TITLE: A Phase 2 Study of Sequential and concurrent chemoradiation for patients with advanced nasopharyngeal carcinoma (NPC)

NCT00896181

Coordinating Center:
Stanford Cancer Institute
Stanford, CA 94305

Principal Investigator:
A. Dimitrios Colevas, M.D.
Associate Professor of Medicine (Oncology)
Stanford University Medical Center
875 Blake Wilbur Drive
Stanford, CA 94305-5826
(650) 724-9707
FAX (650) 498-5800
colevas@stanford.edu

Co- Principal Investigator:
Quynh-Thu Le, MD
Professor
Clinical Research Director
Department of Radiation Oncology
Stanford University
Tel xxx-xxx-xxxx
Fax xxx-xxx-xxxx

Co- Principal Investigator:
Wendy Hara, MD
Clinical Assistant Professor
Department of Radiation Oncology
Stanford University

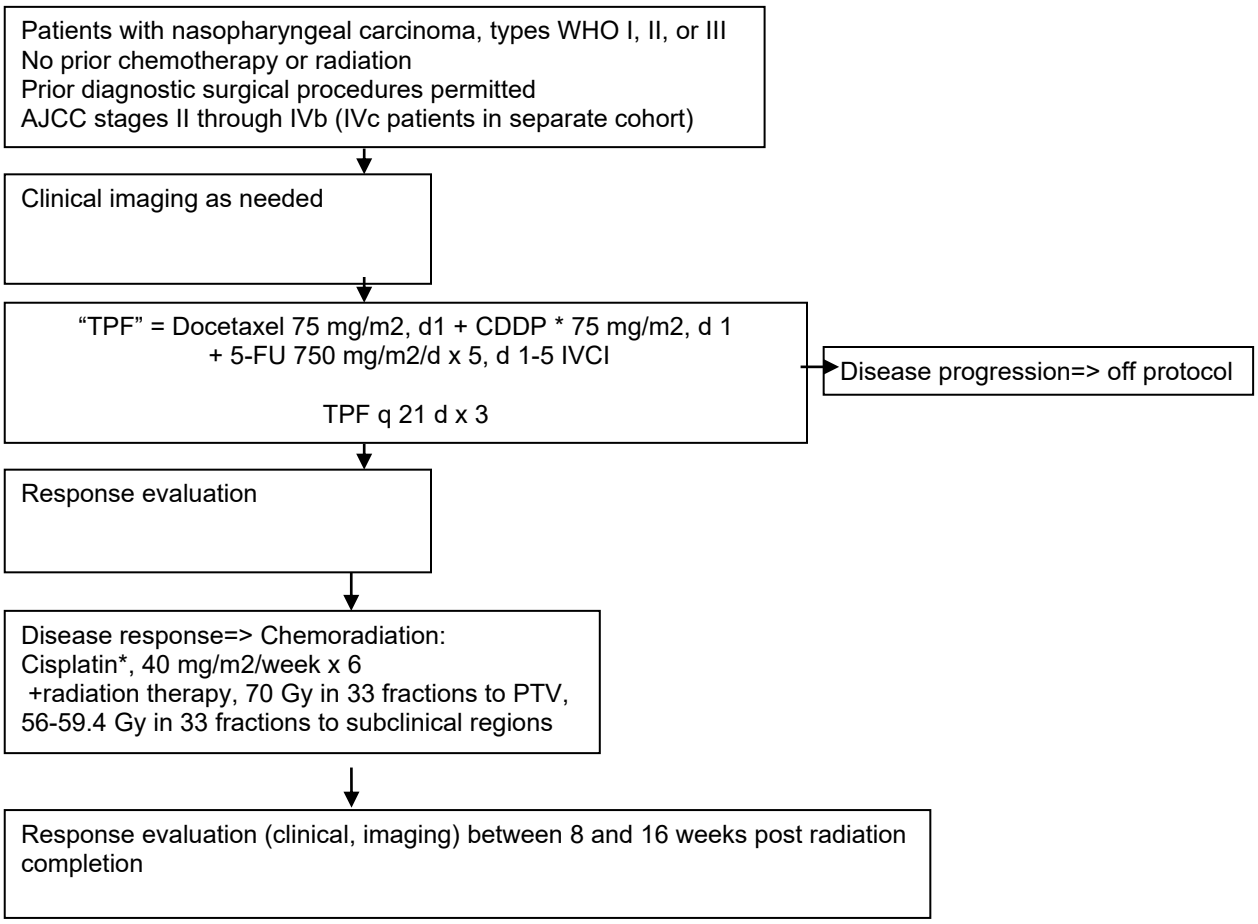
Statistician:
Alex McMillan PhD
Sr Res Scientist-Basic Ls *in* Health Research and Policy – Biostatistics
Redwood Bldg, Stanford, California 94305

Study Coordinators
Mary Anderson May and Stefania Chirita
800 Welch Road FC3C62

TITLE: A Phase 2 Study of Sequential and concurrent chemoradiation for patients with advanced nasopharyngeal carcinoma (NPC)

TITLE: A Phase 2 Study of Sequential and concurrent chemoradiation for patients with advanced nasopharyngeal carcinoma (NPC)

SCHEMA



* Under certain circumstances, carboplatin AUC 6 may be substituted for CDDP in TPF and carboplatin AUC 1.5 may be substituted for CDDP during radiation. See the protocol for specific circumstances under which this is permitted.

TITLE: A Phase 2 Study of Sequential and concurrent chemoradiation for patients with advanced nasopharyngeal carcinoma (NPC)

TABLE OF CONTENTS

1. OBJECTIVES

1.1 **Primary Objective: To establish the progression free survival rate at 2 years, using RECIST criteria, to TPF followed by chemoradiotherapy of locoregionally advanced nasopharyngeal carcinoma**

1.2 **Secondary Objectives: To evaluate complete response rates, safety and feasibility of TFP=> chemoxrt in patients with NPC**

2. BACKGROUND

Background for the rationale of TPF=> chemoradiation

2.1 Nasopharyngeal cancer

Nasopharyngeal cancer (NPC) is a significant problem worldwide. The annual incidence rate worldwide is 1.8/100,000 and the rate climbs to as high as 50/100,000 in Southern China .[1]

2.2 CHEMORADIATION VERSUS RADIATION

Historically, nonmetastatic NPC has been treated with radiation alone. Because of the known chemosensitivity of NPC, a series of randomized controlled trials of chemoradiotherapy versus radiotherapy conducted in the 1990's and early 2000's demonstrated that in patients with advanced local or regional disease, the addition of chemotherapy to radiation was associated with a statistically significant and clinically meaningful survival advantage. [5 6, 7] A smaller subsequent trial suggested that even in the case of patients with advanced local disease but minimal nodal disease (T3-4, N0-1), patients had increased local control with the use of combined chemotherapy and accelerated fractionation radiation versus conventional radiation alone. [8] The table below is a summary of the RCT data supporting either an OS or LRC advantage of chemoradiation versus radiation:

From IJROBP Volume 66, Number 1, 2006 p 150 [8]:

Table 8. Literature reports on concurrent ± adjuvant chemoradiotherapy and/or accelerated radiotherapy for nasopharyngeal carcinoma

Author	Stage AJCC-5	Fractionation	Chemotherapy concurrent ± adjuvant	Time point (year)	Tumor control FFS (%)	PFS (%)	LR-FFR (%)	D-FFR (%)	OS (%)	Toxicity Acute (Crude %)	Toxicity Late (Actuarial %)
Phase III trials comparing concurrent chemoradiotherapy vs. radiotherapy alone											
Al-Sarraf (2, 15)	II-IVB	All CF	P + PF	5		58 vs. 29*			67 vs. 37*	76 vs. 50*	NR
Lin (17)	II-IVB	All CF	PF	5	72 vs. 53*		89 vs. 73* (L)	79 vs. 70†	72 vs. 54*	S	NR
Chan (18)	II-IVB	All CF	P	5	60 vs. 52		NS	NS	70 vs. 59†	S	NR
Kwong (19)	II-IVB	All CF	U ± PF/VBM	3	69 vs. 58		80 vs. 72	85 vs. 71*	87 vs. 77†	S	NR
Wee (16)	III-IVB	All CF	P + PF	3		72 vs. 53*	NR	87 vs. 70*§	80 vs. 65*	S	NR
NPC-9901 (3)	T1-4N2-3	All CF	P + PF	3	72 vs. 62*	70 vs. 61	92 vs. 82*	76 vs. 73	78 vs. 78	84 vs. 53*	28 vs. 13*
NPC-9902	T3-4N0-1	CF Arm	P + PF	3	74 vs. 70	73 vs. 68	81 vs. 85	89 vs. 81	87 vs. 83	82 vs. 55*	31 vs. 14
Phase III trials comparing accelerated fractionation vs. conventional fractionation											
Teo (20)	T1-4N0-2	AF	Nil	5	85 vs. 77		89 vs. 85 (L)	93 vs. 85	85 vs. 87	91 vs. 42*	49 vs. 23*‡
NPC-9902	T3-4N0-1	AF	Nil	3	63 vs. 70	63 vs. 68	78 vs. 85	77 vs. 81	73 vs. 83	69 vs. 55	22 vs. 14
Series treated by combined strategies of concurrent chemoradiotherapy and accelerated fractionation											
Lin (21)	II-IVB	HF	PF + PF	3	64		89 (L)	74	74	>61	
Wolden (23)	II-IVB	AF	P + PF	3		66	89 (L)	79	84	>84	
NPC-9902	T3-4N0-1	AF	P + PF	3	94	88	94	97	88	86	34

Abbreviation: FFS = failure-free survival (failure at any site); PFS = progression-free survival (failure or death); LR-FFR = locoregional failure-free rate; D-FFR = distant failure-free rate; OS = overall survival (death from any cause); L = local failure-free rate alone; CF = conventional fractionation; AF = accelerated fractionation; HF = hyperfractionation; P = cisplatin; F = 5-fluorouracil; UFT = uracil and tegafur; VBM = combination of vincristine, bleomycin and methotrexate; NR = not reported; NS = nonsignificant hazard ratio, but no data on actuarial rate; S = statistically significant, but no corresponding data on overall rate.

* Statistically significant ($p < 0.05$).

† Borderline significance ($p = 0.05$–0.08).

‡ Neurologic damages only.

§ 2-year incidence of freedom from distant failure as the first site of failure.

1.1. Radiation Oncology ● Biology ● Physics Volume 66, Number 1, 2006

The advantage to chemoradiation over radiation in the RCTs was distributed between both local and systemic effects. In the large RCT cited above, there was a substantial reduction in both locoregional recurrence and metastatic disease in the combined treatment arms versus radiation alone.

In all of the RCT, the chemotherapy combined cisplatin – based chemotherapy with XRT, with cisplatin dosing plans including 40 mg/m2 weekly to 100 mg/m2 every 3 weeks to 20mg/m2/d x 4 with concurrent 5FU infusion every 3 weeks. In the US intergroup study, an additional 3 cycles of cisplatin 80 mg/m2 plus 5FU 1000mg/m2/d x 4 days was planned, to be administered after radiation had been completed.

A common theme to all of these recipes is that in all cases cumulative dose of concurrent cisplatin exceeded 180mg/m2. However, in the US intergroup trial, where 300 mg/m2 (three 100 mg/m2 doses) was the intent, only 63% of the patients received three cycles of CDDP. In the Chan et al. trial in which CDDP was administered weekly to an anticipated total of 240 mg/m2, 95% of the patients were compliant with the plan. [9] Therefore, while the optimal concurrent CDDP dosing schedule has yet to be defined, it appears that weekly dosing is more tolerable and in many cases dosing beyond a cumulative dose of 200-240 mg/m2 is not feasible. Additionally, of the 3 RCT discussed here, only one, the US intergroup study, administered adjuvant PF. Only about half of the patients randomized to the adjuvant PF were able to receive 3 cycles, and a third of the patients randomized to that arm received no adjuvant treatment. Therefore, since all 3 RCTs showed an overall survival advantage for patients with advanced disease, it is not clear that adjuvant PF has benefit beyond concurrent chemoradiation, nor is it clear that administration of PF after chemoradiation is feasible.

2.3 Adjuvant versus neoadjuvant (or induction) chemotherapy

The rationale behind administration of adjuvant PF in the intergroup trial was that the additional chemotherapy might reduce the number of distant relapses and therefore offer benefit beyond the concurrent treatment. However, a comparison of the outcome of the US intergroup versus the Chan and Lin trials suggests that the reduction in the development of distant metastasis was approximately 30 to 50% in patients with advanced disease on all of these trials. Therefore the benefit of adjuvant PF on this basis is also questionable. Again, this may be because so few patients in the US intergroup study were able to receive meaningful doses of PF after chemoradiation.

Initial studies of induction chemotherapy added to radiation alone in NPC patients failed to show disease control or survival benefit. [10] Recent pooled analysis of cisplatin- based induction chemotherapy versus radiation alone in NPC patients demonstrated improvement in relapse free and disease specific survival, but did not show an overall survival advantage.[11] Subset analysis of these trials demonstrated a survival advantage of induction chemotherapy for patients with early stage, but not advanced stage disease. This subset analysis suggested that in all groups there was a numerical advantage to induction in terms of distant metastasis free survival in all groups, but because locoregional disease was the major contributor to relapse, it overshadowed any potential benefit to systemic control of disease. Therefore, with the development of better radiation techniques to control locoregional disease, we hypothesize that a more effective treatment of distant disease may translate into an OS advantage now that locoregional control rates have improved.

