2 Supportive Care

- Antiemetics will be ordered at the discretion of the attending physician.
- Administration of sucralfate (Carafate®) suspension (1 gm QD swish and swallow on an empty stomach) can be administered during chemoradiation to ameliorate mucositis/esophagitis. This is strictly optional at the discretion of the treating physician.
- A double lumen venous access device (e.g., Port-a-Cath®) is recommended prior to initiation of therapy.
- Use of a feeding device is recommended for high-risk patients. Placement of a feeding device is left to the discretion of the treating physician/investigator. Commonly applied criteria for feeding device placement include

    i. Loss of > 10% of body weight from the start of therapy

    ii. Dehydration or inability to maintain adequate oral hydration

    iii. Inability to maintain intake of $\geq$ 25 kcal/kg of ideal body weight

- During chemoradiotherapy patients should receive instructions for oral hygiene and prescriptions to include:

    i. Oral nystatin or fluconazole (100mg QD)

    ii. Viscous lidocaine HCl (Xylocaine®) solution) and/or Grade I mouthwash 10ml QID, swish and spit

Table 5: Grade I mouthwash

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

iii. Normal saline mouthwash 10ml QID swish and spit

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

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

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

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

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

ix. Therabite for trismus if appropriate.

x. Replacement for electrolyte imbalances when applicable.

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

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

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

- If Hgb < 10, patients should generally be transfused an amount sufficient to increase Hgb to ≥ 10. The Hgb level should be maintained > 11 mg/dl for the duration of chemoradiotherapy in all patients. The use of erythropoeitin or darbopoeitin is at the discretion of the investigator.

- The use of peg-filgrastim is described in section 5.1.2 and G-CSF (filgrastim) is described in section 5.1.3.

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

5.3 Radiotherapy Guidelines

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

2. All patients will be simulated prior to the start of treatment with an appropriate immobilization device.

3. Appropriate field sizes will be determined at the time of simulation to treat gross disease and areas of potential microscopic disease.

4. Initial fields will encompass all known areas of gross tumor as defined by physical exam or diagnostic studies (CT or MRI). The exact field arrangement will depend on whether 3-D conformal or IMRT techniques are used.

5. Blocking will be individualized for each patient. Either custom Cerrobend blocks or multileaf collimator will be acceptable.

6. Each cycle of treatment will consist of 5 consecutive days of radiation with 150 cGy given bid (300 cGy per day and 1500 cGy per week) in conjunction with chemotherapy. There should be a minimum of 6 hours between fractions. All fields will be treated each day.

7. In the case of mechanical failure or a holiday, one day of BID radiotherapy can be replaced with a single QD fraction of 200 cGy. Accordingly, the final cumulative dose will be slightly less.

8. The disease risk sites will be 1) gross disease (GTV), 2) high risk microscopic disease (PTV2), and 3) low risk microscopic disease (PTV3). Gross disease is all demonstrated disease based on physical exam and radiographic studies before induction chemotherapy. High risk microscopic disease is the first echelon of uninvolved nodes. Low risk microscopic disease is the second echelon of clinically uninvolved nodes. Post-chemotherapy CT scans can be used to define gross disease in nodal sites, but pre-chemotherapy scans must be used to define gross disease at the primary site.

9. Radiation doses: In general, the dose to gross disease will be 74-75 Gy. High-risk microscopic disease will receive 54 Gy. Low risk microscopic disease will receive 39 Gy.

10. The dose limit to the spinal cord will vary depending upon the technique used. Attempts should be made to limit the spinal cord dose to < 40 Gy with conventional 3D radiation treatment. Doses should be limited to 45 Gy with IMRT techniques and reduced fraction size to the spinal cord.

11. Questions regarding RT planning details should be directed to:

    Daniel Haraf, M.D.

    University of Chicago

    (773) 702-5976

5.3.1 Target Volume Definitions

A contrast enhanced CT with immobilization is required for planning. Slice thickness should be no greater than 5 mm. The GTV, PTV1, PTV2, and PTV3 must be defined on all

axial CT slices. Patients in the induction chemotherapy arm should undergo a CT prior to the start of chemotherapy for planning purposes. A post-chemotherapy scan should be obtained prior to the start of treatment. The pre- and post chemotherapy scans should be fused to define the targets as defined below.

GTV will be all gross tumor identified by clinical or radiographic examination. In most cases the pre-chemotherapy CT scan should be used to define the primary tumor. The post-chemotherapy scan can be used to define gross disease in the nodal sites. The GTV will be expanded by 1.5 cm to create PTV1. PTV1 can be modified at the discretion of the treating physician for the constraints of normal tissue tolerance and to avoid extension beyond the skin.

PTV2 will include PTV1 plus the first echelon of uninvolved lymph nodes.

PTV3 will include PTV2 plus the second echelon of uninvolved lymph nodes. In general PTV3 will extend from the base of skull to the supraclavicular fossae.

Variations in anatomy and tumor size make it necessary for the radiation oncologist to carefully define the PTV on each individual CT slice. Reasonable attempts should be made to provide an adequate treatment volume without encroaching upon critical organs (e.g. spinal cord) or extending to the skin.

5.3.2 Target Dose

5.3.2.1 3D conformal technique and prescriptions:

The neck should be treated with opposed lateral fields using a ½ field technique. The lower neck should be treated with an anterior field prescribed to a depth of 3 cm. Opposed fields for the lower neck are permitted in order to improve PTV coverage and increase homogeneity. For 3D techniques the dose variation in the PTV will be +7% and -5% of the prescription point dose. Wedges, tissue compensators or segmented fields should be used to insure uniformity of PTV coverage. Electron boosts of the posterior neck are permitted to limit the dose to the spinal cord. Electron fields shall be prescribed to the depth of maximum dose with the energy and field size chosen so that the target volume is encompassed within 90% of the prescribed dose. A cord block is permitted on the anterior or lateral fields provided it dose not block tumor. Feathering the match line is permitted in cases where a cord block would block tumor.

5.3.2.2 IMRT technique and prescription

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

5.3.2.3 Special situations:

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

5.4 Quality Assurance Documentation

Within three days of the start of radiotherapy, the following data shall be submitted for rapid review of each patient:

- Copies of the Planning CT and/or MR slices (pre-RT) covering all gross target volume (GTV) at 1cm separation, showing the GTV and target volumes on each slice. For patients on Arm A, please also submit a copy of the diagnostic (pre-study) imaging.
- Copies of simulation films or DRRs (digitally reconstructed radiograph) for each field showing lateral projection of all gross disease. If electron field films are not available, patient photos with these fields clearly indicated must be provided.
- Copy of verification (portal) films or hard copy of real time portal images for each treatment field
    - In lieu of submitting sim films/DRRs and portals for each field treated, an orthogonal set of anterior/ posterior and lateral films for isocenter localization for each group of concurrently treated beams should be submitted. This should include both sim films/DRRs and portal films/ hard copy portal images.
- RT-1 or IMRT Dosimetry Summary Form & the Disease Mapping Form (available on WWW.QARC.ORG)
- Photographs of patient in treatment position with fields marked and visible
- Copies of worksheets/ printouts used for calculations of monitor settings to give the prescribed dose & doses to all normal structures
- Color Isodose distributions for all treatment phases and composite (summed plan) with target volumes & prescription point clearly shown in axial, sagittal and coronal planes. Include axial slices through the central axis of the field, through the plane of maximum tumor bulk, and in superior and inferior planes of all target volumes. Composite plan should be in absolute dose.
- DVH (dose volume histogram) for the entire treatment course for PTV1, PTV 2, PTV3, GTV & spinal cord
- Prescription sheet for entire treatment course
- If IMRT is used, a DVH shall be submitted for “unspecified tissue” (tissue contained within the skin but not otherwise identified by containment within any other structure)

- BEV (Beams Eye View) of portals, showing collimator, beam aperture, target volume and critical structures
- REV (Rooms Eye View)

Within one month of the completion of radiotherapy, the following data shall be submitted:

- RT-2 Form (available on WWW.QARC.ORG)
- Copy of patient's daily radiotherapy record
- If changes were made subsequent to the initial review, please submit all data reflecting changes: Diagnostic and Treatment Planning imaging, simulation films/DRRs, verification (portal) films or portal images, RT-1 or IMRT Dosimetry Summary Form, Photographs of patient in treatment position with fields marked and visible, copies of worksheets/printouts used for calculations of monitor settings, color isodose distributions, Dose Volume Histograms, Prescription sheet for entire treatment course, BEVs, REVs, orthogonal films (sims/DRRs and portals).

Data should be submitted and any questions directed to:

Quality Assurance Review Center
272 West Exchange Street, Suite 101
Providence, RI 02903
Phone: (401) 454-4301
Fax: (401) 454-4683
Email: KBERTSCH@QARC.ORG

Please see Appendix VI for checklist and further details.

5.5 Surgical Guidelines

It is expected that patients will undergo concomitant chemoradiotherapy prior to extensive surgery. Simple excision (e.g., transoral laser excision) of the primary lesion may be performed initially if it can be accomplished while preserving organ function. Modified or selective neck dissection may also be performed. When these procedures are not performed initially, neck dissection should be performed following concomitant chemoradiotherapy in all patients. **Surgery at the primary site should be omitted in patients who have achieved biopsy-proven complete response. In patients with pathologically proven residual disease at the primary site, complete excision of disease should be accomplished.** Patients randomized to Arm A should not undergo surgery between induction chemotherapy and chemoradiotherapy. Patients demonstrating progression of disease **at any time** or disease recurrence should be considered for conventional surgical management.

