Clinical protocols

1. 04-LUN-69-UKY- A Phase I Trial of Docetaxel and low-dose fractionated radiation in the Treatment of metastatic or recurrent Non-Small Cell Lung Cancer (NSCLC).
2. 00-H&N-11- Paclitaxel, Carboplatin and Radiotherapy as induction therapy in locally advanced head and neck cancer.
3. 02-H&N-15BMS (CRG-0043-02)- Paclitaxel, carboplatin and low dose radiation as induction therapy in locally advanced head and neck cancer.
4. A phase I study using low dose abdominal radiotherapy as a taxotere chemosensitizer for recurrent/persistent or advanced ovarian cancer.
5. Radiation Therapy to the Abdomen Plus Docetaxel in Treating Patients With Recurrent or Persistent Advanced Ovarian, Peritoneal, or Fallopian Tube Cancer. Sponsors and Collaborators: Gynecologic Oncology Group.

04-LUN-69-UKY

A PHASE I TRIAL OF DOCETAXEL AND LOW-DOSE FRACTIONATED RADIATION IN THE TREATMENT OF METASTATIC OR RECURRENT NON-SMALL CELL LUNG CANCER (NSCLC)

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AGENTS:

Docetaxel
Low-Dose Fractionated Radiation

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1.0 OBJECTIVES

The objectives of this Phase I study are:

1.1 To assess the MTD of low-dose fractionated radiation in combination with Docetaxel in recurrent or metastatic non-small cell lung cancer in the second-line setting.

Secondary Objectives

1.2 To assess quantitative toxicities in this group of patients treated with this regimen.

1.3 To investigate in an exploratory manner, the association of p53, $p21^{waf1/cip1}$, bcl-x_L, bcl-2 and bax markers in pre- and post-treatment biopsies with patient response and toxicity.

2.0 BACKGROUND

Lung cancer will be discovered in 173,770 people and cause death in 160,440 people in the United States in 2004.(1) Non-small cell lung cancer (NSCLC) is the dominant subtype--approximately 80% of all lung cancers are of non-small cell type. Cisplatin-based, combination chemotherapy is the treatment of choice in stage IV disease (as well as in stage IIIB NSCLC with pleural effusion), as evidenced by a large meta-analysis of clinical trials showing improved 1-year survival from 5 to 15% (2) and recent randomized phase III studies (3,4) with encouraging 1-year survival of 33%. Survival in recurrent NSCLC is dismal with a response rate of 10-20% and a median survival of 5.5 to 7 months using the best therapies available.(5-8) These advances in the therapy of relapsed NSCLC are sobering—only slight prolongation of life has been achieved. Novel ideas are needed to improve upon these small gains. One such approach is to utilize radiation in a novel way. Numerous studies have shown improved survival and time-to-relapse when cisplatin-based chemotherapy was added to full dose radiation in locally advanced NSCLC (9-11). Recent reports of full dose radiation plus taxane-platinum combinations have shown enhanced radiation sensitization and improved survival (12) However, full dose radiation in combination with chemotherapy is impractical and too toxic to apply to metastatic and recurrent NSCLC patients who have often had prior irradiation. However, using the lowest doses of radiation in combination with chemotherapy has never been studied in NSCLC.

Until recently, the initial slope of the radiation cell-survival curve (doses of 0-100 cGy) was presumed to be an ineffective dose range for human tumor therapy. However, as techniques to adequately study low dose radiation have improved, quite the opposite effect has been described. Joiner and colleagues revolutionized thinking about low doses of radiation (<100 cGy) by demonstrating an initial phase of hypersensitivity to radiation using doses from 0 to 50 cGy (13). In work from the University of Kentucky, Ahmed and colleagues (14,15) have expanded our understanding of the clinically effective range of radiation by combining multiple low dose fractions of radiation with various chemotherapeutic agents. They have demonstrated enhanced cell death compared to chemotherapy or radiation alone. Significantly, fractionated low dose radiation enhanced pro-apoptotic pathways without inducing pro-survival cascades, thus avoiding the development of radiation resistance seen with higher dose radiation.(16) This may provide one way to overcome radiation resistance, a major cause of treatment failure in NSCLC, while still enhancing cell death. The central theme of this proposal is to use LDFRT combined with chemotherapy in the treatment of metastatic and recurrent NSCLC (in a phase I trial) and to further define the molecular mechanisms underlying this therapy.