There are ongoing RCT designed to definitively answer the question concerning the possible benefit of the addition of PF induction chemotherapy to concurrent chemoradiation in patients with NPC. Lee et al. of the Hong Kong Nasopharyngeal Cancer Study Group are conducting a trial whose primary endpoint is a comparison of induction chemotherapy with Cisplatin + 5-Fluorouracil versus adjuvant chemotherapy with Cisplatin + 5-Fluororacil (PF-P vs P-PF) in the setting of concurrent chemoradiation as a backbone. This trial opened in September 2006 and is planning to enroll 798 patients with an estimated completion date of September 2013. See web site **ClinicalTrials.gov, Identifier:** NCT00379262. Feng et al. of the Taiwan National Health Research Institutes opened in 2003 a multicenter Phase III Trial Comparing Induction Mitomycin, Epirubicin, Cisplatin, Fluorouracil, and Leucovorin Chemotherapy Followed by Concurrent Chemoradiotherapy Versus Concurrent Chemoradiotherapy Alone in Stage IV Nasopharyngeal Carcinoma (NPC), based on 5 year OS of 70% and 5 year distant metastasis rate of 81% in a phase 2 trial. [12] See ClinicalTrials.gov identifier NCT00201396. This 480 patient trial is expected to be completed in 2013.

Therefore, the question of induction plus concurrent chemoradiation using CDDP based chemotherapy in patients with NPC, while still open, should be answered in the next 5 years with 2 large RCT, at least for the specific chemotherapy recipes discussed above

2.4 Carboplatin versus Cisplatin

Carboplatin is probably as efficacious as cisplatin in the treatment of NPC in the curative setting. Evidence for equivalence can be drawn be inference from other diseases and from one recently published robust direct comparison of CDDP and carboplatin in NPC, discussed below.

Multiple studies in NSCLC and ovarian cancer have demonstrated that despite the fact that cisplatin containing regimens often have been associated with higher response rates, carboplatin in almost every study is associated with the same survival and better tolerability. [13] [14-18]

A randomized controlled trial of patients with SCCHN compared weekly carboplatin (100 mg/m2/dose x 4) with daily low dose cisplatin (4mg/m2/dose, cumulative dose 64 mg/m2) , both concurrently administered with definitive radiation (65Gy). Both local control and overall survival were numerically superior in the carboplatin arm, but OS did not reach statistical significance because of the size of the trial, 119 patients. [19] Because many experts regard the dose of CDDP in this trial as inadequate, one can conclude that there is evidence that carboplatin XRT is associated with a better outcome than XRT and suboptimal CDDP dosing, but is silent on the question of standard CDDP dosing in this setting.

A recent study directly compared CDDP versus carboplatin in the curative setting in patients with NPC who were receiving concurrent definitive radiation. In this 206 patient study, the standard US intergroup concurrent plus adjuvant chemoradiation was compared to an identical radiation plan with carboplatin 100mg/m2 weekly instead of concurrent cisplatin, and carboplatin AUC5 instead of cisplatin in the adjuvant setting. [20] There was no difference in overall survival or disease free survival. Toxicity was markedly less in the carboplatin arm, and over twice as many patients in the carboplatin arm (62 versus 26%) completed all intended chemotherapy treatment.

2.5 TAXANES

Taxanes are among the most active anti- cancer agents available for squamous cell carcinoma of the head and neck, with single agent response rates of 40% or higher reported in patients with prior platinum exposure. [21, 22] Three recently reported RCT of the addition of a taxane to the " backbone" PF induction regimen as part of a curative chemoradiation plan have demonstrated that overall survival with TPF is superior to PF when used as induction chemotherapy followed by either radiation alone or chemoradiation in patients with squamous cell cancer of the head and neck. [23 24, 25] Paradoxically, the three drug combination (taxane, platinum, 5-FU) has been associated with a superior QOL than the two drug combination (platinum, 5-FU). This is probably because the dose of infusional 5-FU, which induces severe gastrointestinal toxicity, was reduced in all versions of the three drug regimen tested. These results let the FDA to recently (9/28/07) approve the use of docetaxel explicitly in combination with cisplatin and 5-fluorouracil for induction therapy of locally advanced squamous cell carcinoma of the head and neck (SCCHN) before patients undergo chemoradiotherapy and surgery. [26] Additionally, a recent meta- analysis of 5 RCT suggests that TPF was associated with a robust 20% two year survival improvement over PF in this setting. [27]

This strategy of using a taxane and cisplatin combination is beginning to be tested in NPC. The combination of docetaxel 75 mg/m2 plus cisplatin 75 mg/m2 achieved a response rate of 63% in patients with metastatic NPC [28]and when docetaxel has been combined with PF as induction chemotherapy for NPC patients in early phase 1 and 2 trials, response rates approaching 100% have been seen . [29-32]

2.6 Radiation and NPC

For many years, two-dimensional radiation therapy (2DRT) was considered the standard of care for patients with locally advanced NPC. Because 2DRT delivers substantial radiation doses to the parotid glands, permanent severe xerostomia is a common side effect. Radiation doses as low as 15 Gy can result in permanent dysfunction of the major salivary glands. [46, 47] The permanent xerostomia or oral dryness often results in dysphasia and poor speech function as well as predisposes the patients to fissures, ulcers, dental caries, infection, and in worst cases, osteoradionecrosis. [48 49].

In addition to the parotid glands, there are multiple critical normal tissues surrounding the nasopharynx, such as the optic structures, the temporal lobes and the brain stem, all of which are highly sensitive to radiation injury. The location of such structures precludes dose escalation with 2DRT. Therefore, despite the addition of chemotherapy, the local control rates for the more advanced T3/T4 tumors were typically in the range of 40-60% for 2DRT. [50, 51 52 38, 53] With the introduction of three- dimensional radiation therapy (3DRT) and more recently intensity modulated radiation therapy (IMRT), superior tumor coverage was achieved without exceeding the radiation tolerance to surrounding critical structures.[54-56] Several studies have also compared IMRT to 3DRT plans and demonstrated that IMRT consistently improves tumor target volume coverage while simultaneously significantly reducing radiation exposure to normal structures, in particular the parotid glands, in patients with locally advanced. [57-59] Since then, several centers have reported decreased rates of xerostomia in nasopharyngeal cancer (NPC) patients treated with IMRT[60, 61, 62] There are emerging randomized trial data which confirm the advantage of IMRT in improving salivary gland flow when compared to conventional RT in early stage NPC patients. [63, 64] Besides the dosimetric advantages,

several centers also reported excellent early clinical outcomes in NPC for IMRT. [65] The most mature IMRT clinical data came from UCSF[60] The 4-year local progression-free and regional progression-free rates for 67 loco-regional advanced NPC patients were 97% and 98%, respectively. An update with more patients (n=118), continued to show excellent locoregional control. [60] Several centers from Hong Kong also have shown similar findings. [61, 65] A recent experience from MSKCC reported a 91% locoregional control rate for IMRT treated NPC with a median follow-up of 35 months. [62] The RTOG completed a phase II trial of IMRT with or without chemotherapy for non-stage IVC NPC. Preliminary data showed decreased xerostomia when compared to historical RTOG trials where conventional RT was used. (Lee N, ASTRO proceedings 2007). Based on these results, we propose to use IMRT using the dose and fractionation schedule (70.2 Gy over 6.5 weeks) that has been pioneered at UCSF and validated in the Phase II RTOG study for the radiation treatment of these patients.

2.7 Rationale

Please see the background section for the scientific and clinical basis for this trial. Briefly, this trial is intended to ask several questions concerning a new treatment paradigm for patients with locoregionally advanced NPC. While many of the questions posed will only be definitively answerable in larger controlled trials, there is a need to generate preliminary data supporting the below hypotheses before there will be adequate enthusiasm for dedicating the resources of a multi-institutional, multi-national effort to ask the questions which would definitively address these questions.

Hypothesis which this trial will address:

Primary:

Sequential TPF=> chemoradiation will be associated with a higher complete response rate than the present US standard of care for this group of patients with NPC, chemoradiation=> PF.

Secondary:

Sequential TPF=> chemoradiation for patients with NPC is more feasible than chemoradiation=> PF as administered by the US intergroup 0099 study as measured by the percentage of patients who are able to complete the planned total course of treatment.

Induction TPF is more active than PF and better tolerated, as assessed by complete response rate after chemotherapy and incidence and severity of adverse events during chemotherapy.

3. PATIENT SELECTION

3.1 Eligibility Criteria- Inclusion

Yes_____ NO_____3.1.1 Patients must have histologically or cytologically confirmed nasopharyngeal carcinoma, stages II (minimally T2a,N0,M0 or Tany,N1, M0) through IVb. Patients with metastatic (stage IVc) untreated NPC who otherwise meet all eligibility criteria will be enrolled on a separate cohort and evaluated separately. Stage: T_____ N_____ M _____

Yes_____ NO_____3.1.2 Patients must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm with conventional techniques or as ≥10 mm with spiral CT scan. See Measurement of Effect section for details.

Yes_____ NO_____3.1.3 Prior treatment- Patients may have had diagnostic surgery(s) at the primary site or neck as long as there is still measurable disease present.

Yes_____ NO_____3.1.4 Age > *15 years.* Because no dosing or adverse event data are currently available on the use of the TPF combination in patients <15 years of age, children are excluded from this study, but will be eligible for future pediatric trials.

Yes_____ NO_____3.1.5 Life expectancy of greater than 3 months.

Yes_____ NO_____3.1.6 ECOG performance status <2. PS = _____

Yes_____ NO_____3.1.7 Patients must have normal organ and marrow function as defined below:

-absolute neutrophil count≥1,500/mcL value_____ date_____

-platelets ≥100,000/mcL value_____ date_____

-total bilirubin ≤1.5 X institutional ULN value_____ date_____

-AST(SGOT)/ALT(SGPT)≤2.5 X institutional ULN value_____ date_____

-creatinine ≤ 1.5 mg/dl value_____ date_____

-creatinine clearance ≥ 55 mL/min/1.73 m^2 for patients with creatinine levels above 1.5 mg/dl value_____ date_____ **Patients with creatinine > grade 1 but less than grade 3 are eligible but should receive carboplatin throughout the protocol instead of cisplatin.**

Yes_____ NO_____3.1.9 Peripheral motor/sensory neuropathy < grade 2. **If peripheral neuropathy is grade 2, patients are still eligible but should receive carboplatin throughout the protocol instead of cisplatin. _____neuropathy grade_____ date assessed.**

*****Cisplatin should be substituted with carboplatin for creatinine > grade 1, neuropathy > grade 2 or hearing loss > grade 2*****

Yes_____ NO_____3.1.10 The effects of TPF on the developing human fetus at the recommended therapeutic dose are unknown. For this reason and because these agents could be teratogenic or abortifacient, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately. Patient agrees.

Yes_____ NO_____3.1.11 Ability to understand and the willingness to sign a written informed consent document.

3.2 Exclusion Criteria

Yes_____ NO_____3.2.1 Patients who have had chemotherapy or radiotherapy for nasopharyngeal carcinoma.

Yes_____ NO_____3.2.2 Patients with known brain metastases should be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events. No CNS imaging is required if no clinical indication

Yes_____ NO_____3.2.3 History of allergic reactions attributed to compounds of similar chemical or biologic composition to docetaxel, cisplatin, carboplatin, 5-Fluorouracil or other agents used in the study.

Yes_____ NO_____3.2.4 Pregnant women are excluded from this study. The effects of TPF on the developing human fetus are unknown. These agents as well could be teratogenic or abortifacient. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with TPF, breastfeeding should be discontinued if the mother is treated with TPF. These potential risks may also apply to other agents used in this study.

Yes_____ NO_____3.2.5 HIV-positive patients on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with TPF. In addition, these patients are at increased risk of lethal infections when treated with marrow-suppressive therapy. Appropriate studies will be undertaken in patients receiving combination antiretroviral therapy when indicated. No HIV testing is mandated unless clinical indication

Yes_____ NO_____3.2.6 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

Yes_____ NO_____3.2.7 Patients with clinically significant cardiovascular disease are excluded

Yes_____ NO_____ 3.2.8 History of CVA within 6 months

Yes_____ NO_____3.2.9 Myocardial infarction or unstable angina within 6 months

Yes_____ NO_____ 3.2.10New York heart association grade II or greater congestive heart failure

Yes_____ NO_____3.2.11 Serious and inadequately controlled cardiac arrhythmia

Yes_____ NO_____3.2.12 Significant vascular disease (e.g. aortic aneurysm, history of aortic dissection)

Yes_____ NO_____3.2.13 Clinically significant peripheral vascular disease

3.3 **Inclusion of Women and Minorities**

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

4. REGISTRATION PROCEDURES

A protocol subject number will be assigned to every patient at the time of signing the informed consent. This number will be used to identify specific study information

throughout the trial. To meet the study criteria for enrollment, all patients will have their eligibility criteria confirmed (prior to the start of Cycle 1) and scanned into OnCore as a means for registration.

5. TREATMENT PLAN

5.1 Prophylactic Gastrostomy Feeding Tubes.

Investigators are **STRONGLY ENCOURAGED** to have prophylactic gastrostomy feeding tubes placed in patient **prior to initiation of treatment.** Chemoradiation for NPC patients is known to be associated with a high rate of severe locoregional toxicity including severe oropharyngeal mucositis, skin breakdown, nausea, and presence of thick copious tenacious secretions, often complicated by oropharyngeal candidiasis and superficial ulceration and superficial bleeding oral alimentation and hydration extremely difficult.