5.6 Post-therapy Surveillance

After the 30-day follow-up evaluations, patients should undergo clinical and radiographic disease evaluation every 3 months in year 1, every 6 months in years 2 and 3, and annually

in years 4 and 5. Radiographic assessment should consist of the same imaging modalities previously employed and should include imaging of the head and neck and chest. Laboratory evaluation should consist of at least a CBC, serum electrolytes, serum creatinine, liver enzymes (AST, ALT, alkaline phosphatase), serum calcium, and serum albumin. TSH should be measured at least annually. A final swallowing assessment should be performed 1 year post-treatment.

6 EXPECTED TOXICITIES

6.1 Docetaxel

Common toxicities include:

- Myelosuppression (neutropenia and thrombocytopenia)
- Hepatic dysfunction
- Stomatitis
- Peripheral neuropathy
- Hypersensitivity reactions
- Fluid retention

6.2 Cisplatin

Common toxicities include:

- Hematologic – myelosuppression
- Gastrointestinal – nausea, vomiting, mucositis, diarrhea
- Neurologic – peripheral and central neuropathy and ototoxicity
- Renal – tubular damage, electrolyte imbalance, hypocalcemia, hypomagnesemia
- Ocular toxicity
- Allergic reactions

6.3 5-Fluorouracil

Common toxicities include:

- Gastrointestinal – diarrhea, mucositis, nausea, and vomiting
- Hematologic – myelosuppression

- Dermatologic – photosensitivity, skin dryness, hand-foot syndrome, increased pigmentation of skin, increased pigmentation of veins used for infusion, nail changes

Less commonly observed toxicities include

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

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

6.4 Hydroxyurea

Common side effects include:

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

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

Less common side effects include:

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

6.5 Pegfilgrastim and Filgrastim

Toxicities, warnings, and drug interactions are specified in Sections 8.5 and 8.6.

6.6 Radiation

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

7 DOSE AND SCHEDULE MODIFICATIONS

7.1 During Induction Chemotherapy

No more than two dose modifications should be allowed for any patient. If a patient requires a third dose-reduction study treatment should be discontinued. If such a patient is clinically

benefiting from treatment, and, if the physician believes the toxicity will be alleviated sufficiently with dose modification, further treatment will be permitted at the discretion of the Principal Investigator in consultation with Aventis Pharmaceuticals, U.S. Medical Affairs. **In no case should the two cycles of induction chemotherapy be given over a period exceeding eight (8) weeks.**

7.1.1 Dose Modification

Dose modification

Induction Dose Level	Cisplatin (mg/m^2)	Docetaxel (mg/m^2)	5FU (mg/m^2)
0	75	75	750
–1	60	60	600
–2	50	50	500

7.1.2 Hematologic Toxicity

Prior to receiving any dose of docetaxel, cisplatin, or 5FU patients must have an absolute neutrophil count $\geq$ 1000/mm^3 and a platelet count $\geq$ 50,000/mm^3.

Hematologic toxicity is based on any interval laboratory results within 2 days prior to treatment or on the day of treatment.

Hematologic toxicity

ANC/μl		Platelet count/μl	Dose Modification
> 1000	And	> 50,000	No change, give previous dose
≤ 1000	Or	≤ 50,000	Decrease 1 level*

* Do not treat until ANC > 1000 μl and platelet count > 50,000 μl. Retreat when patient recovers at the lower dose level. If a patient experiences a hematologic or non-hematologic toxicity in induction cycle 1 and cannot receive cycle 2 or the patient experiences a heme or non-heme toxicity in induction cycle 2, the patient should proceed with concomitant chemoradiotherapy. Heme/non-heme toxicity recovery is not a requirement to move forward with chemoradiotherapy. Dose modification of chemoradiotherapy in the presence of heme/non-heme toxicity from induction may be considered at the discretion of the investigator.
ANC = absolute neutrophil count.

The use of pegfilgrastim is described in section 5.1.2 and GCSF (filgrastim) is described in section 5.1.3.

7.1.3 Non-hematologic Toxicities

Modification of cisplatin, 5FU, or docetaxel dosages will occur if the toxicity is considered to be related to study drug. Non-hematologic toxicities will be based on any interval observations between treatments or at the time of each dose.

7.1.4 Motor and/or Sensory Neuropathy

Motor and sensory neuropathy

Neuro-sensory/Motor	Docetaxel	Cisplatin	5FU
Grade 0 – 1	No change	No change	No change
Grade 2	Decrease 1 dose level	Decrease 1 dose level	No change
Grade 3 or greater	Hold until $\underline{\leq}$ grade 1	Hold until $\underline{\leq}$ grade 1	No change

- If grade 3 or greater neuropathy is present on day 1 of any cycle, all treatment should be withheld until neuropathy has resolved to grade 1 or less.
- If neuropathy is ≤ grade 1 on day 1 of any cycle, treat at current dose.
- The docetaxel and cisplatin dose should be reduced for Grade 2 neuropathies without treatment delay.

Treatment should be discontinued or modified for Grade 3/4 neuropathies at investigator discretion.

7.1.5 Fatigue, Arthralgia, Myalgias

Fatigue, arthralgia, myalgias

Arthralgia, Myalgia	Docetaxel	Cisplatin	5FU
Grade 0 – 1 (normal, mild)	No change	No change	No change
Grade 2 (decrease in ability to move)	No change	No change	No change
Grade 3 (disabled)	Hold until ≤ grade 2 (moderate), then decrease 1 dose level	No change	No change

7.1.6 Stomatitis

- If grade 3 or greater stomatitis is present on day 1 of any cycle, docetaxel and 5FU treatment should be withheld until stomatitis has resolved to grade 1 or less and then reduced 1 dose level.
- If stomatitis is ≤ grade 1 on day 1 of any cycle, treat at current dose.
- The docetaxel and 5FU doses should be reduced one dose level for Grade 2 stomatitis without treatment delay.

7.1.7 Hepatic Dysfunction

Liver function tests should be evaluated at a <u>minimum</u> of every 4 weeks.

Patients who develop abnormal liver function tests for any reason while on the study will have the following dose reductions:

Dose Modifications of Docetaxel for Abnormal Liver Function

Both AST and ALT should be drawn. If one or both AST & ALT values are abnormal, dose modification is determined by whichever value is the more abnormal of the two.

	AST or ALT:			
ALK PHOS:	**≤ ULN**	**>1x but ≤1.5x ULN**	**>1.5x but ≤5x ULN**	**>5x ULN**
≤ ULN	Full Dose	Full Dose	Full Dose	Hold*****
>1x but ≤ 2.5x	Full Dose	Full Dose	Reduce Dose by 50%	Hold*****
>2.5x but ≤ 5x	Full Dose	Reduce Dose by 50%	Hold*****	Hold*****
>5x ULN	Hold*****	Hold*****	Hold*****	Hold*****

*****Hold until recovered, maximum 21 days, then re-treat at a reduced dose. "Recovered" is defined as meeting the study baseline eligibility criteria.

<u>Bilirubin</u>: docetaxel should not be administered to patients with serum total bilirubin >ULN. If serum total bilirubin is >ULN on treatment day, hold docetaxel until serum

total bilirubin is ≤ ULN (maximum 21 days), then re-treat at one dose level below current dose.

7.1.8 Nephrotoxicity

If the creatinine is not within institutional normal limits on a value measured within 48 hours of a cisplatin dose, then the cisplatin dose will be held. It may be re-instituted at full dose when the creatinine recovers.

7.1.9 Other non-hematologic toxicity

Hypersensitivity Reactions

See Appendix II for treatment of hypersensitivity reactions. Treatment should be discontinued for Grade 4 hypersensitivity reactions. There are no dose reductions for hypersensitivity reactions.

Fluid Retention

There are no dose reductions for fluid retention.

Patients developing new onset edema, progression of existing edema, or another sign of fluid retention (eg. 2 pound weight gain) are to be treated with oral diuretics. Regimens found to be effective in the management of fluid retention due to Taxotere are listed below.

- Triamterene/hydrochlorothiazide one capsule po qd up to tid.
- Furosemide 40 mg po daily if edema progresses despite Triamterene/hydrochlorothiazide therapy. Potassium supplementation should be given as needed.
- If after a two-week trial, furosemide 40 mg po qd is ineffective, the patient may be treated with furosemide 20 mg po daily plus metolazone 2.5 mg po daily with potassium supplementation as needed.

Others

For Grade 3 and 4 toxicities, treatment should be withheld until the toxicity resolves to Grade 1 or less, then, reinstituted (if medically appropriate) with a dose reduction.

7.2 Dose Modifications during Concomitant Chemoradiotherapy

7.2.1 Myelosuppression

For absolute neutrophil count (ANC) of 500/μl to 1,000/μl or platelet count of 50,000/μl to 74,000/μl on Day 0 – 5 of each cycle, decrease hydroxyurea to 50% and docetaxel to 75% of full dose. On subsequent cycles, a reduced starting dose of hydroxyurea and docetaxel may be used.

For ANC of ≤ 500/μl or platelet count ≤ 50,000/μl on Day 0 – 5 of any cycle, omit hydroxyurea, reduce docetaxel to 50% of full dose, and administer 600 mg/m^2/day of 5-FU and radiotherapy only. On subsequent cycles, a reduced starting dose of hydroxyurea by 50% should be used.

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

The use of pegfilgrastim is described in section 5.1.2 and GCSF (filgrastim) is described in section 5.1.3.

7.2.2 Mucositis and Dermatitis

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

Doses will not be increased on subsequent cycles.

<u>TREATMENT CYCLES WILL NOT BE DELAYED</u> FOR MUCOSITIS, DYSPHAGIA, OR DERMATITIS.