The preliminary data described above suggests a unique synergistic effect between LDFRT and taxane-based chemotherapy. Initially, human subjects with squamous cell carcinoma of the head and neck were evaluated using this concept. (17) Because of the excellent clinical response seen in head and neck cancer, a clinical protocol was developed to study the effect of LDFRT and chemotherapy in metastatic and recurrent NSCLC. Docetaxel was chosen because of its excellent preclinical efficacy with LDFRT (18) and its well-established role in recurrent NSCLC. Because of demonstrated efficacy, weekly Docetaxel will be utilized in order to include

PS 2 patients and to provide weekly exposure to LDFRT and chemotherapy (19-21). Because of the preliminary data described previously, showing maximal HRS at between 50 and 80 cGy (14,15), as well as work in other laboratories confirming the effectiveness of this range of dosing (13), we will escalate the dose of LDRT from 50 to 80 cGy and confirm efficacy at the MTD-1 dose level of radiation. Two doses of ultrafractionation were chosen based on the molecular studies and because they provide the minimum amount of radiation needed for chemopotentiation, while allowing for the least potential toxicity. This study will also help to define the feasibility of this approach in patients who have received prior irradiation to the chest. The central hypothesis of this study is to establish the feasibility and safety of Docetaxel and LDFRT in patients with metastatic or recurrent NSCLC who have failed a prior platinum-containing regimen. It is hoped that this pilot data using radiation as a chemopotentiator will provide the basis for future studies of LDFRT and chemotherapy in NSCLC.

Inclusion of Women and Minorities

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

3.0 DRUG INFORMATION

3.1 Docetaxel

a. DESCRIPTION
Chemical name 4-acetoxy-2α-benzoyloxy-5β, 20-epoxy-1, 7β, 10β-trihydroxy-9-oxotac-11-ene-13-α-yl-(2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy3-phenylpropionate

-Empirical formula: $C_{43}H_{53}O_{14}N$
-Molecular weight: 807.9
-Appearance: White powder

Mechanism of action

Docetaxel is an antineoplastic agent that acts by disrupting the microtubular network in cells that is essential for mitotic and interphase cellular functions. Docetaxel binds to free tubulin and promotes the assembly of tubulin into stable microtubules while simultaneously inhibiting their disassembly. This leads to the production of microtubule bundles without normal function and to the stabilization of microtubules, which results in the inhibition of mitosis in cells. Docetaxel's binding to microtubules does not alter the number of protofilaments in the bound microtubules, a feature which differs from most spindle poisons currently in clinical use.

b. TOXICOLOGY

The major toxic effect of docetaxel which limits dose is neutropenia. Other toxic effects which may be seen include leukopenia, thrombocytopenia, anemia, asthenia, dysgeusia, myalgia, arthralgia, nail changes and conjunctivitis. Severe anaphylactoid reactions, characterized by a flush associated with hypo- or hypertension, with or without dyspnea, may occur. Other toxicities include cutaneous reactions, hypersensitivity reactions (flushing, pruritis, fever, chills, rigors, lower back pain), dyspnea with restrictive pulmonary syndrome, ascites, myopathy, digestive tract toxicities (nausea, vomiting, oral mucositis, diarrhea, anorexia), alopecia, extravasation reactions, reversible peripheral phlebitis, peripheral edema, reversible increase in liver function tests, hepatic failure, neurotoxicity (reversible dysesthesias or paresthesias, peripheral neuropathy, seizures, headaches, lethargy or somnolence). Patients with SGOT > 1.5 times normal and alkaline

phosphatase > 2.5 times normal appear to have decreased docetaxel clearance and appear to be more likely to suffer severe toxicity, including drug-related death.

c. PHARMACOLOGY

Formulation: The formulation consists of a docetaxel vial and a solvent vial.