5.2 Agent Administration

Treatment will usually be administered on an outpatient basis. Reported adverse events and potential risks for the chemotherapeutic agents are described in the Agent Adverse Events section of each agent. Appropriate dose modifications for chemotherapeutic agents and are described in the **DOSING DELAYS/DOSE MODIFICATIONS section below.** No investigational or commercial anti-cancer agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy. Dosing may be +/- 2d of specified cycles start dates to accommodate weekends, holidays, etc.

5.2.1

Induction TPF treatment (note the first day of each cycle =day "1"					
Agent	***Premedications; Precautions***	***Dose***	***Route***	***Schedule***	***Cycle Length***
Docetaxel	*Dexamethasone 8 mg PO the evening of day 0(patient to have taken at home)*	*75 mg/m^2 in 250 cc NS*	*IV over 60 minutes*	*Day 1, all cycles*	*3 weeks(21 days)*
Cisplatin (if substituting carboplatin, see # for directions)	*Antiemetics and Hydration per text below*	*75 mg/m2*	*IV*	*Day 1, all cycles*	
*Carboplatin **(only if substituting for cisplatin***	*Antiemetics and Hydration per text below*	*AUC 6 using the below formula**	*IV over 30 minutes*	*Day 1 all cycles*	
5-Fluorouracil	*Antiemetics and Hydration per text below*	*750 mg/m2/d x 5 doses*	*IV continuous infusion over 24 hours daily*	*Days 1,2,3,4,5 May start 5- FU infusion CONCURRENTLY with Cisplatin infusion start.*	
Ciprofloxacin 500 mg		*500 mg BID*	*PO or per G tube*	*Days 6-15*	
Pegfilgrastim		*6mg SQ once*	*SQ*	*Approximately 24 hours after 5-FU infusion end*	

#Cisplatin should be substituted with carboplatin for creatinine > grade 1, neuropathy > gr2 or hearing loss > grade 2.

* Carboplatin dose = AUC * (GFR+25) Where GFR estimate = (140 - age) * weight in kg / (72 * serum creatinine). Multiply GFR estimate by 0.85 for females. NOTE: Maximum value for GFR is 125 mL/min AND the maximum dose for Carboplatin AUC 6 = 900 mg.

5.2.2 Premedications , antiemetics and intravenous fluid support for TPF during induction chemotherapy

Pre-medications for TPF

On day 1

Prior to docetaxel for cycle 1:

- Dexamethasone 12 mg PO or IV

- Famotidine 20 mg IV or PO or therapeutic equivalent. DO NOT USE CIMETIDINE
- Diphenhydramine 25-50 mg PO or IV

Anti-emetics for TPF

On day 1:

- Granisetron 2 mg PO or therapeutic equivalent
- Aprepitant 125 mg PO or therapeutic equivalent

On days 2 and 3:

- Dexamethasone 8 mg PO or IV
- Aprepitant 80 mg PO

On day 4:

- Dexamethasone 8 mg PO or IV

On any day of the cycle for breakthrough nausea, additional granisetron, metochlopramide, prochlorperazine or lorazepam may be used per local routine.

Additional standard treatments for prophylax against or to treat nausea and vomiting are acceptable.

Intravenous fluid support for TPF

Local institutional practices for IV fluid support may be used as long as all patients receive 3 liters of IVF with corresponding adequate urine output on day 1 and 1-2 liters of IV fluid as needed on days 2 and 3.

IVF and diuresis recommendations: Patient shall in aggregate have received 1 L IVF prior to cisplatin, including fluids in which other agents have been administered. Our practice is to give, in addition to IVF received with other agents, 500 -1000 mL NS over 2 hours, administered concurrently with docetaxel.

- Give 12.5mg Mannitol IVP immediately prior to cisplatin.
- Give concurrently with cisplatin 500 cc NSS containing 5 meq KCl, 1gram Magnesium Sulfate and 25 grams Mannitol.
- Give post cisplatin: 1 liter NSS containing 10 mEq KCL/liter,1 gm Magnesium Sulfate/ l at 500 ml/hr .
- On days 2 and 3, give 1-2 liters NSS IV PRN for poor oral fluid intake

5.2.3 Growth factor support:

G-CSF as filgrastim or pegfilgrastim will be administered per treating institution standard prophylactically during induction cycles

Route: subcutaneously

Schedule: starting approximately 24 hours after the completion of 5-fluorouracil infusion.

5.2.4 Chemotherapy concurrent with radiation:

All patients will receive chemoradiotherapy after the end of TPF with a minimum interval of 3 weeks and no later than 6 weeks after start of the last cycle (day 22 to 42 of last cycle).

Patients must fulfill the following criteria for chemoradiation:

Mucositis < grade 2

ANC ≥ 1500/ microliter

PLT ≥ 100, 000/ microliter

Hemoglobin ≥ 10 g/dL or hematocrit ≥ 30%

Creatinine ≤ 1.5 mg/dl OR creatinine clearance≥55 mL/min/1.73 m^2 for patients with creatinine levels above 1.5 mg/dl. **Cisplatin should be substituted with carboplatin for creatinine > grade 1 , neuropathy > gr2 or hearing loss > grade 2**

Chemotherapy concurrent with radiation				
Agent	***Premedications; Precautions***	***Dose***	***Route***	***Schedule***
Cisplatin (if substituting carboplatin, see text for directions)	*Antiemetics and Hydration per text below*	*40mg/m2*	*IV*	*Weekly during radiation for a total of 6 doses*
*Carboplatin **(only if substituting for cisplatin per the above guidelines)***	*Antiemetics and Hydration per text below*	*AUC 1.5 using the below formula**	*IV over 30 minutes*	*Weekly during radiation for a total of 6 doses*
Radiation therapy	Three dimensional conformal or intensity modulated radiation therapy to 70 Gy to the gross target volume + margins in 33 fractions. See section 5.3 for details			

* Carboplatin dose = AUC * (GFR+25). Where GFR estimate = (140 - age) * weight in kg / (72 * serum creatinine). Multiply GFR estimate by 0.85 for females. NOTE: Maximum value for GFR is 125 mL/min AND the maximum dose for Carboplatin AUC 1.5 = 225 mg.

5.2.5 Premedications , antiemetics and intravenous fluid support for TPF during concurrent chemoradiation

Antiemetics for ***Concurrent CISPLATIN***

On day 1:

- Granisetron 2 mg PO or therapeutic equivalent
- Aprepitant 125 mg PO or therapeutic equivalent
-
- Dexamethasone 12 mg PO or IV

On days 2 and 3:

- Dexamethasone 8 mg PO or IV
- Aprepitant 80 mg PO

On any day for breakthrough nausea, additional granisetron, metochlopramide, prochlorperazine or lorazepam may be used per local routine. Additional standard treatments for prophylax against or to treat nausea and vomiting are acceptable.

Intravenous fluid support ***Concurrent CISPLATIN***

Local institutional practices for IV fluid support may be used as long as all patients receive 2 liters of IVF with corresponding adequate urine output on day 1 and 1-2 liters of IV fluid as needed on days 2 and 3.

Antiemetics for ***concurrent CARBOPLATIN***

On day 1:

- Granisetron 2 mg PO or therapeutic equivalent
- Dexamethasone 8 mg PO or IV.

On any day for breakthrough nausea, additional granisetron, metochlopramide, prochlorperazine or lorazepam may be used per local routine

Intravenous fluid support ***Concurrent CARBOPLATIN****- None needed*

5.3 Radiation therapy treatment plan:

5.3.1 Concurrent cisplatin, and radiation:

Radiation Therapy: 70 Gy at 2.0-2.12 Gy/fraction in 6.5-7 weeks delivered with either 3-dimensional conformal radiotherapy (3DCRT) or intensity modulated radiotherapy (IMRT).

5.3.2 Radiation Therapy (See also Appendix B– Radiation Quality Assurance form)

Allowable treatment approaches include a 3DCRT approach or an IMRT.

Dose specification:

Two different RT dose prescriptions are allowed:

5.3.2.1. Integrated dose prescription

PTV_{70} (planning target volume 70): [GTV (gross target volume) + margin]: will receive 70 Gy at 2.12 Gy/fraction for 33 fractions.

$PTV_{high\ risk}$ [$CTV_{high\ risk}$ (clinical target volume high risk) + margin]: the areas of high risk, sub-clinical disease will receive between 56-59.4 Gy (at the discretion of the treating physician) at 1.7-1.8 Gy/fraction for 33 fractions.

$PTV_{low\ risk}$ ($CTV_{low\ risk}$ + margin): The area of low risk, subclinical disease, which is predominantly the uninvolved low necks, will receive 52 Gy at 1.57 Gy/fraction. Alternatively, the uninvolved low neck can be treated with a conventional AP or APPA supraclavicular field to a total dose of 44-50 Gy at 2Gy fraction for 22-25 fractions. The dose is prescribed to a depth of 3 cm from the anterior surface for the AP field and to the midplane for the APPA field. The junction between the IMRT or 3DCRT fields and the low-neck fields will be dependent on the institutional IMRT techniques; however, each institution is required to record the dosimetric details at the match-line to ensure dose homogeneity and to prevent overdosing of the spinal cord.

5.3.2.2. Sequential dose prescription:

PTV_{70} (planning target volume 70): [GTV (gross target volume) + margin]: will receive 70 Gy at 2.0 Gy/fraction for 35 fractions.

$PTV_{high\ risk}$ [$CTV_{high\ risk}$ (clinical target volume high risk) + margin] (**optional**): the areas of high risk, sub-clinical disease will receive 60 Gy at 2 Gy/fraction for 30 fractions.

$PTV_{low\ risk}$ ($CTV_{low\ risk}$ + margin): The area of low risk, subclinical disease, which is predominantly the uninvolved low necks, will receive 50 Gy at 2 Gy/fraction in 25 fractions. Alternatively, the uninvolved low neck can be treated with a conventional AP or APPA supraclavicular field to a total dose of 46-50 Gy at 2Gy fraction for 23-25 fractions. The dose is prescribed to a depth of 3 cm from the anterior surface for the AP field and to the midplane for the APPA field. The junction between the IMRT or 3DCRT fields and the low-neck fields will be dependent on the institutional IMRT techniques; however, each institution is required to record the dosimetric details at the match-line to ensure dose homogeneity and to prevent overdosing of the spinal cord.

5.3.2.3 Dose Compliance

The reported dose for each PTV should include the prescribed dose, maximal point dose, mean dose, the % of PTV that receive $\geq$ 110%, $\geq$ 115% and $\leq$ 93% of the prescribed dose.

All plans should be normalized so that ≥ 95% of the PTV_{70} receives the prescribed dose. In addition, no more than 20% of the PTV_{70} will receive ≥ 110 % and no more than 5% will receive ≥ 115%

RT will be given as once daily fraction. The first RT treatment should begin on Monday, Tuesday or Wednesday.

5.3.2.4 Technical factors

External beam equipment and beam delivery methods

Megavoltage equipments capable of delivering 3DCRT or IMRT (either static or dynamic) are required.

Treatment planning, imaging and localization requirement

The immobilization device should include at least the head and neck. It is strongly encouraged that the participation centers also utilize shoulder immobilization especially when comprehensive nodal IMRT is utilized.

Treatment planning CT scan will be required to delineate the GTV, CTV and PTV. Other imaging studies such as MRI and PET-CT scans can aid in volume delineation. The treatment planning CT scan should be acquired with the patient immobilized in the same treatment position. All tissue irradiated should be included in the treatment planning CT scan, which should be ≤ 3 mm slice thickness through the regions containing the GTV. Thicker slices (up to 5 mm) may be used for region above or below the GTV; however, thicker slices may compromise the image quality of the digitally reconstructed radiographs (DRR)

Treatment planning/target volumes

The definition of the target volumes should conform to the 1993 ICRU report #50;

Gross target volume (GTV): All known gross disease determined from clinical (including endoscopic) and imaging findings. Grossly involved nodes are defined as any lymph node > 1 cm on CT or MRI in the minimal cross-sectional diameter, any nodes with increased metabolic uptake on FDG PET scan, any node with central necrosis and/or radiographic evidence of extracapsular extension regardless of size.

Clinical target volume (CTV):

CTV_{70}: For grossly positive node, a margin of 5 mm should be added circumferentially to account for microscopic extracapsular extension

$CTV_{high\ risk}$: should include all regions deemed to be at high risk for microscopic disease, all potential routes of spread, and the high risk nodal regions.

$CTV_{low\ risk}$: nodal regions at low risk for microscopic involvement. This usually constitutes the clinically and radiographically low-neck nodes.

Planning target volume: A margin should be used to account for intrafraction and interfraction set up variability. The average recommended PTV margin is 5 mm; however, it will depend on the accuracy of treatment set up and immobilization at each individual treatment site.

5.3.2.5 Treatment Plan

Treatment plan will be based on the analysis of the volumetric dose, including dose-volume histogram (DVH) analyses of the PTVs and critical normal structures. A 3D or an "inverse" planning using computerized optimization should be used. The treatment aim will be the delivery of radiation to the PTVs and the exclusion of non-involved tissues. **HETEROGENEITY CORRECTION SHOULD BE USED**.