7.2.3 Other Non-hematological Toxicity

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

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

Geriatric Use:

Elderly patients may be more sensitive to the effects of hydroxyurea, and may require a lower dose regimen.

This drug is known to be excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

For Other Toxicities on Day 0 of chemoradiotherapy:

7.2.3.1 Hepatotoxicity

Grade 3, 4 – Hold hydroxyurea and adjust docetaxel as per 7.1.7.

7.2.3.2 Peripheral neuropathy, hypersensitivity, fluid retention, hyperlacrimation

Follow instructions specified in section 7.1.4 for adjustment of docetaxel dose.

7.2.3.3 Nephrotoxicity

Grade 2 – Give ½ dose hydroxyurea

Grade 3, 4 – Hold hydroxyurea

8 AGENT FORMULATION AND PROCUREMENT

8.1 Docetaxel

PREPARATION AND ADMINISTRATION

Docetaxel (TAXOTERE) is an antineoplastic chemotherapy agent that is commercially available and should be billed to insurance. TAXOTERE is a cytotoxic anticancer drug and, as with other potentially toxic compounds, caution should be exercised when handling and preparing TAXOTERE solutions. The use of gloves is recommended. Please refer to **Handling and Disposal** section.

If TAXOTERE Injection Concentrate, initial diluted solution, or final dilution for infusion should come into contact with the skin, immediately and thoroughly wash with soap and water. If TAXOTERE Injection Concentrate, initial diluted solution, or final dilution for infusion should come into contact with mucosa, immediately and thoroughly wash with water.

Contact of the TAXOTERE concentrate with plasticized PVC equipment or devices used to prepare solutions for infusion is not recommended. In order to minimize patient exposure to the plasticizer DEHP (di-2-ethylhexyl phthalate), which may be leached from PVC infusion bags or sets, the final TAXOTERE dilution for infusion should be stored in bottles (glass,

polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets.

TAXOTERE Injection Concentrate requires two dilutions prior to administration. Please follow the preparation instructions provided below. **Note:** Both the TAXOTERE Injection Concentrate and the diluent vials contain an overfill to compensate for liquid loss during preparation. This overfill ensures that after dilution with the **entire** contents of the accompanying diluent, there is an initial diluted solution containing 10 mg/mL docetaxel.

The table below provides the fill range of the diluent, the approximate extractable volume of diluent when the entire contents of the diluent vial are withdrawn, and the concentration of the initial diluted solution for TAXOTERE 20 mg and TAXOTERE 80 mg.

Product	Diluent 13% (w/w) ethanol in water for injection Fill Range (mL)	Approximate extractable volume of diluent when entire contents are withdrawn (mL)	Concentration of the initial diluted solution (mg/mL docetaxel)
Taxotere® 20 mg/0.5 mL	1.88 – 2.08 mL	1.8 mL	10 mg/mL
Taxotere® 80 mg/2 mL	6.96 - 7.70 mL	7.1 mL	10 mg/mL

Preparation and Administration

A. Initial Diluted Solution

1. TAXOTERE vials should be stored between 2 and 25°C (36 and 77°F). If the vials are stored under refrigeration, allow the appropriate number of vials of TAXOTERE Injection Concentrate and diluent (13% ethanol in water for injection) vials to stand at room temperature for approximately 5 minutes.

2. Aseptically withdraw the **entire** contents of the appropriate diluent vial (approximately 1.8 mL for TAXOTERE 20 mg and approximately 7.1 mL for TAXOTERE 80 mg) into a syringe by partially inverting the vial, and transfer it to the appropriate vial of TAXOTERE Injection Concentrate. **If the procedure is followed as described, an initial diluted solution of 10mg docetaxel/mL will result.**

Version: 8/11/04, 9/10/04, 11/04/04, 12/13/04, 4/25/05, 7/12/05, 2/6/06, 2/16/06, 11/3/06, 5/30/07

3. Mix the initial diluted solution by repeated inversions for at least 45 seconds to assure full mixture of the concentrate and diluent. Do not shake.

4.The initial diluted TAXOTERE solution (10 mg docetaxel/mL) should be clear; however, there may be some foam on top of the solution due to the polysorbate 80. Allow the solution to stand for a few minutes to allow any foam to dissipate. It is not required that all foam dissipate prior to continuing the preparation process.

The initial diluted solution may be used immediately or stored either in the refrigerator or at room temperature for a maximum of 8 hours.

B. Final Dilution for Infusion

1.Aseptically withdraw the required amount of initial diluted TAXOTERE solution (10 mg docetaxel/mL) with a calibrated syringe and inject into an infusion bag or bottle of either 0.9% Sodium Chloride solution or 5% Dextrose solution to produce a final concentration of 0.3 to 0.74 mg/mL.

2.Thoroughly mix the infusion by manual rotation.

3.As with all parenteral products, TAXOTERE should be inspected visually for particulate matter or discoloration prior to administration whenever the solution and container permit. If the TAXOTERE initial diluted solution or final dilution for infusion is not clear or appears to have precipitation, these should be discarded.

The final TAXOTERE dilution for infusion should be administered intravenously as a 1-hour infusion under ambient room temperature and lighting conditions.

Dosing information: See section 5.1.2

Stability: TAXOTERE infusion solution, if stored between 2 and 25°C (36 and 77°F) is stable for 4 hours. Fully prepared TAXOTERE infusion solution (in either 0.9% Sodium Chloride solution or 5% Dextrose solution) should be used within 4 hours (including the 1 hour i.v. administration).

HOW SUPPLIED

TAXOTERE Injection Concentrate is supplied in a single-dose vial as a sterile, pyrogen-free, non-aqueous, viscous solution with an accompanying sterile, non-pyrogenic, Diluent (13% ethanol in water for injection) vial. The following strengths are available:

TAXOTERE 80 MG/2 ML (NDC 0075-8001-80)

TAXOTERE (docetaxel) Injection Concentrate 80 mg/2 mL: 80 mg docetaxel in 2 mL polysorbate 80 and Diluent for TAXOTERE 80 mg (13% (w/w) ethanol in water for injection). Both items are in a blister pack in one carton.

TAXOTERE 20 MG/0.5 ML (NDC 0075-8001-20)

TAXOTERE (docetaxel)) Injection Concentrate 20 mg/0.5 mL: 20 mg docetaxel in 0.5 mL polysorbate 80 and diluent for TAXOTERE 20 mg (13% (w/w) ethanol in water for injection). Both items are in a blister pack in one carton.

Storage: Store 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.

Handling and Disposal: Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published[1-7]. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

REFERENCES

1.OSHA Work-Practice Guidelines for Controlling Occupational Exposure to Hazardous Drugs. *Am J Health-Syst Pharm.* 1996; 53: 1669-1685.

2.American Society of Hospital Pharmacists Technical Assistance Bulletin on Handling Cytotoxic and Hazardous Drugs. *Am J Hosp Pharm.* 1990; 47(95): 1033-1049.

3.AMA Council Report. Guidelines for Handling Parenteral Antineoplastics. *JAMA.* 1985; 253 (11): 1590-1592.

4.Recommendations for the Safe Handling of Parenteral Antineoplastic Drugs. NIH Publication

No. 83-2621. For sale by the Superintendent of Documents, US Government Printing Office,

Washington, DC 20402.

5.National Study Commission on Cytotoxic Exposure - Recommendations for Handling Cytotoxic Agents. Available from Louis P. Jeffry, Chairman, National Study Commission on Cytotoxic Exposure. Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, MA 02115.

6.Clinical Oncological Society of Australia. Guidelines and Recommendations for Safe Handling of Antineoplastic Agents. *Med J Austr.* 1983; 426-428.

7.Jones, RB, et al. Safe Handling of Chemotherapeutic Agents: A Report from the Mt. Sinai Medical Center. *CA-A Cancer Journal for Clinicians.* 1983; Sept/Oct: 258-263.

Prescribing Information as of April 2003

8.2 Cisplatin

Formulation: Cisplatin is a sterile aqueous solution, each mL containing 1 mg cisplatin and 9 mg sodium chloride. Cisplatin is supplied in multidose vials of 50 mg and 100 mg cisplatin.

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

Storage and Stability: Storage Store intact vials at room temperature 15°C to 25°C (59°F to 77°F) and protect from light. Do not refrigerate solution as a precipitate may form. Further dilution stability is dependent on the chloride ion concentration and should be mixed in solutions of NS (at least 0.3% NaCl). After initial entry into the vial, solution is stable for 28

days protected from light or for at least 7 days under fluorescent room light at room temperature.

Adverse effects: Leukopenia, thrombocytopenia, anemia, nausea, vomiting, nephrotoxicity, ototoxicity, peripheral neuropathy, electrolyte imbalance, hypocalcemia, hypomagnesemia, ocular toxicity, and allergic reactions. Infrequent: cardiac abnormalities, anorexia, elevated SGOT, rash, alopecia, and acute myeloid leukemia.

NOTE: Aminoglycoside antibiotics given before, with, or after cisplatin may potentiate renal toxicity and should be avoided whenever possible.

Severe renal toxicity can largely be avoided by induction of a diuresis before, during and after treatment. Mild renal dysfunction is a common complication (10%) of chronic therapy and may require discontinuation of therapy according to protocol specifications.

Refer to package insert for complete details.

Availability: Cisplatin is commercially available from Bristol Laboratories Oncology Products and should be billed to insurance.

8.3 Fluorouracil

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

8.4 Hydroxyurea

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

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

Geriatric Use:

Elderly patients may be more sensitive to the effects of hydroxyurea, and may require a lower dose regimen.