Preparation and Administration:

Docetaxel Injection Concentrate requires two dilutions prior to administration.

Initial Diluted Solution: Docetaxel vials should be stored between 2 and 25°C (36 and 77°F). If the vials are stored under refrigeration, allow the appropriate number of vials of Docetaxel Injection Concentrate and diluent (13% ethanol in water for injection) vials to stand at room temperature for approximately 5 minutes. Aseptically withdraw the entire contents of the appropriate diluent vial (approximately 1.8 mL for Docetaxel 20 mg and approximately 7.1 mL for Docetaxel 80 mg) into a syringe by partially inverting the vial, and transfer it to the appropriate vial of Docetaxel Injection Concentrate. If the procedure is followed as described, an initial diluted solution of 10mg docetaxel/mL will result.

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. 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.

Final Dilution for Infusion: Aseptically withdraw the required amount of initial diluted Docetaxel solution (10 mg docetaxel/mL) with a calibrated syringe and inject into a 250 mL infusion bag or bottle of either 0.9% Sodium Chloride solution or 5% Dextrose solution to produce a final concentration of 0.3 to 0.74 mg/mL. If a dose greater than 200 mg of Docetaxel is required, use a larger volume of the infusion vehicle so that a concentration of 0.74 mg/mL Docetaxel is not exceeded. Thoroughly mix the infusion by manual rotation. 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 initial diluted solution or final dilution for infusion is not clear or appears to have precipitation, these should be discarded.

Infusion: The final Docetaxel dilution for infusion should be administered intravenously as a 1-hour infusion 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.

Stability: Docetaxel solution, if stored between 2 and 25°C (36 and 77°F) is stable for 8 hours after initial dilution and for 8 hours after final dilution.

HOW SUPPLIED

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

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

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

4.0 STAGING CRITERIA

This section is not applicable to this study.

5.0 ELIGIBILITY CRITERIA

Each of the criteria in the following section must be met in order for a patient to be considered eligible for registration. Use the spaces provided to confirm a patient's eligibility.

Patient No. _____

Patient's Initials (L, F, M) _____

_____ 5.1 Patients must be 18 years of age or greater and have histologically or cytologically proven non-small cell lung cancer that is either metastatic or recurrent and failed at least one prior platinum-based chemotherapeutic regimen. Patients who have recurred after previous surgery and/or radiation may participate in this trial, and patients may have had prior neoadjuvant or adjuvant therapy. No restriction is placed on the number of cycles of prior therapy and patients must not have received prior single-agent, weekly Docetaxel chemotherapy.

_____ a. metastatic

_____ b. recurrent

_____ 5.2 Patients with known brain metastases are eligible for this clinical trial if their disease has been treated and they are clinically stable (based on the assessment of their treating physician) and documented by a stable or improved pretreatment CT or MRI scan of the brain to evaluate for CNS disease within 28 days prior to registration.

Date CT/MRI scan _____

_____ 5.3 Patients must have measurable OR non-measurable disease (see Section 10.1) documented by CT, MRI, X-ray or nuclear exam (FDG-PET). Measurable disease must be assessed within 28 days prior to registration and non-measurable disease must be assessed within 42 days prior to registration. Pleural effusions, ascites and laboratory parameters are not acceptable as the only evidence of disease.

Date Measurable disease assessed _____ Test Used _____

Date Non-Measurable disease assessed _____ Test Used _____

_____ 5.4 Patients must have progressed after at least one prior platinum-based chemotherapy. Prior biologic therapy or prior radiation is permitted; however, at least two weeks must have elapsed since the completion of prior therapy and patients must have recovered from all associated toxicities at the time of registration.

Date prior platinum therapy completed _____
Regimen_____ Number of cycles _____

Date prior biologic therapy completed _____ (if applicable)
Name of compound used _____

Date prior radiation therapy completed _____ (if applicable)

Patient No. _____

Patient's Initials (L, F, M) _____

_____ 5.5 At least three weeks must have elapsed since surgery (thoracic or other major surgeries) and patients must have recovered from all associated toxicities at the time of registration. Measurable or non-measurable disease must be present outside the area of surgical resection.