5.3.2.6 Critical structures

Surrounding critical normal structures, including the brainstem, temporal lobes (if the tumor is near the skull base), spinal cords, optic nerves, eyes, optic chiasm, parotid glands, the inner and middle ears (if the targets are near by), oral cavity, mandible and glottic larynx should be outlined. If there is grossly involved tumor in the low neck, then the brachial plexus should also be delineated.

Unspecified tissues, defined as the tissues within the skin, subtracted all target volumes and delineated normal tissues, should also be taken into account of the treatment planning and evaluation. No more than 5% of the unspecified tissue can receive > 70 Gy and no more than 1% or 1 cc of this tissue can receive >= 77 Gy. **Participants are strongly encouraged to remain within these limits.**

Dose constraints for certain normal tissues are shown in the following table.

Table 1: Required critical structure dose constraints

Structure	Maximal dose (Gy)
Brainstem	54
Spinal cord	45
Optic nerves	54
Optic chiasms	54
Eyes	50
Mandible	70
Brachial plexus	66

Table 2: Suggested normal structure dose constraints

Structure	Mean dose (Gy)
Parotid	< 26 for 1 gland or < 30 for 50% of 1 gland or < 20 for 20 cc volume of both glands
Oral cavity	< 40 if tumors outside the oral cavity
Inner/middle ear	< 45 or ≤ 5% volume receives > 55 Gy
Glottic larynx	< 50 for tumor outside the larynx and hypopharynx
Esophagus/post cricoid pharynx	< 50 for tumor outside the larynx and hypopharynx

5.3.2.7 Documentation requirements:

Weekly verification of orthogonal films through the treatment isocenter is required. If the IMRT or 3DCRT fields are matched to an AP supraclavicular field, then the supraclavicular field should also be included during weekly portal verification. **Appendix B is the radiation quality assurance form that should be submitted at the completion of radiation therapy**.

5.3.2.8 Radiation adverse events and allowed interruption

Radiation adverse events will be graded as per CTCAE v4.0. RT interruption may be necessary due to severe acute RT - related reactions such as severe skin or mucosal reaction or any other acute complications. Interruptions will be left at the discretion of the treating physicians but strongly discouraged. The cause of interruption should be recorded.

Placement of feeding gastrostomy tube may be necessary for nutritional support in this frail population. The date and reason for placement of a feeding gastrostomy tube (either prophylactic in preparation for RT or for active nutritional support due to significant weight loss before or during RT) should also be recorded. The duration of feeding tube dependence after completion of RT should also be recorded.

5.4 **Duration of Follow Up**

Patients will be followed for a minimum of 1 year after removal from study or until death, whichever occurs first. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

Patients will be seen quarterly in follow- up the first year after completion of radiation, and subsequently per local standards of care.

6. DOSING DELAYS/DOSE MODIFICATIONS

Doses will be modified in case of severe hematological and/or non-hematological toxicities. Dose adjustments are to be made according to the CTCAE v4 system showing the greatest degree of toxicity. Toxicities will be graded using the CTCAE v4 criteria.

6.1 DOCETAXEL dose modifications

Febrile Neutropenia or Documented Neutropenic Infection

Adverse event	Action to be taken for subsequent cycles
• Febrile neutropenia • Documented infection	The first episode of febrile neutropenia or documented grade 3 /4 neutropenia with documented infection will result in the addition of GM-CSF or G-CSF to all subsequent cycles . If there is a second episode, the patient will remain on Ciprofloxacin and GM-CSF or G-CSF and additionally, during the subsequent cycles, Docetaxel dose will be reduced from 75 to 60 mg/m^2

Action Taken Following Results of CBC Counts On first day of each TPF cycle

ANC ($x10^9$/L)	Action to be taken
≥ 1.5 (grade 1)	Treat on time
< 1.5 (GRADE 2 OR HIGHER)	1. Delay TPF 1 week and repeat complete blood count . 2. If ANC > 1.5 x 10^9/L, then proceed with full dose chemotherapy 3. If ANC < 1.5 x 10^9/L, then consider addition of G-CSF or GM-CSF for 7 days • On day 35, perform complete blood count with differential • Proceed with full dose chemotherapy if ANC > 1.5 • And consider use of GM-CSF or G-CSF in remaining cycles 4. If there is no recovery by day 35, (ANC < 1.5 x 10^9/L), the patient will go off TPF chemotherapy
Thrombocytopenia	Action to be taken
Plt <LLN – 75,000/mm3 (grade 1)	Treat on time
Plt < 75,000 (grade 2 -4)	1. Delay TPF 1 week and repeat complete blood count . 2. If plt ≥ 100,000, then proceed with full dose chemotherapy 3. If plt 75,000-<100,000, dose reduction of docetaxel from 75 to 60 mg/m^2 for all subsequent cycles of TPF. 4. if plt < 75,000, patient will go off TPF chemotherapy If patient has recurrent thrombocytopenia after docetaxel reduction to 60 mg/m2 without recovery to 75,000 by day 28 of subsequent cycles, patient will go off TPF therapy

Action Taken for other <u>Docetaxel AEs</u>

Mucositis oral

If mucositis oral is present on day 1 of any cycle, treatment should be withheld until resolved.

If Grade 3/4 mucositis oral occurs at any time, the dose of Docetaxel should be reduced for subsequent cycles, Docetaxel dose will be reduced from 75 to 60 mg/m²

Peripheral motor Neuropathy and peripheral sensory neuropathy

Docetaxel dose will be reduced from 75 to 60 mg/m² for Grade 2 neuropathies without treatment delay.

Treatment should be discontinued for Grade 3/4 neuropathies.

Dermatological/ Skin

Grade 0, 1, and 2: no change

Grade 3: Delay until < grade 1 and retreat with a dose reduction of Docetaxel from 75 to 60 mg/m². If no recovery to < grade 1 within 2 weeks delay, patient will go off protocol therapy.

Grade 4: The patient will go off chemotherapy.

Nausea and/or vomiting

Prophylactic antiemetic regimen with 5-HT3 antagonist should be administered from the first cycle. In addition, the corticosteroids used during 3 days for the prophylaxis of fluid retention should also reduce the incidence and severity of emesis.

Patients with nausea and vomiting despite these measures may be treated with another antiemetic regimen (i.e. high dose metochlopramide) as appropriate.

Bilirubin and Impaired liver function:

In the event that bilirubin levels are abnormal during study, the next cycle will be delayed by a maximum of 2 weeks. If no recovery, the patient should be taken off chemotherapy.

In the event that AST and/or ALT and/or alkaline phosphatase levels are abnormal in the absence of progressive disease, the following dose modifications will apply:

Table :Dose Modifications for docetaxel for Abnormal Liver Function

	AST or ALT:			
ALK PHOS #:	**≤ ULN**	**>1x but ≤1.5x**	**>1.5x but ≤5x**	**>5x ULN**
≤ ULN	Full Dose	Full Dose	Full Dose	Hold*
>1x but ≤ 2.5x	Full Dose	Full Dose	Reduce Dose to 60 mg/m2	Hold*
>2.5x but ≤ 5x	Full Dose	Reduce Dose to 60 mg/m2	Hold*	Hold*
>5x ULN	Hold*	Hold*	Hold*	Hold*

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

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

**Reduced doses of Docetaxel will be at 60mg/m^2. After Docetaxel is dose is reduced, there will be no re-escalation. There will be only one dose reduction.

If alkaline phosphatase is clinically related to local bone erosion, for purposes of docetaxel dose reductions, consider alk phos < ULN, i.e. dose adjust based on other clinical and lab parameters.

6.2 CISPLATIN and CARBOPLATIN dose modifications:

Cisplatin dose reductions during TPF for hematologic adverse events:

There will be no planned CDDP dose reductions for ANC or platelet AEs. See Docetaxel section for dose reduction and TPF delay and discontinuance parameters for ANC and platelet AEs. Note that after one reduction in docetaxel for hematological AEs, high grade persistent or recurrent AEs will result in discontinuance of TPF per the algorithm outlined for docetaxel dose modification.

Cisplatin dose reductions during TPF for non-hematologic adverse events:

CDDP dose levels during TPF	
-1	Starting dose

60 mg/m2	75 mg/m2

Peripheral motor Neuropathy and peripheral sensory neuropathy

Grade 0, 1: no change

Grade > 2: Carboplatin may be substituted for Cisplatin

Ototoxicity

Cisplatin is known to cause high frequency hearing loss. If grade 1 or 2 hearing loss occurs, the risk of additional hearing loss versus the potential benefit of continuing Cisplatin chemotherapy should be made. Grade 3 and 4 hearing loss is an indication to discontinue the drug. In case of grade 3 or 4 ototoxicity, Carboplatin may be used to replace Cisplatin .

Creatinine

Grade 1 (creatinine <1.5): no CDDP dose change
Grade 2 (creatinine > 1.5-3):
first incidence decrease one dose level, consider change to carboplatin.
second incidence: switch to carboplatin.
Grade 3 -4 (creatinine >3): discontinue CDDP, switch to carboplatin.

All other non- hematological AEs attributable to CDDP:
Grade 1-2 : no dose change of CDDP
Grade 3-4:Hold TPF up to one week for resolution of AEs to grade 2 or less, then re-treat with one level dose reduction of CDDP. If AEs not resolved to grade 2 after 1 week, discontinue TPF treatment

<u>Carboplatin dose reductions during TPF</u>

Hematological AEs during TPF :

There will be no planned Carboplatin dose reductions for ANC or platelet AEs. See Docetaxel section for dose reduction and TPF delay and discontinuance parameters for ANC and platelet AEs. Note that after one reduction in docetaxel for hematological AEs, high grade persistent or recurrent AEs will result in discontinuance of TPF per the algorithm outlined for docetaxel dose modification.

All other non- hematological AEs attributable to carboplatin:
Grade 1-2 : No dose change of carboplatin or TPF delay.
Grade 3-4: Hold TPF up to one week for resolution of AEs to grade 2 or less, then re-treat with one level dose reduction. If AEs not resolved to grade 2 after 1 week, discontinue TPF treatment.

Cisplatin and carboplatin dose reductions during concurrent radiation for hematological toxicities

CDDP dose levels during radiation		
-2	-1	Starting dose

25 mg/m2/week	30 mg/m2/week	40mg/m2/week

Carboplatin dose levels during radiation*		
-2	-1	Starting dose
AUC 0.8/week	AUC 1.1/week	AUC 1.5 /week

*Refer to page 13 for Carboplatin maximum dose value calculation during radiation treatment. Maximum GFR value is 125 mL/min AND maximum Carboplatin AUC 1.5 = 225 mg.

CDDP or Carboplatin must not be administered concurrently with radiation until the ANC ≥ 1,000 and platelets are ≥ 100,000. If not, delay one week. If the patient still has not recovered, continue to hold on a week by week basis until the above criteria are met, then resume dosing according to the below table.

ANC		Plt count	Dose reduction/ delay
Greater or = to 1500	and	Greater or = 75,000	No change in dose
1000-1499	or	50,000-74,999	Decrease by one dose level
Less than 1000	or	Less than 50,000	Hold until ANC>1000 and plt> 75,000 and decrease by one dose level.

There will be no reduction below dose level -2. If a patient is already at dose level -2 and experiences AEs as defined above, discontinue CDDP or carboplatin.

Cisplatin or carboplatin dose reductions during concurrent radiation for non-hematological toxicities:

Concurrent platinum and radiation for patients with nasopharyngeal cancer is known to be associated with a high rate of severe locoregional toxicity including severe mucositis oral, skin breakdown, nausea, and presence of thick copious tenacious secretions, often complicated by oropharyngeal candidiasis and superficial ulceration and superficial bleeding. Patients commonly are not able to adequately aliment or hydrate themselves orally during chemoradiation and for several weeks afterwards. Every effort should be made to manage patient symptomatically using IV hydration, and clinicians are STRONGLY ENCOURAGED to have prophylactic gastrostomy feeding tubes placed prior to initiation of treatment. Severe mucositis oral and skin breakdown in the radiation field based on ulceration and superficial bleeding should not be considered inherently dose limiting.

Radiation associated mucositis oral or dermatitis:

Grade 4: hold CDDP or carboplatin until resolution to grade 3 then dose reduce by one dose level. There will be no dose reductions below dose level minus 2. In the case that a

patient is being treated at dose level minus 2, once AEs are grade 3 or less, the patient should be treated again at dose level minus 2.

Peripheral motor Neuropathy and peripheral sensory neuropathy

Grade 0, 1: no change

Grade > 2: Carboplatin may be substituted for Cisplatin Should a new grade > 2 peripheral motor/sensory neuropathy develop on carboplatin, hold carboplatin until resolution to grade 2 then dose reduce 1 level.

Ototoxicity

Cisplatin is known to cause high frequency hearing loss. If grade 1 or 2 hearing loss occurs, the risk of additional hearing loss versus the potential benefit of continuing cisplatin chemotherapy should be made. Grade 3 and 4 hearing loss is an indication to discontinue the drug. In case of grade 3 or 4 ototoxicity, carboplatin may be used to replace cisplatin. Should new grade > 2 ototoxicity develop on carboplatin, hold carboplatin until resolution to grade 2 then dose reduce 1 level.