This drug is known to be excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

8.5 Pegfilgrastim (Neulasta®) Drug Information

Packaging and Formulation

Pegfilgrastim is commercially available. Pegfilgrastim is a clear, colorless, sterile liquid. It is supplied as a preservative-free solution containing 6 mg (0.6 mL) of pegfilgrastim (10 mg/mL) in a single-dose syringe with a 27 gauge, 1/2 inch needle with an UltraSafe® Needle Guard. The formulation is 10.0 mg pegfilgrastim (PEGr-metHuG-CSF) per mL of solution containing acetate (0.35 mg), sorbitol (30.0 mg), polysorbate 20 (0.02 mg), and sodium (0.02 mg) in water for injection, USP, pH 4.0.

Storage Conditions and Stability

Pegfilgrastim should be stored refrigerated at 2° to 8°C (36° to 46°F); syringes should be kept in their carton to protect from light until time of use. Shaking should be avoided. Before injection, pegfilgrastim may be allowed to reach room temperature for a maximum of 48 hours but should be protected from light. Pegfilgrastim left at room temperature for more than 48 hours should be discarded. Freezing should be avoided; however, if accidentally frozen, pegfilgrastim should be allowed to thaw in the refrigerator before administration. If frozen a second time, pegfilgrastim should be discarded.

Since pegfilgrastim provided for clinical trials contains no preservatives, prefilled syringes are designed for single use only. Contact your Amgen representative, or their designee, if storage conditions fall out of the specified range. Before investigational product that has been exposed to storage conditions out of the specified range can be used, Amgen's Stability Department must issue a memo. This memo must be sent to and maintained at the site.

Records of the actual storage conditions during the period of the study must be maintained (eg, records of the date and time and initials of person checking, and the daily temperatures of the refrigerator used for storage of investigational product, continuous temperature recordings, or regularly maintained temperature alarm systems).

Preparation and Administration

No preparation is required for administration of pegfilgrastim. Each subject will receive a fixed dose of 6 mg of pegfilgrastim. The entire contents of the 0.6 mL prefilled syringe should be administered irrespective of the subject's actual weight.

Adverse Reactions

The most common adverse event attributed to pegfilgrastim in clinical trials was medullary bone pain, reported in 26% of subjects, which was comparable to the incidence in Filgrastim-treated patients. This bone pain was generally reported to be of mild-to-moderate severity. Approximately 12% of all subjects utilized non-narcotic analgesics and less than 6% utilized narcotic analgesics in association with bone pain. No patients withdrew from the study due to bone pain. Reversible elevations in LDH, alkaline phosphatase and uric acid have been observed in clinical trials. Pegfilgrastim has been associated with leukocytosis (defined as WBC > 100 x 10^9/L) in <1% of 465 subjects with nonmyeloid malignancies, when observed is was not associated with any adverse event. Transient thrombocytopenia has also been noted in patients receiving Filgrastim.

Overdosage

The maximum amount of pegfilgrastim that can be safely administered in single or multiple doses has not been determined. Single doses of 300 mcg/kg have been administered SC to 8 normal volunteers and 3 patients with non-small cell lung cancer without serious adverse effects. These subjects experienced a mean maximum ANC of 55 x 10^9/L, with a corresponding mean maximum WBC of 67 x 10^9/L. The absolute maximum ANC observed was 96 x 10^9/L with a corresponding absolute maximum WBC observed of 120 x 10^9/L. The duration of leukocytosis ranged from 6 to 13 days. Leukapheresis should be considered in the management of symptomatic individuals.

Toxicity/Warnings

Pegfilgrastim is contraindicated in patients with known hypersensitivity to *E coli*-derived proteins, pegfilgrastim, Filgrastim, or any other component of the product. Rare cases of splenic rupture have been reported following the administration of the parent compound of pegfilgrastim, Filgrastim, for PBPC mobilization in both healthy donors and patients with cancer. Some of these cases were fatal. Pegfilgrastim has not been evaluated in this setting. Patients receiving pegfilgrastim who report left upper abdominal or shoulder tip pain should be evaluated for an enlarged spleen or splenic rupture. Rare cases of splenic rupture have been reported with pegfilgrastim in the post-marketing setting. Similar events have been reported following the administration of the parent compound of pegfilgrastim, Filgrastim, for PBPC mobilization in both healthy donors and patients with cancer. Some of these cases with Filgrastim were fatal. Pegfilgrastim has not been evaluated in this setting, therefore, pegfilgrastim should not be used for PBPC mobilization. Patients receiving pegfilgrastim who report left upper abdominal or shoulder tip pain should be evaluated for an enlarged spleen or splenic rupture. Adult respiratory distress syndrome (ARDS) has been reported in

neutropenic patients with sepsis receiving filgrastim, the parent compound of pegfilgrastim, and is postulated to be secondary to an influx of neutrophils to sites of inflammation in the lungs. Neutropenic patients receiving pegfilgrastim who develop fever, lung infiltrates, or respiratory distress should be evaluated for the possibility of ARDS. In the event that ARDS occurs, pegfilgrastim should be discontinued and/or withheld until resolution of ARDS and patients should receive appropriate medical management for this condition. Rare cases of allergic-type reactions have been experience by patients receiving pegfilgrastim in the post-marketing setting. This is similar to allergic-type reactions, including anaphylaxis, skin rash, and urticaria, occurring on initial or subsequent treatment that have been reported with the parent compound of pegfilgrastim, filgrastim. In some cases, symptoms have recurred with rechallenge with Filgrastim, suggesting a causal relationship. If a serious allergic reaction or anaphylactic reaction occurs, appropriate therapy should be administered and further use of pegfilgrastim should be discontinued. Severe sickle cell crisis have been reported in patients with sickle cell disease (specifically homozygous sickle cell anemia, sickle/hemoglobin C disease, and sickle+ thalassemia) who received filgrastim, the parent compound of pegfilgrastim, for PBPC mobilization or following chemotherapy. One of these cases was fatal.

Pregnancy and Lactation

There are no adequate and well-controlled studies in pregnant women. The risks of the study drug to an unborn or newborn child, are not known. In addition, it is not known whether pegfilgrastim is secreted in human milk. Therefore, pregnant or nursing mothers may not take part in this study.

Drug Interactions

No formal drug interaction studies between pegfilgrastim and other drugs have been performed. Drugs such as lithium may potentiate the release of neutrophils; patients receiving lithium and pegfilgrastim should have more frequent monitoring of neutrophil counts.

8.6 Filgrastim (Neupogen®) Drug Information

Packaging and Formulation

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

Storage Conditions and Stability

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

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

Preparation and Administration

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

Adverse Reactions

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

Overdosage

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

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

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

Toxicity/Warnings

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

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

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

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

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

PREGNANCY AND LACTATION

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

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

DRUG INTERACTIONS

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

Nursing Guidelines

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

9 MEASUREMENT OF EFFECT

For the purposes of this study, patients should be reevaluated for response after induction therapy and within 8 weeks of completing chemoradiotherapy.

9.1 Definitions

Response and progression will be evaluated in this study using the new international criteria proposed by the RECIST Committee[45]. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria. Note: Lesions are either measurable or non-measurable using the criteria provided below. The term "evaluable" in reference to measurability will not be used because it does not provide additional meaning or accuracy.

9.1.1 Measurable Disease

Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm with conventional techniques (CT, MRI, x-ray) or as ≥ 10 mm with spiral CT scan. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

9.1.2 Non-measurable Disease

All other lesions or sites of disease, including small lesions (longest diameter < 20 mm with conventional techniques or < 10 mm using spiral CT scan), are considered non-

measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all non-measurable.

9.1.3 Target Lesions

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

9.1.4 Non-target Lesions

All other lesions or sites of disease should be identified as non-target lesions and should also be recorded at baseline. Non-target lesions include measurable lesions that exceed the maximum numbers per organ or total of all involved organs as well as non-measurable lesions. Measurements of these lesions are not required but the presence or absence of each should be noted throughout follow-up.

9.2 Guidelines for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.
Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. Given the nature of locoregional failure after prior irradiation characteristic of head and neck cancer, these areas are considered as progression of disease and will be included. If doubt exists on appropriate scans, then biopsy will be necessary to measure disease.

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

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

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

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

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

Tumor markers. Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific additional criteria for standardized usage of prostate-specific antigen (PSA) and CA-125 response in support of clinical trials are being developed.

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

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

9.3 Response Criteria

9.3.1 Evaluation of Target Lesions

Complete Response (CR):	Disappearance of all target lesions
Partial Response (PR):	At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD
Progressive Disease (PD):	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions

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

9.3.2 Evaluation of Non-target Lesions

Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level
Incomplete Response/ Stable Disease (SD):	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits
Progressive Disease (PD):	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions

Although a clear progression of "non-target" lesions only is exceptional, in such circumstances the opinion of the treating physician should prevail, and the progression status should be confirmed at a later time by the review panel (or study chair).

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

9.3.3 Evaluation of Overall Response

The overall response will be recorded as the response after induction chemotherapy (for Arm A only) and after chemoradiotherapy (for Arms A and B, 30-day post-treatment evaluation, see Table 3) compared to the pre-treatment. Post-chemoradiotherapy surgical intervention (see Section 6.4) will be used to assess pathologic response only. Response will be recorded as "clinical" based on clinical measurement of disease, "radiographic" based on radiographic measurement of disease, and "pathologic" based on pathologic examination of post-treatment biopsy and neck dissection. The patient's best response assignment will be recorded in the following order of precedence: pathologic, clinical, and radiographic.

Table 6 Lesions

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

CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease.