Date of prior surgery _____ (if applicable)

_____ 5.6 Patients must have an ANC ≥ 1,500/μl and platelet count ≥ 100,000/μl obtained within 28 days prior to registration.

ANC _____ Date obtained _____PLTS _____ Date obtained _____

_____ 5.7 Patients must have adequate hepatic function documented by a serum bilirubin ≤ 1.5 times institutional upper limit of normal and liver enzymes (SGOT or SGPT) ≤ 2.5 x the institutional upper limit of normal obtained within 28 days prior to registration.

Bilirubin _____ IULN _____ Date obtained _____

SGOT or SGPT (circle one) _____ IULN _____ Date obtained _____

_____ 5.8 Patients requiring lung radiation must have an FEV1 of ≥ 1000 liters obtained within 28 days prior to registration and must have pulmonary function tests with DLCO.

_____ 5.9 All patients must have a Zubrod Performance Status of 0,1 or 2 (see Section 10.4).

Performance Status _____

_____ 5.10 Peripheral neuropathy, if present, must be ≤ Grade 1 (NCI Common Terminology Criteria for Adverse Events Version 3.0).

_____ 5.11 No other prior malignancy is allowed except for the following: adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, adequately treated Stage I or II cancer from which the patient is currently in complete remission or other cancer from which the patient has been disease-free for 5 years.

_____ 5.12 Pregnant or nursing women may not participate in this trial because of the increased risk of fetal harm including fetal death from the chemotherapeutic agents. Women/men of reproductive potential may not participate unless they have agreed to use an effective contraceptive method (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.

_____ 5.13 Patients must be informed of the investigational nature of this study and must sign and give written informed consent in accordance with institutional and federal guidelines.

If Day 28 or 42 falls on a weekend or holiday, the limit may be extended to the next working day.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday four weeks later would be considered Day 28.

6.0 STRATIFICATION FACTORS

There are no stratification factors for this study.

7.0 TREATMENT PLAN

For questions relating to treatment or dose modifications, please contact Dr. Arnold at (859)323-8043 or (859)257-6011.

7.1 Good Medical Practice

The following pre-study tests should be obtained within 28 days prior to registration in accordance with good medical practice. Results of these tests do not determine eligibility and minor deviations would be acceptable if they do not impact on patient safety in the clinical judgment of the treating physician. **Dr. Susanne Arnold must be contacted if there are significant abnormalities in the values of these tests.**

a. Albumin and LDH.

b. Serum sodium, creatinine and alkaline phosphatase.

c. Chest X-ray.

d. EKG.

e. Bone scan to document bone metastases, if clinically indicated.

f. CT scan of the abdomen if clinically indicated.

g. Patients should not have psychological, familial, sociological or geographical conditions that do not permit weekly medical follow-up and compliance with the study protocol.

h. Patients should not have dementia or significantly altered mental status that would prohibit the understanding and giving of informed consent.

i. Patient should not have significant history of cardiac disease, i.e., uncontrolled high blood pressure, unstable angina, congestive heart failure, myocardial infarction within the past year, or cardiac ventricular arrhythmias requiring medication.

j. Patients should not have any immediate life-threatening complications of their malignancies.

7.2 Treatment

Drug Administration

Treatment will be administered on an inpatient or outpatient basis. Expected toxicities and appropriate dose modifications for Docetaxel or low-dose radiation are described in Section 8.0. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

DRUG	DOSE	ROUTE	DAYS	INTERVAL
Dexamethasone	4 mg	PO BID day prior and day of chemotherapy	0, 1, 7, 8 14, 15	q 28 days
Docetaxel	30 mg/m2	IV over 60 minutes	1, 8, 15	q 28 days x 6 cycles
Low-dose Radiation	50 – 80 cGy	BID to areas of bulk disease	1, 8, 15	q 28 days x 6 cycles or criteria in Section 7.6 is met.

a. Docetaxel

Please see section 3.1.c for complete instructions on toxicity and administration of Docetaxel. Docetaxel should be administered prior to low-dose radiation.