Creatinine
Grade 1 (creatinine <1.5): no CDDP dose change
Grade 2 (creatinine > 1.5-3):
First incidence decrease one dose level, consider change to carboplatin.
Second incidence: switch to carboplatin.
Grade 3 -4 (creatinine >3): discontinue CDDP, switch to carboplatin. Should a new grade > 2 creatinine develop on carboplatin, hold carboplatin until resolution to grade 2 then dose reduce 1 level.
Non- hematological AEs attributable to CDDP or carboplatin excluding AEs discussed above:

Grade 1-2 : No dose change of CDDP or carboplatin.

Grade 3-4: Hold CDDP or carboplatin until resolution of AEs to grade 2 or less, then dose reduce by one dose level. There will be no dose reductions below dose level minus 2. In the case that a patient is being treated at dose level minus 2, once AEs resolve to grade 2 or less, the patient should be treated again at dose level minus 2.

6.3: 5- Fluorouracil (5-FU) dose modifications during TPF

5-FU dose levels during TPF		
-2	-1	Starting dose
480 mg/m2 IVCI/d x 5 d	600 mg/m2 IVCI/d x 5 d	750 mg/m2 IVCI/d x 5 d

Hematological AEs during TPF:

There will be no planned 5-FU dose reductions for ANC or platelet AEs. See Docetaxel section for dose reduction and TPF delay and discontinuance parameters for ANC and platelet AEs. Note that after one reduction in docetaxel for hematological AEs, high

grade persistent or recurrent AEs will result in discontinuance of TPF per the algorithm outlined for docetaxel dose modification.

Non- Hematological AEs during TPF:

Mucositis oral or dermatitis

Grade 3 lasting more than 96 hours or grade 4 **:** Dose reduce one level.

Diarrhea

In the case of severe diarrhea, octreotide is recommended. If the patient has a significant diarrhea occurrence again (> 3 loose stools/24 hr), the patient should be treated prophylactically in the subsequent cycles with 2 tablets of loperamide or diphenoxylate in addition to 1 or 2 tablets after each loose stool. The maximum daily dose of Loperamide is 16mg and Diphenoxylate is 20mg/day.

Grade 4 diarrhea, or grade 3 diarrhea lasting > 7 days despite the prophylactic treatment: dose reduce one level.

All other non- hematological AEs attributable to 5-FU:

Grade 1-2 : No dose change of 5-FU or TPF delay.

Grade 3-4: Hold TPF up to one week for resolution of AEs to grade 2 or less, then re-treat with one dose level reduction . If AEs not resolved to grade 2 after 1 week, discontinue TPF treatment.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

7.1 Adverse Event List(s) for Commercial Agent(s)

7.1.1 Docetaxel is commercially available. See package insert for details.

Side Effects may include:

1. Cardiac: arrhythmias, pericardial effusions.
2. Hematologic: dose-related neutropenia, leukopenia, thrombocytopenia, anemia, hypoglycemia, hypernatremia.
3. Gastrointestinal: nausea and vomiting, diarrhea, oral mucositis oral, pancreatitis, esophagitis.
4. Neurologic: reversible dysthesias or paresthesias, peripheral motor/sensory neuropathy mild or moderate lethargy or somnolence, headache, seizures.
5. Hypersensitivity: hypersensitivity (local or general skin rash, flushing, pruritus, drug-fever, chills and rigors, low back pain), severe anaphylactoid reactions (flushing with hypo- or hypertension, with or without dyspnea).
6. Dermatologic: alopecia, desquamation following localized pruriginous maculopapular eruption, skin erythema with edema, extravasation reaction (erythema, swelling, tenderness, pustules), reversible peripheral phlebitis, nail changes.
7. Hepatic: increased transaminase, alkaline phosphatase, bilirubin; hepatic

failure; hepatic drug reaction.

8. Pulmonary: dyspnea with restrictive pulmonary syndrome, pleural effusions.
9. Other: asthenia, dysgeusia, anorexia, conjunctivitis, arthralgia, muscle aches, myopathy, peripheral edema, fluid retention syndrome, ascites.

Prolonged treatment with weekly docetaxel results in chronic toxicities, which include asthenia (fatigue), anemia, edema, excessive lacrimation (epiphora), and onycholysis.

7.1.2 Cisplatin is commercially available. See package insert for details.

Side Effects may include:

1. Hematologic: Leukopenia and thrombocytopenia occur, but are rarely dose-limiting; anemia.
2. Dermatologic: Alopecia (uncommon).
3. Gastrointestinal: Nausea and vomiting are common and may persist for up to 24-96 hours; anorexia.
4. Renal: Nephrotoxicity is dose-related and relatively uncommon with adequate hydration and diuresis; elevated serum creatinine and BUN.
5. Hepatic: Elevated AST and ALT.
6. Neurologic: Peripheral motor/sensory neuropathy (paresthesias), common and dose-limiting when the cumulative cisplatin dose exceeds 400 mg/m^2; rarely seizures; ototoxicity manifested initially by high frequency hearing loss; vestibular toxicity (dizziness) uncommon; tetany (caused by hypomagnesemia); rarely Lhermitte's sign.
8. Other: Hypomagnesemia, hypocalcemia, hyponatremia, vein irritation, papilledema, rarely retrobulbar neuritis, rarely anaphylaxis, fatigue.

7.1.3 Carboplatin is commercially available. See package insert for details.

Side Effects may include:

1. Hematologic: Thrombocytopenia, neutropenia, leukopenia, more pronounced in patients with compromised renal function and heavily pretreated patients; may be cumulative.
2. Gastrointestinal: Nausea and vomiting (less severe than with cisplatin), treatable with moderate doses of antiemetics.
3. Dermatologic: Rash, urticaria.
4. Hepatic: Abnormal liver function tests, usually reversible with standard doses.
5. Neurologic: Rarely peripheral motor/sensory neuropathy.
6. Renal: Elevations in serum creatinine, BUN, electrolyte loss (Na, Mg, K,

Ca).

7.Other: Pain, asthenia.

7.1.4 5- Fluorouracil is commercially available. See package insert for details.

Side Effects may include:

Hematologic: Leukopenia, thrombocytopenia, anemia (can be dose limiting, less common with continuous infusion); Dermatologic: Dermatitis, nail changes, hyperpigmentation, Hand-Foot Syndrome with protracted infusions, alopecia; Gastrointestinal: Nausea, vomiting, anorexia, diarrhea (can be dose limiting); mucositis oral

(is common with 5-day infusion, occasionally dose limiting); Neurologic: Cerebellar Syndrome (headache and cerebellar ataxia); Cardiac: Angina, noted with continuous infusion; Ophthalmic: Eye irritation, nasal discharge, watering of eyes, blurred vision.

7.2 Adverse Event Reporting

The Protocol Director (PD) or designee will assess each Adverse Event (AE) to determine whether it is unexpected according to the Informed Consent, Protocol Document, and related to the investigation. All Adverse Events (AEs) and Serious Adverse Events (SAEs) will be tracked until resolution or until 30 after the last dose of the study treatment.

.

SAEs CTCAE v 4.0 Grade 3 and above, and all subsequent follow-up reports will be reported to the CCTO Safety Office regardless of the event's relatedness to the investigation. Following review by the CCTO Safety Officers, any events meeting the IRB definition of 'Unanticipated Problem' will be reported to the IRB using eProtocol within 10 working days of the review, or within 5 working days for deaths or life-threatening experiences.

7.3 Routine AE collection

All AEs grade 2 and above attributed to treatment will be recorded on case report forms and saved in a secure environment within the research offices of the PI and scanned into Oncore upon their completion. All AEs will be assessed for treatment attribution and noted to be either '*Related to Treatment'* or '*Not Related*'. AEs will be evaluated for all patients according the schedule specified in the study calendar.

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the commercial agents administered in this study can be found in Section 7.1.

8.1 *Commercial Agent(s)*

8.1.1 Docetaxel - (Commercially available. Please refer to the package insert for further information)

Other Names Taxotere, RP 56976, NSC #628503. Classification: Antimicrotubule agent.

Mode of Action: Docetaxel, a semisynthetic analog of paclitaxel, promotes the assembly of tubulin and inhibits microtubule depolymerization. Bundles of microtubules accumulate and interfere with cell division.

Storage and Stability:

Docetaxel infusion solution, if stored between 2 and 25ºC (36 and 77ºF) is stable

for 4 hours. Fully prepared docetaxel infusion solution (in either 0.9% Sodium

Chloride solution or 5% Dextrose solution) should be used within 4 hours (including the administration time). Store between 2 and 25°C (36 and 77ºF). Retain in the original package toprotect from bright light. Freezing does not adversely affect the product.

Preparation:

Docetaxel is a cytotoxic anticancer drug and, as with other potentially toxic compounds, caution should be exercised when handling and preparing docetaxel solutions. The use of gloves is recommended. If docetaxel 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 docetaxel concentrate, initial diluted solution, or final dilution for infusion should come into contact with mucosa, immediately and thoroughly wash with water. Docetaxel for Injection Concentrate requires two dilutions prior to administration.

Please follow the preparation instructions provided below. **Note:** Both the docetaxel for Injection Concentrate and the diluent vials contain an overfill.

A. Preparation of the Initial Diluted Solution

1. Gather the appropriate number of vials of docetaxel for Injection

Concentrate and diluent (13% Ethanol in Water for Injection). If the vials were refrigerated, allow them to stand at room temperature for approximately 5 minutes.

2. Aseptically withdraw the contents of the appropriate diluent vial into a syringe and transfer it to the appropriate vial of docetaxel for Injection Concentrate. **If the procedure is followed as described, an initial diluted solution of 10mg docetaxel/mL will result.**

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 docetaxel 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. Preparation of the Final Dilution for Infusion

1. Aseptically withdraw the required amount of initial diluted docetaxel solution (10mg 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 0.74mg/mL. Thoroughly mix the infusion by manual rotation.

2. As with all parenteral products, docetaxel should be inspected visually for particulate matter or discoloration prior to administration whenever the solution and container permit. If the docetaxel for Injection, initial diluted solution, or final dilution for infusion is not clear or appears to have precipitation, these should be discarded. The final docetaxel dilution for infusion should be administered intravenously as per protocol under ambient room temperature and lighting conditions. Contact of the docetaxel 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 docetaxel dilution for infusion should be stored in bottles (glass,

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

Route of Administration:

Docetaxel will be administered as a 60 minute infusion in saline or D5W through an administration set that does not contain phthalate plasticizers along the fluid pathway that is connected to the patient's vascular access catheter.

Incompatibilities:

Contact of the undiluted concentrate with plasticized PVC equipment or devices used to prepare solutions for infusion should be avoided. Diluted docetaxel solution should be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets. The metabolism of docetaxel may be modified by the concomitant administration of compounds that induce, inhibit, or are metabolized by cytochrome P450 3A4, such as cyclosporine, terfenadine, ketoconazole, erythromycin, and troleandomycin. Caution should be exercised with these drugs when treating patients receiving docetaxel as there is a potential for a significant interaction.

Availability:

Docetaxel (Taxotere®) is a commercial drug. The combination of docetaxel, cisplatin, and 5-FU for the treatment of patients with SCCHN is approved by the FDA and exempt from the requirements of an IND as described under Title 21 CFR 312.2(b).

Docetaxel vials of 80 mg in 2 ml polysorbate 80 and 20mg in 0.5ml polysorbate 80 with accompanying diluent (13% w/w ethanol in Water for Injection) are commercially available from Sanofi Pharmaceuticals. (The vials contain 15% overfill to compensate for liquid lost during preparation). Docetaxel for Injection Concentrate is supplied in a single-dose vial as a sterile, pyrogen-free, non-aqueous, viscous solution with an accompanying sterile, nonpyrogenic, diluent (13% ethanol in Water for Injection) vial. The following strengths are available:

TAXOTERE 80 mg (NDC 0075-8001-80)

TAXOTERE (docetaxel) 80 mg Concentrate for Infusion: 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 (NDC 0075-8001-20)

TAXOTERE (docetaxel) 20 mg Concentrate for Infusion: 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.

Nursing/Patient Implications:
1. Monitor CBC with differential and platelet count prior to drug administration.
2. Symptom management of expected nausea, vomiting, and mucositis oral.
3. Advise patients of possible hair loss.
4. Patients should be observed closely for hypersensitivity reactions, especially during the first and second infusions. Insure that recommended premedications are given.
5. Resuscitation equipment and medications to treat hypersensitivity reactions should be available during docetaxel administration.
6. Monitor liver function tests.
7. Evaluate site regularly for signs of infiltration.
8. Monitor for symptoms and signs of fluid retention, peripheral motor/sensory neuropathy, and cutaneous reactions.

8.1.2 Cisplatin- (Commercially available. Please refer to the package insert for further information)

Other Names Cis-diaminedichloroplatinum Cis-diaminedichloroplatinum (II), diaminedichloroplatinum,cis-platinum, platinum, Platinol®, Platinol-AQ®, DDP, CDDP, DACP, NSC 119875. Classification: Alkylating agent.

Mode of Action:

Inhibits DNA synthesis by forming inter- and intra-strand crosslinks. Other possible mechanisms include chelation of DNA and binding to cell membranes thereby stimulating immune mechanisms.

Storage and Stability:

Intact vials of cisplatin are stored at room temperature. Solutions diluted with sodium chloride or dextrose are stable for up to 72 hours at room temperature. Due to the risk of precipitation, cisplatin solutions should **not** be refrigerated.

Preparation:

The desired dose of cisplatin is diluted with 250 - 1000 ml of saline and/or dextrose solution. Varying concentrations of 0.225 - 5% sodium chloride and 5% dextrose may be used. To maintain stability of cisplatin, a final sodium chloride concentration of at least 0.2% is recommended.