Note:

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

9.4 Duration of Response

9.4.1 Duration of Overall Response

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

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

9.5 Progression-Free, Distant Failure Free, Overall Survival, Local Progression, Distant Progression

Progression-free (time to progression): From the date of registration to the date of progressive disease or death

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

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

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

10 ADVERSE EVENTS

Definitions

A **serious adverse event** (experience) or reaction is any untoward medical occurrence that at any dose: results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability / incapacity, or is a congenital anomaly / birth defect.

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

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

Expedited Adverse Event Reporting

Expedited Reporting Guidelines – (including **hospitalization** defined in bullet 1 below)

UNEXPECTED EVENT		**EXPECTED EVENT**	
GRADES 2 – 3 Attribution of Possible, Probable or Definite	**GRADES 4 and 5 Regardless of Attribution**	**GRADES 1 - 3**	**GRADES 4 and 5 Regardless of Attribution**
Expedited report within 5 working days. (Grade 1 Adverse Event Expedited Reporting NOT required.)	Report by phone to UCCRC Clinical Trials Office within 24 hrs. Expedited report to follow within 5 working days. Deaths to be reported by phone to UCCRC Clinical Trials Office within 24 hrs. Expedited report to follow within 48 hours. This includes all deaths within 30 days of the last dose of treatment with an investigational agent regardless of attribution. Any late death attributed to the agent (possible, probable, or definite) should be reported within 48 hours of site's knowledge.	Adverse Event Expedited Reporting NOT required.	Expedited report within 5 working days. This includes all deaths within 30 days of the last dose of treatment with an investigational agent regardless of attribution. Any late death attributed to the agent (possible, probable, or definite) should be reported within 48 hours of site's knowledge.

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

Reporting a Serious Adverse Event

Within 24 hours of knowledge of Serious Adverse Event:

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

- The following information is required when calling in the event:

-Reporter's Name and Telephone Number

-Patient Initials

-Patient Medical Record Number

-IRB Protocol Number

-PI of Study

-Treating Physician

-Date of Event

-Description of Event (including grade of the event and if the event required hospitalization)

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

Within 5 working days of knowledge of Serious Adverse Event:

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

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

Forms

The UC IRB Serious and Unexpected Adverse Event form is available on-line at: HTTP://ORS/IRB/AESERIOUS.PDF. The UC IRB Fatal/Life-Threatening Event form is available on-line at: HTTP://ORS/IRB/AEFATAL.PDF. The MedWatch form is available at HTTP://WWW.FDA.GOV/MEDWATCH/SAFETY/3500A.PDF.

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

These reports will be sent by **FAX** or **E-MAIL to:**

Reports will be forwarded by the University of Chicago to Aventis Pharmaceuticals Global Pharmacovigilance and Epidemiology Department (908-231-4827), and Amgen, Inc. via facsimile (866-814-1889), within 24 hours of receipt by investigator / sponsor. **FAX transmission will include the following on the provided GIA SAE REPORT, fax cover form (appendix III):**

Grant-In-Aid study number (GIA # 15043); Study Title; Name of Principal Investigator

Reports by **E-MAIL** will be sent to: GPEMAILBOX@AVENTIS.COM , within 24 hours of receipt by investigator / sponsor. **E-Mail transmission will include the following:**

Grant-In-Aid study number (GIA # 15043); Study Title; Name of Principal Investigator

11 RESEARCH BIOPSY

11.1 Background

Little is known about the molecular determinants of outcome or toxicity in SCCHN with most reports examining specific factors in a retrospective manner. These studies have implicated several genes or proteins that are linked with a poorer prognosis but the significance and applicability of the findings are difficult to ascertain because of heterogeneity of the population studied, differences in therapy administered, the retrospective nature of most trials, and different assay systems employed. Many of these studies also suffered from small sample size, limited clinical data, and did not subject their data to multivariate analysis. Thus results from different trials have often been contradictory.

Prognosis in individual patients with advanced head and neck cancer (HNC) currently relies on clinical variables. However, within patients grouped by similar performance status, tumor location, tumor size, and nodal involvement there is still considerable variability in outcome. At this time it is unknown which patients would benefit from or could be spared more aggressive therapies.

At clinical presentation, a squamous cell carcinoma of the head and neck has accumulated a plethora of molecular alterations. The current trial will enroll only treatment naïve patients with locally advanced disease; will administer chemoradiotherapy to all patients with or without induction chemotherapy; and will follow patients prospectively for up to 5 years. Patients will be randomized to one of two treatment arms providing comparability of different markers between groups. This format should serve to enhance the quality of conclusions made regarding molecular markers.

11.2 Tissue Procurement

11.2.1 Tissue Biopsy

At the time of surgical resection or biopsy, tissue in excess of what is necessary for diagnostic purposes will be obtained <15 minutes after removal from the patient, embedded in TissueTek OCT medium (VWR Scientific Products Corporation, San Diego, CA), and frozen in liquid nitrogen. Sample should be at least an 18-gauge core (preferably 14-gauge) and at least 1 inch in length.

11.2.2 Genotyping studies

Blood will be obtained from all patients enrolled in the study for pharmacogenomic evaluation. Investigation of the relevant polymorphisms will take place in germline DNA extracted from peripheral whole blood (10 ml) collected in plastic EDTA (purple top) vacutainers (BD catalog#366643). Blood samples should be stored at -80°C immediately after drawn and may be batched on dry ice as specified in Section 11.5. Samples should be labeled with institution, protocol number, patient initials, patient registration number, and the date and time of draw. DNA extraction for genotyping will be performed according to commercially available DNA isolation kits, such as Puregene (Gentra Systems, Inc., Minneapolis, MN). Samples ideally should be collected prior to initiation of therapy; however, sample collections missed at the initiation of therapy still **can be collected at any time**, as genotype is not expected to change. Genotyping for the selected variants will be performed based on previously published methods for the variants of interest.

11.2.3 Serum studies

Blood samples will be collected prior to therapy on all patients in a 7-10 cc gold top tube. Blood in the serum collection tube should be allowed to clot for 60 minutes and then centrifuged to separate serum. Serum should be stored in 2mL cyrovial tubes (Nalgene Cat# 5000-0020) in 410uL aliquots. Samples should be labeled with institution, protocol number, patient initials, patient registration number, and the date and time of draw. Serum samples should be stored at -80°C to be shipped in batched samples on dry ice as specified in Section 11.5.

11.2.4 Peripheral Blood RNA studies

The collection of high quality RNA is critical to the successful completion of gene expression profiling studies using peripheral blood. We therefore will employ new RNA isolation product called PaxGene (PreAnalytiX, BD/Qiagen). This technology uses a proprietary solution that immediately stabilizes blood cell RNA as the blood is being drawn thus eliminating the possibility of gene expression changes occurring *ex vivo*. Four PaxGene tubes will be drawn per

patient (2.5 cc blood per tube, 10 cc total). Because the PaxGene system uses the patented Vacutainer® format for blood drawing no special equipment is needed other than the PaxGene tube themselves. Following the blood draw the tubes are shipped overnight at ambient temperature and stored at -80°C until RNA extraction (See Section 12.5, **please note these samples are shipped directly to the Oklahoma Medical Research Foundation**). At -80°C the RNA is stable indefinitely.

11.2.5 Sample labeling

For the protection of patients' rights and privacy, all tissue and blood samples and clinical information before banking will be coded and labeled with a unique PIN code (Processing Identification Number) by the tissue bank staff. The basis of this code for invasive cancers will be: Letter indicating the institution (C) followed by a four-digit number, followed by letters and numbers if subsampling is performed. For example: C0001-AF1 would be the first sample taken, reflecting tumor tissue, frozen sample 1 (subsampling will occur in multicentric cases). For small specimens with dysplasia or in situ cases, only frozen materials will be obtained. The OCT blocks will carry only the PIN numbers. This ensures that no individual external to the study will be able to link any sample or information to a particular patient. Archival formalin fixed samples embedded in paraffin will retain their pathology designations, as they will initially be placed into the pathology files. When archival blocks are retrieved for validation studies, a tape label with the PIN number will be placed on the non-cutting face of the block. Whenever those fixed tissues are cut or processed (such as for the tissue arrays) only the unique PIN number will be used to label the generated materials. Pathology reports will be collected and independently stored in locked file cabinets. Each will have its unique PIN number. Any computer entries or pathology reviews that are conducted will be coded by the PIN number only. All personnel with access to the databases will also be required to use a password.

While it is preferred that all correlative samples defined in section 11.2 are collected, this portion of the study is optional. If correlative sample collection is omitted, a small portion of the funds allotted for each patient enrolled on the study will be withheld. Please see subcontract for details.

11.3 Microarray Methodology

The tissues will be sectioned at 7 um in a cryostat, mounted on uncoated glass slides, and immediately stored at –80°C. Slides containing frozen sections will be immediately fixed in 70% ethanol for 30 seconds, stained with H&E, followed by 5 second dehydration steps in 70, 95, and 100% ethanol and a final dehydration step in xylene. Once air-dried, the sections will be laser microdissected with the LCM facility within the Department of Pathology. Samples are only used that are estimated to be >98% pure as determined by microscopic visualization of the captured cells. No experiments will be performed on the snap frozen portion of the tissue until a definitive diagnosis has been rendered on the other portion of the specimen.

Approximately 10,000 cells (8-12 LCM caps), are required to consistently yield an adequate amount of RNA. Linear RNA amplification using the Wang protocol is then performed to obtain sufficient working material to perform the microarray hybridizations. Briefly, a First Strand cDNA synthesis using an oligo dT(15)-T7 primer is used along with the Template Switch (TS)

oligo primer. Second strand synthesis using dNTPs and Advantage Polymerase (Clontech) is performed. Following a clean up step, in vitro transcription is performed using the Ambion T7 Megascript Kit. The aRNA is then purified using TRIzol reagent. A second round of amplification is then performed and this product is subsequently labeled for hybridization. Affymetrix glass slides containing 22,000 known human genes will be used for these experiments, utilizing the UC Functional Genomics Facility.