NOTE: Day 8 and 15 treatment with docetaxel will be given based on ANC and platelet counts (see Section 8.2a & 8.2b).

b. Low-Dose Radiation

1. Equipment and Localization Requirements

Megavoltage equipment, linear accelerators, are used to provide appropriate photon energies *(4-6 MV)* and a wide range of electron energies *(6-20 Mev)*. Treatment distances must be $\geq$ 80 cm SSD or SAD.
Treatment prescription should include total dose, fraction size, field description and beam energy for each field.

Simulation of all fields is mandatory. Patients must be reproducibly immobilized. The use of customized blocks or multi-leaf collimator to shape treatment fields is also mandatory (excluding bone metastasis). Beam verification (port) films must be obtained initially and repeated every week during treatment and whenever any field adjustments are made.

Isodose distributions should be submitted for each field. A composite distribution should be submitted for fields undergoing significant modification. The spinal cord dose should be calculated for fields involving any area of the spinal cord.

Note: The use of CT based treatment planning may be used at the discretion of the treating radiation oncologist.

2. Low-Dose Radiation Fields

Treatment Volume - Includes shaped fields encompassing gross disease (all lesions greater than 2 cm) with a minimum of 1.5cm margin. Areas to be targeted will include areas of gross metastatic disease > 2cm, the whole or partial lung if pulmonary metastases or pleural effusion are present, whole or partial liver if liver metastasis are present, locally recurrent disease, even if previously irradiated, at the discretion of the treating radiation oncologist. The dose to the whole lung will be limited to 1200cGy total dose (based on previous studies of whole lung irradiation), unless a greater than 25% drop in FEV1 is noted, at which point whole lung radiation will be terminated. The dose to the whole liver will be limited to 2500cGy total dose. Treating radiation oncologists may choose to target specific areas of the lung or liver after whole lung or liver irradiation has

been discontinued if it is in the best interest of the patient and no grade 3 or greater toxicity is encountered. Mucosal or organ toxicities of grade 3 or greater (based on CTCAE 3.0) that are determined to be radiation induced by the investigator will result in that portal being removed from treatment (see Section 8.3).

A minimum of 4 hours should elapse between each low-dose fraction of radiation.

The spinal cord will be excluded from the photon radiation field if the total dose including prior doses of irradiation exceeds 4500cGy (conventional fraction schemes).

3. Dose and Schedule

Doses of 50 – 80 cGy will be administered with each fraction as follows:

Dose Escalation Schedule		
Dose Level	**Dose***	
	Low Dose Radiation (cGy)	***Docetaxel (mg/m2)***
Level 1	50	30
Level 2	60	30
Level 3	70	30
Level 4	80	30
**Doses are stated as exact dose in units (e.g., mg/m^2, mcg/kg, etc.) rather than as a percentage.*		

All fields will be treated on Days 1, 8, and 15 of therapy (two fractions per day). The first fraction will be given within 1 hour after completion of chemotherapy and separated by at least 4 hours from the second fraction.

c. Research Biopsy—Day 1

Between three hours and 24 hours after completion of the second fraction of radiation (Day 1 or 2), patients will undergo repeat biopsy of an easily accessible site of tumor or nodal disease wherever possible. If a biopsy of the tumor is not possible, two skin biopsies (one from within and one from outside the radiation port) will be sufficient. (See Section 15.0 for complete instructions).

7.3 Definition of Dose-Limiting Toxicity

Management and dose modifications associated with the above adverse events are outlined in Section 8.0.

The following adverse events will be considered dose-limiting toxicities:

TYPE OF ADVERSE EVENT	**GRADE**	**DURATION**
Hematologic neutropenia neutropenic fever anemia thrombocytopenia	4 or greater	Greater than 2 weeks

*With the exception of alopecia of any grade and nausea/vomiting (which may be Grade 4 severity).
**Those determined to be related to the radiation directly (i.e. within the radiation port or as determined by the treating physician to be related to LDFRT)

Dose escalation will proceed within each cohort according to the following scheme. Dose-limiting toxicity (DLT) is defined above.