Route of Administration:

Cisplatin should be administered as a 1 mg/ml intravenous infusion. Antiemetics should be given in conjunction with Cisplatin. Cisplatin is highly emetogenic. A suggested regimen is aprepitant 125 mg po on day 1 and 80 mg po on days 2 and 3 plus ondansetron (8 mg mg IV or 24 mg PO) or granisetron (1 mg IV or 2 mg PO) plus dexamethasone 12 mg po on day 1, 8 mg po on days 2-4) [83]

Metochlopramide 20-40 mg 2-4 times daily is suggested for patients with delayed nausea. Other antidopaminergic agents such as haloperidol can be used in patients with refractory symptoms.

Incompatibilities:

Amsacrine, cefepime, gallium nitrate, mesna, piperacillin, sodium bicarbonate, thiotepa. Cisplatin may react with aluminum which is found in some syringe needles or IV sets, forming a black precipitate.

Compatibilities:

Admixture: Amphotericin-B, aztreonam, carmustine, cefazolin, cephalothin, droperidol, etoposide, floxuridine, hydroxyzine, ifosphamide, leucovorin, magnesium sulfate, mannitol, potassium chloride.

Y-site: Allopurinol, bleomycin chlorpromazine, cimetidine, cyclophosphamide, dexamethasone, diphenhydramine, doxapram, doxorubicin, famotidine, filgrastim, fludarabine, fluorouracil, furosemide, ganciclovir, heparin, hydromorphone, lorazepam, melphalan, methotrexate, methylprednisolone, metoclopramide, mitomycin, morphine, ondansetron, paclitaxel, prochlorperazine, ranitidine, sargramostim, vinblastine, vincristine, vinorelbine.

Consult your pharmacist regarding specific concentrations.

Availability:

Commercially available as a mg/ml solution in 50 and 100 mg vials. Vials of lyophilized powder are no longer commercially available, but may be obtained directly from the manufacturer for chemoembolization use.

Nursing Implications:
1. Assess labs prior to administration (esp. CBC, platelet count, Cr).
2. Assess urine output prior to each dose. Maintain hydration. Urine output should be 500-150 ml/hr. Diuretics may be ordered.
3. Administer antiemetics before cisplatin, then q 2-4 h for 3-5 doses.
4. Observe carefully for signs of anaphylaxis.
5. Monitor for signs of neurotoxicity, hearing loss.

8.1.3 Carboplatin - (Commercially available. Please refer to the package insert for further information) Other Names: CBDCA, Paraplatin, JM-8, NSC 241240.

Classification: Second generation tetravalent organic platinum compound.

Mode of Action:

Like cisplatin, carboplatin produces predominately interstrand DNA crosslinks rather than DNA-protein crosslinks. Cell-cycle nonspecific.

Storage and Stability:

Intact vials are stored at room temperature and protected from light. The reconstituted solution is stable for at least 24 hours. When further diluted in glass or polyvinyl plastic

to a concentration of 500 mg/ml, solutions have the following stability: in normal saline, 8 hours at 25°C; in 5% dextrose (when reconstituted in sterile water), 24 hours at 5 of 25°C.

Preparation:

Add 5, 15, or 45 ml sterile water, normal saline, or 5% dextrose to the 50, 150 or 450 mg vial, respectively. The resulting solution contains 10 mg/ml. The desired dose is further diluted, usually in 5% dextrose.

Administration:

Administer as a 30 minute infusion

Incompatibilities:

Forms a precipitate when in contact with aluminum.

Compatibilities:

Carboplatin (0.3 mg/ml) and etoposide (0.4 mg/ml) are chemically compatible in normal saline or 5% dextrose for 24 hours at room temperature.

Availability:

Commercially available in 50, 150, and 450 mg vials.

Nursing Implications
1. Monitor CBC and platelet count; nadir occurs at approximately day 21 with recovery by day 28-30.
2. Premedicate with antiemetics – evaluate effectiveness.
3. Monitor fluid status – maintain adequate hydration.
4. Assess skin/mucous membranes.
5. Assess for signs of peripheral motor/sensory neuropathy – coordination, sensory loss.

8.1.4 5-Fluorouracil- (Commercially available. Please refer to the package insert for further information).

Other Names

5-FU, Adrucil, Efudex.

Formulation

Available in 500 mg/10 mL ampules and vials, and 1 gm/ 20 ml. For further information, see package insert.

Administration: 5- Fluorouracil will be administered as a continuous IV infusion during induction chemotherapy following the completion of bevacizumab and docetaxel administration. 5-**Fluorouracil may be begin concurrently** with the cisplatin or carboplatin infusion. [31]

Drug Interactions

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

Allopurinol: Oxypurinol, a metabolite of allopurinol, can potentially interfere with 5-FU anabolism via orotate phosphoribosyltransferase. Although this was originally used as a

strategy to protect normal tissues from 5-FU-associated toxicity, further laboratory studies suggested possible antagonism of the anticancer activity of 5-FU in some tumor models. If a patient is receiving allopurinol, the need for taking this medicine should be ascertained. If possible, allopurinol should be discontinued prior to starting on this regimen, and another agent substituted for it.

Storage

Stable for prolonged periods of time at room temperature, if protected from light. Inspect for precipitate; if apparent, agitate vial vigorously or gently heat to not greater than 140°F in a water bath. Do not allow to freeze.

9. STUDY CALENDAR

Baseline evaluations are to be conducted within 1 week prior to start of protocol therapy. Scans and x-rays must be done within 1 month prior to the start of therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

Induction Chemotherapy with TPF study calendar (separate calendar for radiation portion and post radiation follow-up is below)

	Pre study	**Induction Week #**									**End of induction** (Assessment maybe combined in same visit as first week of XRT)
		1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	
TPF		**A**			**A**			**A**			
Informed consent	**x**										
Demographics	**x**										
Medical history	**x**										
Concurrent meds	**x**	**x**			**x**			**x**			**x**
Physical exam	**x**	**x**			**x**			**x**			**x**
Vital signs	**x**	**x**			**x**			**x**			**x**
Height	**x**										
Weight	**x**										
Performance status	**x**										**x**
CBC w/diff, plts[b]	**x**	**x**			**x**			**x**			**x**
Comp. metab. profile [a,b]	**x**	**x**			**x**			**x**			**x**
EKG (as indicated)	**x**										
Adverse event evaluation	**x**	**x**			**x**			**x**			**x**
Tumor measurements per clinical routine	**x**	**x**			**x**			**x**			**x**
Radiological evaluation [d]	**x**										**x**

A: TPF: *Docetaxel 75 mg/m2 and cisplatin 75 mg/m2 on day 1 of each cycle. 5-FU, 750 mg/m2 on days 1,2,3,4,5 of each cycle as IVCI,*

a: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.

b: While the protocol mandates a blood tests only prior to each dose of TPF, good clinical practice should be used in ordering additional lab tests as part of routine care for patients receiving chemotherapy.

c: Basic metabolic panel: calcium, CO2, chloride, creatinine, glucose, potassium, sodium, BUN

d: Radiological evaluation will be tailored to the patient with the following parameters: There must be CT or MRI evaluation of the primary site and neck, and a baseline evaluation for metastatic disease to include at minimum chest CT or total body FDG PET scan. Imaging modality should be consistent for each patient throughout. Response

to induction may be made using the planning PET CT for radiation as the primary imaging modality response.

Concurrent chemoradiation study calendar (separate calendar for induction TPF is above, use same footnotes)

	Concurrent ChemoXRT Week #							**1 mo f/u**	**3,6,9, 12 , 24mo f/u**
	1	**2**	**3**	**4**	**5**	**6**	**7**		
Radiation treatment	x	x	x	x	x	x			
Cisplatin(or carboplatin)	x	x	x	x	x	x			
Physical exam									x
Vital signs									
CBC	x	x	x	x	x	x	x		
Basic metabolic profile [c]	x	x	x		x	x			
Comp. metab. Profile [a]				x			x		
AE evaluation	x	x	x	x	x	x	x	x*	
Tumor measure per clinical routine									x*
Radiological evaluation									x#

*= 1-3 months after radiation completion
Only at 3, 12, and 24 month followup (+/- 1 month). For the first post- XRT imaging, a window of 8-16 weeks post RT is acceptable. For the 1 and 2 year followup imaging, +/- 2 months is acceptable.

10. MEASUREMENT OF EFFECT

10.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be reevaluated for response after TPF and 3, 12, and 24 months after the completion of radiation. The primary endpoint of response assessment will be based on MRI and or CT imaging and physical exam using a modification of the RECIST criteria (see below).While other modalities for response assessment (e.g. PET scanning, serum tumor markers) will be collected and may be used for clinical planning, they will not be used to evaluate the primary endpoint.

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee [*JNCI* 92(3):205-216, 2000]. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria.

10.1.1 **Definitions**

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment .

Evaluable for objective response. Only those patients who have measurable disease present at baseline, have received at least one cycle of TPF, and have had their disease re-evaluated will be considered evaluable for response.

10.1.2 **Disease Parameters**

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).

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.

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

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 10 target lesions should be identified as **non-target lesions**

and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

10.1.3 **Methods 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.

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

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

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

Tumor markers Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a 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.

10.1.4 **Response Criteria**

10.1.4.1 **Evaluation of Target Lesions**

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

10.1.4.2 **Evaluation of Non-Target Lesions**

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level
Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.
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, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

10.1.4.3 **Evaluation of Best Overall Response**

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). This is a modification of RECIST in that confirmatory imaging is not practical at the 3, 12, and 24 month imaging intervals, does not contribute to the sense of " best response" achieved, and is not a primary endpoint of the study.

Target Lesions	**Non-Target Lesions**	**New Lesions**	**Overall Response**	**Best Response following radiation for this Category Also Requires:**
CR	CR	No	CR	
CR	Non-CR/Non-	No	PR	

	PD			
PR	Non-PD	No	PR	
SD	Non-PD	No	SD	
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD*	Yes or No	PD	
Any	Any	Yes	PD	

* In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration"*. Every effort should be made to document the objective progression even after discontinuation of treatment.

10.1.5 **Duration of Response**

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that 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.

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

10.1.6 **Progression-Free Survival**

Progression – free survival will be calculated as the interval between date of registration and date of documented cancer progression or death, whichever occurs first.

10.1.7 **Response Review**

All radiological images used for response assessment must be available to the principal investigator for response assessment review. For patients imaged at Stanford Cancer center/ Stanford Hospital, images available within the Hospital radiology system fulfill this criterion. For images acquired outside of the Stanford system, images must be transferred to a separate , portable medium (i.e. CD or DVD), labeled with the patient's anonymized Oncore protocol registration number and scan date, and sent to the clinical trial coordinator at the address on the first page of this protocol.

11. STATISTICAL CONSIDERATIONS

11.1 **Study Design/Endpoints**

The primary endpoint for this trial will be progression free survival 2 years following chemoradiotherapy.

The US intergroup CR rate to chemoradiotherapy was 49%, using SWOG response criteria that did not include PET imaging. [5] However, many have argued that this CR rate was atypically low when compared to other studies conducted primarily in Asia . Because the CR rates reported in many other studies are so high and because PFS rates at one year in many RCTS of chemoradiaton in NPC are so high, [5-7, 11] we have decided to make PFS at 2 years following the end of chemoradiation as the primary endpoint of this study. In the 4 studies referenced above, the average 2 year PFS for the superior arm was 0.7 and no single study achieved a PFS greater than 0.85. Therefore we will evaluate 40 patients in a single stage design for progression free survival at 2 years post radiation, which will give an alpha of 0.1 and a power of 0.9 to distinguish a 2 year PFS of 0.88 from 0.7 .

It is not feasible with the accrual rate planned to introduce an early stopping rule for a PFS at 2 years. Therefore, in order to avoid accruing up to 40 patients to a study that is unlikely to be of interest, we will have an early stopping rule based on RECIST determined CR rates. If there are less than 10 CRs in the first 18 patients, we would stop the trial. If the trial goes to the second stage, the treatment will be considered worthy of further study if 33 or more of the 40 patients are progression-free at 2 years.

11.2 **Sample Size/Accrual Rate**

18-40 evaluable patients. 2-4 per month. All patients who are not evaluable will be replaced. Any patient who starts treatment with TPF will be considered evaluable for response.

11.3 **Stratification Factors**

No stratification

11.4 **Analysis of Secondary Endpoints:**

1. Progression free survival and overall survival will be estimated according to the methods of Kaplan and Meier.

2. Rates of adverse events will be analyzed as follows:

The acceptable incidence of AEs resulting in protocol treatment discontinuance is 3% or less, and the unacceptable rate is 15% or greater. The rates of AEs resulting in protocol treatment discontinuation will be estimated using a binomial distribution along with their associated 95% confidence intervals. Only adverse events assessed definitely, probably, or possibly related to protocol treatment will be considered. 40 evaluable patients will be able to distinguish between the above null and alternative hypothesis with and alpha error of .03 and power .87.

11.5 **Reporting**

11.5.1 **Evaluation of toxicity.** All patients will be evaluable for toxicity from the time of their first treatment .

11.5.2 **Evaluation of response.** All patients who receive one cycle of TPF will be considered evaluable for response. Response categories will be: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data).

REFERENCES

1.Licitra L, Bernier J, Cvitkovic E, et al. Cancer of the nasopharynx. Critical Reviews in Oncology-Hematology 2003;45:199-213.