Subsequent to obtaining expression profiles the expression of potential OPMs of interest will be initially validated using RTQ-PCR. Briefly, the Platinum Quantitative PCR SuperMix-UDG (Life technologies) will be used in a two-step RT-PCR procedure following cDNA synthesis with the SuperScript First-Strand Synthesis System for RTQ-PCR (Life Technologies). RNA that was isolated from the LCM is reverse-transcribed using Random Hexamers, 10 mM dNTP mix and 50 units SuperScript II at 42ºC for 50 min. The resulting 1st strand-cDNA is used as template for the RTQ-PCR analysis. The 5` nuclease activity of Taq DNA Polymerase generates a real-time quantitative DNA assay in the presence of oligonucleotide hybridization probes with 5` fluorescent dye and 3` quencher. Relative standard curve representing five 10-fold dilutions of stock cDNA (1000 pg-0.1 pg) are always performed. The sequences of the selected gene are confirmed using National Center for Biotechnology Information (NCBI) GenBank and Unigene databases and appropriate clones are selected for the linear regression analysis. The primers and probe are designed with the help of the software Oligo Analyzer 2.5 available online. The specificity of the primers and probe sequences are confirmed by the NCBI blast module and by gel analysis of the amplicons generated by PCR. The iCycler iQ Multi-color Real Time PCR Detecting System (BioRad) is used to generate the gene expression level.

11.4 Blood Draw and Shipping Instructions For RNA Analysis

If you have any questions, please call the University of Minnesota toll-free 1-800-515-8787

1. Use a butterfly/extension tubing collection set for the draw

2. Using the tubes provided, draw FOUR PAXgene (orange top) tubes. Hold the tube vertically, below the participant's arm, during the blood collection. Allow at least 10 seconds/tube for a complete draw. IMPORTANT: INVERT EACH PAXgene TUBE 8-10 TIMES TO PROPERLY MIX PRESERVATIVE WITH CELLS.

3. Do not spin, separate, or refrigerate the tubes.

4. Wrap the vacutainers in the bubble wrap, fastening with a rubber band.

5. Place the wrapped vacutainers in the **clear** Biohazard bag with the thin white absorbent square (the square should already be inside the clear bag).

6. Follow the preprinted "To Close" instructions on the **clear** Biohazard bag to seal the bag.

7. Place the sealed **clear** Biohazard bag inside the **white** Tyvek envelope and remove tape to seal this envelope.

8. Put the white Tyvek envelope inside cardboard box.

9. Put cardboard box into the plastic FedEx Diagnostic Specimen envelope.

10. **BEFORE** you send the package, email Dr. Patrick Gaffney at gaffneyp@lupus.omrf.org to let them know:

    - Date that the package is being shipped
    - FedEx 12 digit tracking number (located on the upper portion of the air bill).

11. **Ship the specimens the day of collection.** Call **FedEx (1-800-GO-FEDEX)** to schedule pickup. Any information that you may need will be on the FedEx air bill. Do not put the specimen in a FedEx drop box.

12. Address the FedEx Airbill to:

    DeCIDE Protocol RNA Study
    Oklahoma Medical Research Foundation
    ATTN Patrick Gaffney
    755 Research Parkway, Suite 466
    Oklahoma City, OK 73104

11.5 Shipping Instructions for all other samples (Tissue, serum, Genotyping studies)

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

Dr. Mark Lingen (773-702-5548), email: MLINGEN@UCHOSPITALS.EDU)

University of Chicago
FMI Dock/Lab Supply
5830 S. Ellis Ave
Room G-02
Chicago, IL 60637

Attn: Leslie Martin (773-834-9814, email: LMARTIN@BSD.UCHICAGO.EDU)

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

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

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

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

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

12 STATISTICAL CONSIDERATIONS

12.1 Data Collection and Reporting

Data will be collected onto case report forms and entered into a database that will be maintained by Dr. Cohen and his research staff. This system provides secure, password protected online forms for demographic, clinical, toxicity, and response data along with data quality monitoring capabilities.

12.2 Primary Endpoint and Power Considerations

Patients will be randomized to the two treatment arms using the method of permuted blocks, stratified by clinical site. Overall survival, i.e., the time from randomization to death from any cause, will be the primary endpoint of the study. Survival rates will be estimated by the Kaplan-Meier[46] method and compared between the two groups using the logrank test[47]. All patients randomized on study will be included in the analysis (i.e. intent to treat analysis). As stated in the introduction, in previous trials conducted in the Chicago Oral Cancer Center Network of FHX without induction chemotherapy, the three-year survival rate among patients with stage N_2 or N_3 disease was 54%. This rate improved to 70% when induction chemotherapy was added. Survival rates from other reported studies have been similar although not quite as high. Assuming a true three-year survival rate of 50% in the CRT arm and 65% in the induction plus CRT, which corresponds to a hazard ratio of approximately 1.6 (under exponential survival), a sample size of 400 patients (200 per treatment arm) will provide 88% statistical power[48]. This

assumes a 2.5-year recruitment period, an accrual rate of 10 patients per month during the first 20 months and 20 patients per month during the last 10 months, and a subsequent 2.5-year follow-up period, for total study duration of five years. It also allows for a small dropout rate (1.7% per year) in each treatment arm. Confidence intervals for the median survival time will be determined using the method of Brookmeyer and Crowley[49] and Cox[50] proportional hazards regression models will be fit to assess and adjust for the effects of covariates.

12.3 Secondary Endpoints and Analyses

Distant failure-free survival (time to distant failure or death from any cause) and progression-free survival (time to local-regional/distant failure or death from any cause) will be secondary endpoints and will be analyzed in a manner similar to that described above. For each of the time-to-event analyses, it is known that the logrank test provides maximum power against proportional hazards alternatives. The proportional hazards assumption will therefore be checked graphically using martingale residuals[51] and if there is evidence of lack of fit an alternative analysis, based on comparison of the restricted means at four years[52, 53] will be performed.

Since a fair number of patients in this trial may die from causes other than head and neck cancer, a competing risks analysis will also be conducted[54-56]. Deaths will be reviewed and the cause of death assigned as head and neck cancer, other cancer, or other non-cancer. These categories will be treated as competing risks, and two techniques for analyzing the data will then be utilized. Log-rank tests will be used to compare the identifiable cause-specific hazard rates between treatment groups for the specific causes of death, and cumulative incidence functions will be used to estimate cumulative probabilities for deaths due to head and neck cancer and other causes[57]. Statistical tests to directly compare cumulative incidence curves will also be performed[58, 59].

Quality of life scores in the two groups will be analyzed using repeated measures analysis of variance and/or random effects models to compare the changes in scores over time. For discrete QOL outcomes, generalized estimating equation (GEE) models will be fit[60]. One anticipated problem in all of these analyses is that of missing data, since the mechanism leading to the missing data may well not be ignorable. For example, patients may not complete the QOL questionnaire if they are feeling poorly or have experienced treatment toxicities. We will attempt to assess the reasons for missing data and will perform Diggle's test[61] for random dropouts. Another source of bias is informative censoring due to early deaths[62], i.e., patients with steeper rates of decline in their QOL may be more likely to fail early. To address this problem we will employ the conditional linear model described in Wu and Bailey as well as the mixed effects model for longitudinal and time-to-event data proposed by Schlucter[63]. Schlucter's approach jointly models the rate of change of a repeated measurement and the (log) survival time in order to obtain estimates that are unbiased and efficient. For other types of missing data we will use the multiple imputation technique of Rubin[64], although this method assumes that the data are missing at random.

The pattern of disease failure (local-regional vs. distant) and response rates (CR or PR) among patients with measurable disease (we expect that 90% of patients will have measurable disease), as well as adverse event rates in the two groups, will be compared using chi-square or Fisher exact tests as appropriate. For toxicity endpoints, the study has 93% statistical power to detect differences of 10% in toxicity rates for infrequent events (e.g., 5% vs. 15%), a little over 80% power to detect differences of 10% for more frequently occurring events (e.g.10% vs. 20%), and 87% power to detect a difference of 15% for more common side effects (e.g. 30% vs. 45%).

Results of genomic microarray processing described in section 12.3 will be used to predict patients at high risk of local failure, distant failure, and mortality. Multivariable logistic and Cox regression analysis will be applied to determine the association of the gene expression pattern and clinical parameters including age, gender, tumor stage, nodal stage, and performance status with local failure, time to distant failure, and overall survival.

Patients with disease of the nasopharynx will comprise a small (approximately 5%) but important subgroup, as these individuals are at higher risk of distant recurrence. We will therefore perform a subset analysis of these patients. Specifically, we will compare total survival and distant failure-free survival between the two treatment arms, using a logrank test.

12.4 Data and Safety Monitoring Plan

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

An independent Data and Safety Monitoring Board (DSMB) composed of a medical oncologist, radiation oncologist, and a biostatistician will be established to review the safety and efficacy data at periodic intervals. Reports will be generated and provided to the DSMB by the UC statisticians. An O'Brien-Fleming[65] type monitoring bound will be used as a guideline for early stopping. Four interim and one final analysis will be performed and submitted to the DSMB for review at approximately equal "information" times. These times will be based on the primary endpoint of overall survival, for which a total of 175 deaths are expected assuming a 50% three-year survival rate in the CRT group and a 65% rate in the induction plus CRT arm (see power calculation in 12.2 above). Thus, formal interim analyses will be conducted after 35, 70, 105, and 140 deaths have occurred. To preserve the overall type I error rate at the nominal 5% level, the O'Brien-Fleming boundary requires z-values of 4.55, 3.22, 2.63, and 2.28, respectively, for early stopping, and the critical z-value for the final analysis is set at 2.04. (Should the DSMB prefer, we would use the Lan-DeMets error rate spending function $\alpha(t) = 2\left\{1 - \Phi\left(z_{\alpha/2} / \sqrt{t}\right)\right\}$, where t denotes information time, which corresponds closely to the O'Brien-Fleming boundary but provides greater flexibility for scheduling reviews.)