2.Kantakamalakul W, Chongkolwatana C, Naksawat P, et al. Specific IgA antibody to Epstein-Barr viral capsid antigen: a better marker for screening nasopharyngeal carcinoma than EBV-DNA detection by polymerase chain reaction. Asian Pacific Journal of Allergy & Immunology 2000;18:221-6.

3.Leung SF, Zee B, Ma BB, et al. Plasma Epstein-Barr viral deoxyribonucleic acid quantitation complements tumor-node-metastasis staging prognostication in nasopharyngeal carcinoma. Journal of Clinical Oncology 2006;24:5414-8.

4.Le QT, Jones CD, Yau TK, et al. A comparison study of different PCR assays in measuring circulating plasma epstein-barr virus DNA levels in patients with nasopharyngeal carcinoma. Clinical Cancer Research 2005;11:5700-7.

5.Al-Sarraf M, LeBlanc M, Giri PG, et al. Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: phase III randomized Intergroup study 0099. Journal of Clinical Oncology 1998;16:1310-7.

6.Lin JC, Jan JS, Hsu CY, Liang WM, Jiang RS, Wang WY. Phase III study of concurrent chemoradiotherapy versus radiotherapy alone for advanced nasopharyngeal carcinoma: positive effect on overall and progression-free survival.[see comment]. Journal of Clinical Oncology 2003;21:631-7.

7.Chan AT, Leung SF, Ngan RK, et al. Overall survival after concurrent cisplatin-radiotherapy compared with radiotherapy alone in locoregionally advanced nasopharyngeal carcinoma. Journal of the National Cancer Institute 2005;97:536-9.

8.Lee AW, Tung SY, Chan AT, et al. Preliminary results of a randomized study (NPC-9902 Trial) on therapeutic gain by concurrent chemotherapy and/or accelerated fractionation for locally advanced nasopharyngeal carcinoma. International Journal of Radiation Oncology, Biology, Physics 2006;66:142-51.

9.Chan AT, Teo PM, Ngan RK, et al. Concurrent chemotherapy-radiotherapy compared with radiotherapy alone in locoregionally advanced nasopharyngeal carcinoma: progression-free survival analysis of a phase III randomized trial.[see comment]. Journal of Clinical Oncology 2002;20:2038-44.

10.Chua DT, Sham JS, Wei WI, Ho WK, Au G, Choy D. Control of regional metastasis after induction chemotherapy and radiotherapy for nasopharyngeal carcinoma. Head & Neck 2002;24:350-60.

11.Chua DT, Ma J, Sham JS, et al. Long-term survival after cisplatin-based induction chemotherapy and radiotherapy for nasopharyngeal carcinoma: a pooled data analysis of two phase III trials.[see comment]. Journal of Clinical Oncology 2005;23:1118-24.

12.Hong RL, Ting LL, Ko JY, et al. Induction chemotherapy with mitomycin, epirubicin, cisplatin, fluorouracil, and leucovorin followed by radiotherapy in the treatment of locoregionally advanced nasopharyngeal carcinoma. Journal of Clinical Oncology 2001;19:4305-13.

13.Paccagnella A, Favaretto A, Oniga F, et al. Cisplatin versus carboplatin in combination with mitomycin and vinblastine in advanced non small cell lung cancer. A multicenter, randomized phase III trial. Lung Cancer 2004;43:83-91.

14.Scagliotti GV, De Marinis F, Rinaldi M, et al. Phase III randomized trial comparing three platinum-based doublets in advanced non-small-cell lung cancer. Journal of Clinical Oncology 2002;20:4285-91.

15.Fossella F, Pereira JR, von Pawel J, et al. Randomized, multinational, phase III study of docetaxel plus platinum combinations versus vinorelbine plus cisplatin for advanced non-small-cell lung cancer: the TAX 326 study group.[see comment]. Journal of Clinical Oncology 2003;21:3016-24.

16.Aravantinos G, Fountzilas G, Kosmidis P, et al. Paclitaxel plus carboplatin versus paclitaxel plus alternating carboplatin and cisplatin for initial treatment of advanced ovarian cancer: long-term efficacy results: a Hellenic Cooperative Oncology Group (HeCOG) study. Annals of Oncology 2005;16:1116-22.

17.du Bois A, Luck HJ, Meier W, et al. A randomized clinical trial of cisplatin/paclitaxel versus carboplatin/paclitaxel as first-line treatment of ovarian cancer. Journal of the National Cancer Institute 2003;95:1320-9.

18.Ozols RF, Bundy BN, Greer BE, et al. Phase III trial of carboplatin and paclitaxel compared with cisplatin and paclitaxel in patients with optimally resected stage III ovarian cancer: a Gynecologic Oncology Group study.[see comment]. Journal of Clinical Oncology 2003;21:3194-200.

19.Homma A, Shirato H, Furuta Y, et al. Randomized phase II trial of concomitant chemoradiotherapy using weekly carboplatin or daily low-dose cisplatin for squamous cell carcinoma of the head and neck. Cancer Journal 2004;10:326-32.

20.Chitapanarux I, Lorvidhaya V, Kamnerdsupaphon P, et al. Chemoradiation comparing cisplatin versus carboplatin in locally advanced nasopharyngeal cancer: randomised, non-inferiority, open trial. European Journal of Cancer 2007;43:1399-406.

21.Forastiere AA, Shank D, Neuberg D, Taylor SGt, DeConti RC, Adams G. Final report of a phase II evaluation of paclitaxel in patients with advanced squamous cell carcinoma of the head and neck: an Eastern Cooperative Oncology Group trial (PA390). Cancer 1998;82:2270-4.

22.Dreyfuss AI, Clark JR, Norris CM, et al. Docetaxel: an active drug for squamous cell carcinoma of the head and neck. Journal of Clinical Oncology 1996;14:1672-8.

23.Hitt R, Grau J, Lopez- Puose A, et al. Randomized phase II/III clinical trial of induction chemotherapy (ICT) with either cisplatin/5-fluorouracil (PF) or docetaxel/cisplatin/5-fluorouracil (TPF) followed by chemoradiotherapy (CRT) vs. crt alone for patients (pts) with unresectable locally advanced head and neck cancer (LAHNC). Journal of Clinical Oncology 2006;24:5515.

24.Vermorken JB, Remenar E, van Herpen C, et al. Cisplatin, fluorouracil, and docetaxel in unresectable head and neck cancer. New England Journal of Medicine 2007;357:1695-704.

25.Posner MR, Colevas AD. Induction chemotherapy in the management of squamous cell cancer of the head and neck.[comment]. Cancer Journal From Scientific American 1997;3:73-5.

26.Administration USFaD. Approval History New Drug Application # 020449 for docetaxel.

27.Pignon JP, Syz N, Posner M, et al. Adjusting for patient selection suggests the addition of docetaxel to 5-fluorouracil-cisplatin induction therapy may offer survival benefit in squamous cell cancer of the head and neck. Anti-Cancer Drugs 2004;15:331-40.

28.Chua DT, Sham JS, Au GK. A phase II study of docetaxel and cisplatin as first-line chemotherapy in patients with metastatic nasopharyngeal carcinoma. Oral Oncology 2005;41:589-95.

29.Haddad R, Colevas AD, Tishler R, et al. Docetaxel, cisplatin, and 5-fluorouracil-based induction chemotherapy in patients with locally advanced squamous cell carcinoma of the head and neck: the Dana Farber Cancer Institute experience. Cancer 2003;97:412-8.

30.Colevas AD, Busse PM, Norris CM, et al. Induction chemotherapy with docetaxel, cisplatin, fluorouracil, and leucovorin for squamous cell carcinoma of the head and neck: a phase I/II trial.[see comment]. Journal of Clinical Oncology 1998;16:1331-9.

31.Colevas AD, Norris CM, Tishler RB, et al. Phase II trial of docetaxel, cisplatin, fluorouracil, and leucovorin as induction for squamous cell carcinoma of the head and neck.[see comment]. Journal of Clinical Oncology 1999;17:3503-11.

32.Colevas AD, Norris CM, Tishler RB, et al. Phase I/II trial of outpatient docetaxel, cisplatin, 5-fluorouracil, leucovorin (opTPFL) as induction for squamous cell carcinoma of the head and neck (SCCHN). American Journal of Clinical Oncology 2002;25:153-9.

33.Kyzas PA, Cunha IW, Ioannidis JP. Prognostic significance of vascular endothelial growth factor immunohistochemical expression in head and neck squamous cell carcinoma: a meta-analysis. Clinical Cancer Research 2005;11:1434-40.

34.Wakisaka N, Wen QH, Yoshizaki T, et al. Association of vascular endothelial growth factor expression with angiogenesis and lymph node metastasis in nasopharyngeal carcinoma. Laryngoscope 1999;109:810-4.

35.Qian CN, Zhang CQ, Guo X, et al. Elevation of serum vascular endothelial growth factor in male patients with metastatic nasopharyngeal carcinoma. Cancer 2000;88:255-61.

36.Krishna SM, James S, Balaram P. Expression of VEGF as prognosticator in primary nasopharyngeal cancer and its relation to EBV status. Virus Research 2006;115:85-90.

37.Druzgal CH, Chen Z, Yeh NT, et al. A pilot study of longitudinal serum cytokine and angiogenesis factor levels as markers of therapeutic response and survival in patients with head and neck squamous cell carcinoma. Head & Neck 2005;27:771-84.

38.Sanguineti G, Geara FB, Garden AS, et al. Carcinoma of the nasopharynx treated by radiotherapy alone: determinants of local and regional control.[see comment]. International Journal of Radiation Oncology, Biology, Physics 1997;37:985-96.

39.Okunieff P, de Bie J, Dunphy EP, Terris DJ, Hockel M. Oxygen distributions partly explain the radiation response of human squamous cell carcinomas. British Journal of Cancer - Supplement 1996;27:S185-90.

40.Jain RK. Normalization of tumor vasculature: an emerging concept in antiangiogenic therapy. Science 2005;307:58-62.

41.Winkler F, Kozin SV, Tong RT, et al. Kinetics of vascular normalization by VEGFR2 blockade governs brain tumor response to radiation: role of oxygenation, angiopoietin-1, and matrix metalloproteinases.[see comment]. Cancer Cell 2004;6:553-63.

42.Willett CG, Boucher Y, di Tomaso E, et al. Direct evidence that the VEGF-specific antibody bevacizumab has antivascular effects in human rectal cancer.[see comment][erratum appears in Nat Med. 2004 Jun;10(6):649]. Nature Medicine 2004;10:145-7.

43.Taghian AG, Abi-Raad R, Assaad SI, et al. Paclitaxel decreases the interstitial fluid pressure and improves oxygenation in breast cancers in patients treated with neoadjuvant chemotherapy: clinical implications. Journal of Clinical Oncology 2005;23:1951-61.

44.Batchelor TT, Sorensen AG, di Tomaso E, et al. AZD2171, a pan-VEGF receptor tyrosine kinase inhibitor, normalizes tumor vasculature and alleviates edema in glioblastoma patients.[see comment]. Cancer Cell 2007;11:83-95.

45.Yeh SH, Liu RS, Wu LC, et al. Fluorine-18 fluoromisonidazole tumour to muscle retention ratio for the detection of hypoxia in nasopharyngeal carcinoma. European Journal of Nuclear Medicine 1996;23:1378-83.

46.Leslie MD, Dische S. The early changes in salivary gland function during and after radiotherapy given for head and neck cancer. Radiotherapy & Oncology 1994;30:26-32.

47.Mira JG, Wescott WB, Starcke EN, Shannon IL. Some factors influencing salivary function when treating with radiotherapy. International Journal of Radiation Oncology, Biology, Physics 1981;7:535-41.

48.Harrison LB, Zelefsky MJ, Pfister DG, et al. Detailed quality of life assessment in patients treated with primary radiotherapy for squamous cell cancer of the base of the tongue.[see comment]. Head & Neck 1997;19:169-75.

49.Cooper JS, Fu K, Marks J, Silverman S. Late effects of radiation therapy in the head and neck region. International Journal of Radiation Oncology, Biology, Physics 1995;31:1141-64.

50.Wang CC. Carcinoma of the nasopharynx. In: Wang CC, ed. Radiation Therapy for Head and Neck

Neoplasms: Indications, Techniques, and Results 2ed. Chicago: Year Book Medical Publishers; 1990:261-83.

51.Bailet JW, Mark RJ, Abemayor E, et al. Nasopharyngeal carcinoma: treatment results with primary radiation therapy. Laryngoscope 1992;102:965-72.

52.Hoppe RT, Goffinet DR, Bagshaw MA. Carcinoma of the nasopharynx. Eighteen years' experience with megavoltage radiation therapy. Cancer 1976;37:2605-12.

53.Chu AM, Flynn MB, Achino E, Mendoza EF, Scott RM, Jose B. Irradiation of nasopharyngeal carcinoma: correlations with treatment factors and stage. International Journal of Radiation Oncology, Biology, Physics 1984;10:2241-9.

54.Teo PM, Ma BB, Chan AT. Radiotherapy for nasopharyngeal carcinoma--transition from two-dimensional to three-dimensional methods. Radiotherapy & Oncology 2004;73:163-72.

55.Sultanem K, Shu HK, Xia P, et al. Three-dimensional intensity-modulated radiotherapy in the treatment of nasopharyngeal carcinoma: the University of California-San Francisco experience. International Journal of Radiation Oncology, Biology, Physics 2000;48:711-22.

56.Liu WS, Su MC, Wu MF, Tseng HC, Kuo HC. Nasopharyngeal carcinoma treated with precision-oriented radiation therapy techniques including intensity-modulated radiotherapy: preliminary results. Kaohsiung Journal of Medical Sciences 2004;20:49-55.

57.Xia P, Fu KK, Wong GW, Akazawa C, Verhey LJ. Comparison of treatment plans involving intensity-modulated radiotherapy for nasopharyngeal carcinoma.[see comment]. International Journal of Radiation Oncology, Biology, Physics 2000;48:329-37.

58.Wolden SL, Zelefsky MJ, Hunt MA, et al. Failure of a 3D conformal boost to improve radiotherapy for nasopharyngeal carcinoma. International Journal of Radiation Oncology, Biology, Physics 2001;49:1229-34.

59.Hunt MA, Zelefsky MJ, Wolden S, et al. Treatment planning and delivery of intensity-modulated radiation therapy for primary nasopharynx cancer. International Journal of Radiation Oncology, Biology, Physics 2001;49:623-32.

60.Lee N, Xia P, Quivey JM, et al. Intensity-modulated radiotherapy in the treatment of nasopharyngeal carcinoma: an update of the UCSF experience.[see comment]. International Journal of Radiation Oncology, Biology, Physics 2002;53:12-22.

61.Kwong DL, Pow EH, Sham JS, et al. Intensity-modulated radiotherapy for early-stage nasopharyngeal carcinoma: a prospective study on disease control and preservation of salivary function. Cancer 2004;101:1584-93.

62.Wolden SL, Chen WC, Pfister DG, Kraus DH, Berry SL, Zelefsky MJ. Intensity-modulated radiation therapy (IMRT) for nasopharynx cancer: update of the Memorial Sloan-Kettering experience. International Journal of Radiation Oncology, Biology, Physics 2006;64:57-62.

63.Pow EH, Kwong DL, McMillan AS, et al. Xerostomia and quality of life after intensity-modulated radiotherapy vs. conventional radiotherapy for early-stage nasopharyngeal carcinoma: initial report on a randomized controlled clinical trial. International Journal of Radiation Oncology, Biology, Physics 2006;66:981-91.

64.Kam M, Leung S, Zee B, et al. Prospective Randomized Study of Intensity-Modulated Radiotherapy on Salivary Gland Function in Early-Stage Nasopharyngeal Carcinoma Patients. Journal of Clinical Oncology 2007;25:4873-9.

65.Kam MK, Teo PM, Chau RM, et al. Treatment of nasopharyngeal carcinoma with intensity-modulated radiotherapy: the Hong Kong experience. International Journal of Radiation Oncology, Biology, Physics 2004;60:1440-50.

66.Presta LG, Chen H, O'Connor SJ, et al. Humanization of an anti-vascular endothelial growth factor monoclonal antibody for the therapy of solid tumors and other disorders. Cancer Research 1997;57:4593-9.

67.Kim KJ, Li B, Winer J, et al. Inhibition of vascular endothelial growth factor-induced angiogenesis suppresses tumour growth in vivo. Nature 1993;362:841-4.

68.Borgstrom P, Gold DP, Hillan KJ, Ferrara N. Importance of VEGF for breast cancer angiogenesis in vivo: implications from intravital microscopy of combination treatments with an anti-VEGF neutralizing monoclonal antibody and doxorubicin. Anticancer Research 1999;19:4203-14.

69.Shaheen RM, Ahmad SA, Liu W, et al. Inhibited growth of colon cancer carcinomatosis by antibodies to vascular endothelial and epidermal growth factor receptors. British Journal of Cancer 2001;85:584-9.

70.Bergers G, Song S, Meyer-Morse N, Bergsland E, Hanahan D. Benefits of targeting both pericytes and endothelial cells in the tumor vasculature with kinase inhibitors.[see comment]. Journal of Clinical Investigation 2003;111:1287-95.

71.Cobleigh MA, Langmuir VK, Sledge GW, et al. A phase I/II dose-escalation trial of bevacizumab in previously treated metastatic breast cancer. Seminars in Oncology 2003;30:117-24.

72.Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer.[see comment]. New England Journal of Medicine 2004;350:2335-42.

73.Miller KD, Chap LI, Holmes FA, et al. Randomized phase III trial of capecitabine compared with bevacizumab plus capecitabine in patients with previously treated metastatic breast cancer. Journal of Clinical Oncology 2005;23:792-9.

74.Yang JC, Haworth L, Sherry RM, et al. A randomized trial of bevacizumab, an anti-vascular endothelial growth factor antibody, for metastatic renal cancer.[see comment]. New England Journal of Medicine 2003;349:427-34.

75.Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report.[see comment][erratum appears in JAMA. 2003 Jul 9;290(2):197]. JAMA 2003;289:2560-72.

76.Novotny W, Holmgren, E., Griffing, S., et al. Identification of squamous cell histology and central, cavitary tumors as possible risk factors for pulmonary hemorrhage in patients with advanced NSCLC receiving bevacizumab. Proc Am Soc Clin Oncol 2001:20:A1318.

77.Scappaticci FA, Skillings JR, Holden SN, et al. Arterial thromboembolic events in patients with metastatic carcinoma treated with chemotherapy and bevacizumab. Journal of the National Cancer Institute 2007;99:1232-9.

78.Scappaticci FA, Fehrenbacher L, Cartwright T, et al. Surgical wound healing complications in metastatic colorectal cancer patients treated with bevacizumab. Journal of Surgical Oncology 2005;91:173-80.

79.Karp JE, Gojo I, Pili R, et al. Targeting vascular endothelial growth factor for relapsed and refractory adult acute myelogenous leukemias: therapy with sequential 1-beta-d-arabinofuranosylcytosine, mitoxantrone, and bevacizumab. Clinical Cancer Research 2004;10:3577-85.

80.Allen JA, Adlakha A, Bergethon PR. Reversible posterior leukoencephalopathy syndrome after bevacizumab/FOLFIRI regimen for metastatic colon cancer. Archives of Neurology 2006;63:1475-8.

81.Glusker P, Recht L, Lane B. Reversible posterior leukoencephalopathy syndrome and bevacizumab. New England Journal of Medicine 2006;354:980-2; discussion -2.

82.Ozcan C, Wong SJ, Hari P. Reversible posterior leukoencephalopathy syndrome and bevacizumab. New England Journal of Medicine 2006;354:980-2; discussion -2.

83.American Society of Clinical O, Kris MG, Hesketh PJ, et al. American Society of Clinical Oncology guideline for antiemetics in oncology: update 2006. Journal of Clinical Oncology 2006;24:2932-47.

84.Rajendran JG, Krohn KA. Imaging hypoxia and angiogenesis in tumors. Radiologic Clinics of North America 2005;43:169-87.

85.Ziemer LS, Evans SM, Kachur AV, et al. Noninvasive imaging of tumor hypoxia in rats using the 2-nitroimidazole 18F-EF5. European Journal of Nuclear Medicine & Molecular Imaging 2003;30:259-66.

86.Reischl G, Dorow DS, Cullinane C, et al. Imaging of tumor hypoxia with [124I]IAZA in comparison with [18F]FMISO and [18F]FAZA--first small animal PET results. Journal of Pharmacy & Pharmaceutical Sciences 2007;10:203-11.

87.Graham MM, Peterson LM, Link JM, et al. Fluorine-18-fluoromisonidazole radiation dosimetry in imaging studies. Journal of Nuclear Medicine 1997;38:1631-6.

APPENDIX A: Performance Status Criteria

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

APPENDIX B: Radiation Quality Assurance Form

Patient Initials:_____ Patient No.:_____ Sex: M ☐ F ☐

Radiotherapy Dept.:_____ Radiation Oncologist:_____

DOSE PRESCRIPTION

Target Volume:_____ Date of first treatment:_____

Dose per Fraction to Prescription Volume (cGy)		Maximum Dose per Fraction in the Planning Target Volume	
Prescription to which Isodose Surface (e.g. 95%)		Minimum Dose per Fraction in the Planning Target Volume	
Intended Number of Fractions		**Patient's weight pre-tretment**	
Intended Dose to Prescription Volume		**Patient's weight post-treatment**	

Planning System	
Treatment Machine	
Patient Position	

IMRT ☐ ***OR*** 3D ☐	Form of IMRT SMLC (step & shoot):_____ DMLC (sliding window):_____ Serial tomotherapy (MIMiC):_____ Other:_____	Integrated boost ☐ ***OR*** Sequential boost ☐	Supraclavicular field matching: Yes ☐ No ☐

List Names Of Target Volumes Corresponding To Those On RT-1 Forms, Record Boost Volumes Separately			
Names of Target Volume (i.e. PTV1, Chest)			
Date of First Treatment			

to the Target Volume			
Number of Treatments			
Date of Last Treatment			
Total Dose To Prescription Point			
Number of Fields			
Beam Energy			
Monitor Unit/Fraction			
Critical Structure	**Max Dose (Gy)**	**Critical Structure**	**Max Dose (Gy)**
A. Brainstem	54	**F .** Optic nerves	54
B. Spinal cord	45	**G.** Optic chiasms	54
C. Eyes	50	**H.** Other	
D. Brachial plexus	66	**I.** Other	
E. Mandible	70	**J.** Other	
Interruptions			
From:	**To:**	**Reason:**	
From:	**To:**	**Reason:**	
From:	**To:**	**Reason:**	
From:	**To:**	**Reason:**	
Off Protocol Therapy			
Date:	**Reason:**		
Discontinued Radiotherapy			
Date:	**Reason:**		

APPENDIX C: Provide all supporting documentation for confirmation of patient eligibility.

Inclusion/Exclusion Criteria

Inclusion Criteria	
___Yes ___NO	Patient has histologically or cytologically confirmed nasopharyngeal carcinoma, stages II (minimally T2a,N0,M0 or Tany,N1, M0) through IVb. Patients with metastatic (stage IVc) untreated NPC who otherwise meet all eligibility criteria will be enrolled on a separate cohort and evaluated separately. Stage: T_____N_____ M _____
___Yes ___NO	Patient has measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm with conventional techniques or as ≥10 mm with spiral CT scan. See Measurement of Effect

	section for details.
___Yes ___NO	Has patient received any prior treatment(s)? [Patients may have had diagnostic surgery(s) at the primary site or neck as long as there is still measurable disease present.]
___Yes ___NO	Patient is at least Age >15 years. [No dosing or adverse event data are currently available on the use of the TPF combination in patients <15 years of age, children are excluded from this study but will be eligible for future pediatric trials]
___Yes ___NO	Patient has a life expectancy of greater than 3 months.
___Yes ___NO	Patients' ECOG performance status <2. PS = ____
___Yes ___NO	Patients has normal organ and marrow function as defined below: -absolute neutrophil count≥1,500/mcL value_____ date_____ -platelets ≥100,000/mcL value_____ date_____ -total bilirubin ≤1.5 X institutional ULN value_____ date_____ -AST(SGOT)/ALT(SGPT)≤2.5 X institutional ULN value_____ date_____ -creatinine ≤ 1.5 mg/dl value_____ date_____ -creatinine clearance≥55 mL/min/1.73 m^2 for patients with creatinine levels above 1.5 mg/dl value_____ date_____ **Patients with creatinine > grade 1 but less than grade 3 are eligible but should receive carboplatin throughout the protocol instead of cisplatin.**
___Yes ___NO	-Peripheral motor/sensory neuropathy < grade 2. **If peripheral neuropathy is grade 2, patients are still eligible but should receive carboplatin throughout the protocol instead of cisplatin. _____neuropathy grade_____ date assessed. Cisplatin should be substituted with carboplatin for creatinine > grade 1 , neuropathy > grade 2 or hearing loss > grade 2**
___Yes ___NO	Patient agrees to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation if a women of child-bearing potential or male. [Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.]
___Yes ___NO	Patient has the ability to understand and the willingness to sign a written informed consent.
Exclusion Criteria	
___Yes ___NO	Has patient had chemotherapy or radiotherapy for nasopharyngeal carcinoma?
___Yes ___NO	Does patient have known brain metastases? No CNS imaging is required if no clinical indication
___Yes ___NO	Does patient have a history of allergic reactions attributed to compounds of similar chemical or biologic composition to docetaxel, cisplatin, carboplatin, 5- Fluorouracil, or other agents used in the study?
___Yes ___NO	Is the patient HIV-positive and on combination antiretroviral therapy? No HIV testing is required if no clinical indication
___Yes ___NO	Does patient have an uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements?
___Yes ___NO	Does patient have clinically significant cardiovascular disease?
___Yes ___NO	Does patient have a history of CVA within 6 months?
___Yes ___NO	Has patient had a myocardial infarction or unstable angina within 6 months?

___Yes ___NO	Does patient have a New York heart association grade II or greater congestive heart failure?
___Yes ___NO	Does patient have a serious and inadequately controlled cardiac arrhythmia?
___Yes ___NO	Does patient have significant vascular disease (e.g. aortic aneurysm, history of aortic dissection)?
___Yes ___NO	Does patient have clinically significant peripheral vascular disease?

Confirmation of Eligibility:

My signature below attests the eligibility for this patient was confirmed by at least two (2) personnel prior to being enrolled onto study. Patient was found to be: **Eligible / Not Eligible**

Primary Investigator / Treating Physician_____

Signature & Date

Secondary Reviewer _____

Signature & Date