These bounds will only be used as guidelines, however, as any decision regarding early stopping must take into consideration other issues such as toxicity, secondary endpoints, etc. These interim meetings will be held at least annually either in person or by conference call and the DSMB will make recommendations regarding continuation of the study.

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APPENDIX I: AJCC Head and Neck Nodal Staging

Oral Cavity

Definition of TNM

Primary Tumor (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor 2 cm or less in greatest dimension
T2	Tumor more than 2 cm but not more than 4 cm in greatest dimension
T3	Tumor more than 4 cm in greatest dimension
T4 (lip)	Tumor invades through cortical bone, inferior alveolar nerve, floor of mouth, or skin of face, i.e., chin or nose
T4a (oral cavity)	Tumor invades adjacent structures (e.g., through cortical bone, into deep (extrinsic) muscle of tongue (genioglossus, hyoglossus, palatoglossus, and styloglossus), maxillary sinus, skin of face)
T4b	Tumor invades masticator space, pterygoid plates, or skull base and/or encases internal carotid artery

Note: Superficial erosion alone of bone/tooth socket by gingival primary is not sufficient to classify a tumor as T4.

Regional Lymph Nodes (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
N2	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension; or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimensions; or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N2a	Metastasis in single ipsilateral lymph node more than 3 cm but not more than 6 cm in greatest dimension
N2b	Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
N2c	Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N3	Metastasis in a lymph node more than 6 cm in greatest dimension

Distant Metastasis (M)

MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Stage Grouping

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage IVA	T4a	N0	M0
	T4a	N1	M0
	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	T4a	N2	M0
Stage IVB	Any T	N3	M0
	T4b	Any N	M0
Stage IVC	Any T	Any N	M1

Pharynx

Definition of TNM

Primary Tumor (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	carcinoma in situ

Nasopharynx

T1	Tumor confined to the nasopharynx
T2	Tumor extends to soft tissues
	T2a Tumor extends to the oropharynx and/or nasal cavity without parapharyngeal extension*
	T2b Any tumor with parapharyngeal extension*
T3	Tumor involves bony structures and/or paranasal sinuses
T4	Tumor with intracranial extension and/or involvement of cranial nerves, infratemporal fossa, hypopharynx, orbit, or masticator space

*Note: Parapharyngeal extension denotes posterolateral infiltration of tumor beyond the pharyngobasilar fascia

Oropharynx

T1	Tumor 2 cm or less in greatest dimension
T2	Tumor more than 2 cm but not more than 4 cm in greatest dimension
T3	Tumor more than 4 cm in greatest dimension
T4a	Tumor invades the larynx, deep/extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible
T4b	Tumor invades lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, or skull base of encases carotid artery

Hypopharynx

T1	Tumor limited to one subsite of hypopharynx and 2 cm or less in greatest dimension
T2	Tumor invades more than one subsite of hypopharynx or an adjacent site, or measures more than 2 cm but not more than 4 cm in greatest diameter without fixation of hemilarynx
T3	Tumor more than 4 cm in greatest dimension or with fixation of hemilarynx
T4a	Tumor invades thyroid/cricoid cartilage, hyoid bone, thyroid gland, esophagus, or central compartment soft tissue*
T4b	Tumor invades prevertebral fascia, encases carotid artery, or involves mediastinal structures

*Note: Central compartment soft tissue includes prelaryngeal strap muscles and subcutaneous fat.

Regional Lymph Nodes (N)

Nasopharynx

The distribution and the prognostic impact of regional lymph node spread from nasopharynx cancer, particularly of the undifferentiated type, are different from those of other head and neck mucosal cancers and justify the use of a different N classification scheme.

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Unilateral metastasis in lymph node(s), 6 cm or less in greatest dimension, above the supraclavicular fossa*
N2	Bilateral metastasis in lymph node(s), 6 cm or less in greatest dimension, above the supraclavicular fossa*
N3	Metastasis in a lymph node(s)* > 6 cm and/or to supraclavicular fossa
	N3a Greater than 6 cm in dimension
	N3b Extension to the supraclavicular fossa**

*Note: Midline nodes are considered ipsilateral nodes

**Supraclavicular zone or fossa is relevant to the staging of nasopharyngeal carcinoma and is the triangular region originally described by Ho. It is defined by three points: (1) the superior margin

of the sternal end of the clavicle, (2) the superior margin of the lateral end of the clavicle, (3) the point where the neck meets the shoulder. Note that this would include caudal portions of Levels IV and V. All cases with lymph nodes (whole or part) in the fossa are considered N3b.

Oropharynx and Hypopharynx

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
N2	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension, or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension, or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N2a	Metastasis in a single ipsilateral lymph node more than 3 cm but not more than 6 cm in greatest dimension
N2b	Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
N2c	Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N3	Metastasis in a lymph node more than 6 cm in greatest dimension

Distant Metastasis (M)

MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Stage Grouping: Nasopharynx

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage IIA	T2a	N0	M0
Stage IIIB	T1	N1	M0
	T2	N1	M0
	T2a	N1	M0
	T2b	N0	M0
	T2b	N1	M0
Stage III	T1	N2	M0
	T2a	N2	M0
	T2b	N2	M0
	T2b	N2	M0
	T3	N0	M0
	T3	N1	M0
	T3	N2	M0
Stage IVA	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
Stage IVB	Any T	N3	M0
Stage IVC	Any T	Any N	M1

Stage Grouping: Oropharynx, Hypopharynx

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage IVA	T4a	N0	M0
	T4a	N1	M0
	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	T4a	N2	M0
Stage IVB	T4b	Any N	M0
	Any T	N3	M0
Stage IVC	Any T	Any N	M1

Larynx

Definition of TNM

Primary Tumor (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ

Supraglottis

T1	Tumor limited to one subsite of supraglottis with normal vocal cord mobility
T2	Tumor invades mucosa of more than one adjacent subsite of supraglottis or glottis or region outside the supraglottis (e.g., mucosa of base of tongue, vallecula, medial wall of pyriform sinus) without fixation of the larynx
T3	Tumor limited to larynx with vocal cord fixation and/or invades glottic space, and/or minor thyroid cartilage erosion (e.g., inner cortex)
T4a	Tumor invades through the thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of neck including deepextrinsic muscle of the tongue, strap muscles, thyroid, or esophagus)
T4b	Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures

Glottis

T1	Tumor limited to the vocal cord(s) (may involve anterior or posterior commissure) with normal mobility
T1a	Tumor limited to one vocal cord
T1b	Tumor involves both vocal cords
T2	Tumor extends to supraglottis and/or subglottis, and/or with impaired vocal cord mobility
T3	Tumor limited to the larynx with vocal cord fixation and/or invades paraglottic space, and or minor thyroid cartilage erosion (e.g., inner cortex)
T4a	Tumor invades through the thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus)
T4b	Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures

Version: 8/11/04, 9/10/04, 11/04/04, 12/13/04, 4/25/05, 7/12/05, 2/6/06, 2/16/06, 11/3/06, 5/30/07

Subglottis

T1	Tumor limited to the subglottis
T2	Tumor extends to vocal cord(s) with normal or impaired mobility
T3	Tumor limited to larynx with vocal cord fixation
T4a	Tumor invades cricoid or thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of neck including deep extrinsic muscles of the tongue, strap muscles, thyroid, or esophagus)
T4b	Tumor invades prevertebral space, encases carotid artery, or invadesmediastinal structures

Regional Lymph Nodes (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
N2	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension, or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
N2a	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension
N2b	Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
N2c	Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N3	Metastasis in a lymph node, more than 6 cm in greatest dimension

Distant Metastasis (M)

MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Stage Grouping

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage IVA	T4a	N0	M0
	T4a	N1	M0
	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	T4a	N2	M0
Stage IVB	T4b	Any N	M0
	Any T	N3	M0
Stage IVC	Any T	Any N	M1

Nasal Cavity and Paranasal Sinuses

Definition of TNM

Primary Tumor (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ

Maxillary Sinus

T1	Tumor limited to maxillary sinus mucosa with no erosion or destruction of bone
T2	Tumor causing bone erosion or destruction including extension into the hard palate and/or middle nasal meatus, except extension to posterior wall of maxillary sinus and pterygoid plates
T3	Tumor invades any of the following: bone of the posterior wall of maxillary sinus, subcutaneous tissues, floor or medial wall of orbit, pterygoid fossa, ethmoid sinuses
T4a	Tumor invades anterior orbital contents, skin of cheek, pterygoid plates, infratemporal fossa, cribriform plate, sphenoid or frontal sinuses
T4b	Tumor invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than maxillary division of trigeminal nerve (V_2), nasopharynx, or clivus

Nasal Cavity and Ethmoid Sinus

T1	Tumor restricted to any one subsite, with or without bony invasion
T2	Tumor invading two subsites in a single region or extending to involve an adjacent region within the nasoethmoidal complex, with or without bony invasion
T3	Tumor extends to invade the medial wall or floor of the orbit, maxillary sinus, palate, or cribriform plate
T4a	Tumor invades any of the following: anterior orbital contents, skin of nose or cheek, minimal extension to anterior cranial fossa, pterygoid plates, sphenoid or frontal sinuses
T4b	Tumor invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than (V_2), nasopharyngeal, or clivus

Regional Lymph Nodes (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
N2	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension, or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
N2a	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6b cm in greatest dimension
N2b	Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
N2c	Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N3	Metastasis in a lymph node, more than 6 cm in greatest dimension

Distant Metastasis (M)

MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Stage Grouping

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage IVA	T4a	N0	M0
	T4a	N1	M0
	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	T4a	N2	M0
Stage IVB	T4b	Any N	M0
	Any T	N3	M0
Stage IVC	Any T	Any N	M1

APPENDIX II: TAXOTERE HYPERSENSITIVITY REACTIONS

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

MANAGEMENT OF ACUTE HYPERSENSITIVITY

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

APPENDIX III

Aventis Pharmaceuticals
Global Pharmacovigilance and Epidemiology
200 Crossing Boulevard
P.O. Box 6890
Mailstop BX4 – 412-i
Bridgewater, NJ 08807
Fax: 908-231-4827

Aventis Pharmaceuticals, Inc

Fax GIA SAE REPORT

To: Global Pharmacovigilance and Epidemiology

Fax: 908-231-4827	
Date:	Pages:
From:	Phone:

GIA#:	**15043**
Study Title:	**A Phase III Randomized Trial of Docetaxel Based Induction Chemotherapy in Patients with N2/N3 Locally Advanced Head and Neck Cancer**
PI Name: Insert PI name	**Ezra Cohen, MD;** University of Chicago

Causality:	**All serious, related adverse events will be reported and documented on Form FDA 3500 A (MedWatch Form) and forwarded directly to Aventis Pharmaceuticals. This includes serious, related, labeled (expected) and serious, related, unlabeled (unexpected) adverse experiences.** **For Comparator Drugs / Secondary Suspects (Concomitant Medications), all serious adverse experiences will be forwarded to the product manufacturer.**

Check one:	
	<u>Unrelated</u>: The adverse event is clearly <u>NOT</u> related.
	<u>Unlikely to be related</u>: The adverse event is doubtfully related.
	<u>Possibly related</u>: The adverse event may be related.
	<u>Probably related</u>: The adverse event is likely related.
	<u>Definitely related</u>: The adverse event is clearly related.

Version: 8/11/04, 9/10/04, 11/04/04, 12/13/04, 4/25/05, 7/12/05, 2/6/06, 2/16/06, 11/3/06, 5/30/07

Appendix IV: Sample Transmission Form and Instructions

Protocol

The University of Chicago

Tissue and Blood Sample Collection Form

Clinician/Research Nurse: Please Fill Out

Tissue Samples

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

Patient Protocol ID #:_____ Date Tissue Obtained: _____

Date of Birth: _____ Attending Physician: _____

Site of Biopsy: _____ Institution: _____

Date consent was signed: _____ Diagnosis:_____

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

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

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

Blood Samples*

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

*Please label tubes as serum.

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

Researcher: Please Fill Out

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

Name of Data Manager informed: _____ Date Informed:_____

Location in –80C freezer **-** _____

Approximate size of tissue: _____

Notes:

Version: 8/11/04, 9/10/04, 11/04/04, 12/13/04, 4/25/05, 7/12/05, 2/6/06, 2/16/06, 11/3/06, 5/30/07

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

SHIPPING DIRECTIONS

All shipments must contain a completed Sample Identification form.

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

Leslie Martin: lmartin@.bsd.uchicago.edu

Tissue Samples should be at least an 18-gauge core (preferably 14-gauge) and at least 1 inch in length. These samples need to be shipped on **dry ice**; may be batched at institution and shipped with serum samples to the below address:

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

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

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

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

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

Version: 8/11/04, 9/10/04, 11/04/04, 12/13/04, 4/25/05, 7/12/05, 2/6/06, 2/16/06, 11/3/06, 5/30/07

Appendix V: PAXGENE Sample Transmission Form and Instructions

OMRF

Oklahoma Medical Research Foundation

Protocol

PAXGENE Sample Collection Form

Clinician/Research Nurse: Please Fill Out

Tissue Samples

Patient Protocol ID #:_____

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

Blood Sample

	date drawn	time	date shipped	Shipping instructions
4 PaxGene Tubes				Ship overnight at room temperature on the day sample was drawn

Oklahoma Medical Research Foundation Use Only

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

Notes:

Version: 8/11/04, 9/10/04, 11/04/04, 12/13/04, 4/25/05, 7/12/05, 2/6/06, 2/16/06, 11/3/06, 5/30/07

SHIPPING DIRECTIONS

All shipments must contain a completed Sample Transmission form.

Please ship PaxGene tubes at room temperature overnight the day the sample was drawn.

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

Oklahoma Medical Research Foundation
ATTN Patrick Gaffney
755 Research Parkway, Suite 466
Oklahoma City, OK 73104
gaffneyp@lupus.omrf.org

Version: 8/11/04, 9/10/04, 11/04/04, 12/13/04, 4/25/05, 7/12/05, 2/6/06, 2/16/06, 11/3/06, 5/30/07

Appendix VI: QA Documentation Checklist

QARC
QUALITY ASSURANCE REVIEW CENTER

DeCIDE Trial QA Documentation Checklist

Version Date: May 13, 2005

Patient Initials: _____ _____
Patient ID

* **Date patient started radiotherapy**: _____

Interventional Review: *To be submitted within three days of starting radiotherapy. If planning of later phases of treatment is* deferred, *the aggregate plan must be submitted no later than the fifth week of treatment.*

**Color documentation must be submitted in color.*

IMRT/3D Planning Treatment

_____ **Copies of the Planning CT and/or MR slices (pre-RT) covering all gross target volume (GTV) at 1cm separation, showing the GTV and target volumes on each slice.**

For patients on Arm A, please also submit a copy of the diagnostic (pre-study) imaging.

_____ **Copies of simulation films or DRRs (digitally reconstructed radiograph) for each field showing lateral projection of all gross disease. If electron field films are not available, patient photos with these fields clearly indicated must be provided.**

_____ **Copy of verification (portal) films or hard copy of real time portal images for each treatment field**

_____ **In lieu of submitting sim films/DRRs and portals for each field treated, an orthogonal set of anterior/ posterior and lateral films for isocenter localization for each group of concurrently treated beams should be submitted. This should include both sim films/DRRs and portal films/ hard copy portal images.**

_____ **RT-1 or IMRT Dosimetry Summary Form & the Disease Mapping Form (available on www.qarc.org)**

_____ **Photographs of patient in treatment position with fields marked and visible**

_____ **Copies of worksheets/ printouts used for calculations of monitor settings to give the prescribed dose & doses to all normal structures**

_____ **Color Isodose distributions for all treatment phases and composite (summed plan) with target volumes & prescription point clearly shown in axial, sagittal and coronal planes. Include axial slices through the central axis of the field, through the plane of maximum tumor bulk, and in superior and inferior planes of all target volumes. Composite plan should be in absolute dose.**

_____ **DVH (dose volume histogram) for the entire treatment course for PTV1, PTV 2, PTV3, GTV & spinal cord**

_____ **Prescription sheet for entire treatment course**

_____ **If IMRT is used, a DVH shall be submitted for "unspecified tissue" (tissue contained within the skin but not otherwise identified by containment within any other structure)**

_____ **BEV (Beams Eye View) of portals, showing collimator, beam aperture, target volume and critical structures**

_____ **REV (Rooms Eye View)**

Final Data: ***To be submitted within one month of completing radiotherapy***

_____ **RT-2 Form (available on www.qarc.org)**

_____ **Copy of patient's daily radiotherapy record**

_____ **If changes were made subsequent to the initial review, please submit all data reflecting changes: Diagnostic and Treatment Planning imaging, simulation films/DRRs, verification (portal) films or portal images, RT-1 or IMRT Dosimetry Summary Form, Photographs of patient in treatment position with fields marked and visible, copies of worksheets/printouts used for calculations of monitor settings, color isodose distributions, Dose Volume Histograms, Prescription sheet for entire treatment course, BEVs, REVs, orthogonal films (sims/DRRs and portals).**

Continued on pg 2

Version: 8/11/04, 9/10/04, 11/04/04, 12/13/04, 4/25/05, 7/12/05, 2/6/06, 2/16/06, 11/3/06, 5/30/07

QARC
QUALITY ASSURANCE REVIEW CENTER

DeCIDE Trial QA Documentation Checklist

Version Date: May 13, 2005

*** Please be sure to include this information. Without it, we cannot verify receipt of data:**

Person completing this form: **Print Name:** _____

Signature: _____

Email we should use to return this form: _____

Date: _____

***Note: If sending patient data on a CD, only send one patient per CD.**

Diagnostic Imaging Scans
CT and MRI scans in DICOM format files can be submitted to QARC on CD. Each CD should include only one patient's studies, but, multiple studies for the same patient may be on the same CD. Please be sure to send a copy of the Diagnostic Imaging report for each study submitted.

RT Data
Currently, we can not accept DicomRT or RTOG Data Exchange format files. Data documenting the treatment plan can be saved as screen captures (.jpg or .bmp) from the treatment planning system and burned to a CD.

Screenshots of the DRR's, BEV's, DVH's and the isodose distributions in all planes can be saved as image files and put into a PowerPoint presentation documenting all phases of treatment.

Please submit data to:

QARC
272 West Exchange Street, Suite 101
Providence, RI 02903-1025 USA
Phone: 401-454-4301
Fax: 401-454-4683
Email: KBertsch@QARC.org