Number of Patients with DLT at a Given Dose Level	**Escalation Decision Rule**
0 out of 3	Enter 3 patients at the next dose level.
≥2	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
1 out of 3	Enter at least 3 more patients at this dose level. • If 0 of these 3 patients experience DLT, proceed to the next dose level. • If 1 or more of this group suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
≤1 out of 6 at highest dose level below the maximally administered	This is generally the recommended phase 2 dose. At least 6 patients must be entered at the recommended

dose	phase 2 dose.

7.4 Supportive Care Guidelines

a. Anti-emetic choice is at the discretion of the treating physician. 5-HT3 receptor antagonist (granisetron, ondansetron, etc) prior to each treatment, is suggested.

b. Other appropriate supportive care medications may be administered at the treating physician's discretion.

7.5 Duration of Therapy

a. Patients will be treated weekly for three consecutive weeks, with a one week break. Cycles are every 28 days.

b. Patients will be evaluated for response every 2 cycles of therapy (including radiographic measures, and for patients receiving lung radiation spirogram during therapy, and spirogram with diffusion (DLCO) prior to therapy and at the end of therapy).

c. Patients who have a complete response, partial response or stable disease will be allowed to continue for up to a total of 6 cycles.

d. Patients will undergo an end of study evaluation 30 days after the last dose of study medication and radiation. Patients will be followed for assessment of disease by routine physical examination, laboratory tests (as deemed appropriate by the treating physician) and radiographic studies (identical to the pre-treatment assessment) every 3 months for the first year then every 6 months for the following two years from the time of initial registration, and then as deemed appropriate by the treating physician.

7.6 Criteria for Removal from Protocol Treatment:

a. Disease progression (as defined in Section 10.2d) or symptomatic deterioration

b. Intercurrent illness that prevents further administration of treatment

c. Unacceptable toxicity

d. The patient may withdraw from the study at any time for any reason

e. General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the treating physician.

f. Treatment delay in chemotherapy for any reason ≥ 3 weeks.

7.7 All patients will be followed until death or 3 years after initial registration, whichever is first.

8.0 TOXICITIES TO BE MONITORED AND DOSAGE MODIFICATIONS

8.1 This study will utilize the CTCAE (NCI Common Toxicity Criteria) Version 3.0 for toxicity and Adverse Event reporting. A copy of the CTCAE Version 3.0 can be downloaded from the CTEP home page (http://ctep.cancer.gov). **All appropriate treatment areas should have access to a copy of the CTCAE Version 3.0.**

NOTE: Interruptions and delays of Docetaxel and LDFRT will be allowed for up to 3 weeks for Grade 3 or 4 toxicities. Greater than 3 week delay will require the patient to be removed from study.

NOTE: All dose reductions are permanent.

8.2 Docetaxel

a. Dose Modification Table

Dose Level	Docetaxel Dose (mg/m2)
Full Dose	30
-1	25
-2	20

b. Hematologic Toxicity

Day 1 Docetaxel administration requires an absolute granulocyte count of ≥ 1,000 and platelet count of ≥ 100,000 on treatment day. Day 8 and 15 Docetaxel dose adjustments will be made based on the following hematologic criteria:

Absolute Neutrophil Count ($x10^6$/L)	Platelets (x 10^6/L)	Dose
≥ 1,000	AND ≥ 100,000	Full Dose
500 - 999	AND 50,000-99,999	Decrease 1 Dose Level
< 500	OR < 50,000	HOLD*

*Dose held during a course of therapy will be omitted and will not be administered at a later time.

If a patient experiences a grade 2 or greater hematologic toxicity in the preceding cycle OR if treatment is held for > 7 days due to neutropenia and/or thrombocytopenia, then the subsequent Docetaxel doses will be at dose level -1.

NOTE: In instances where conflicting dose attenuations are indicated by hematologic and non-hematologic toxicity, the greater dose reduction will apply.

Neurologic Toxicity

For grade 2 or greater neurotoxicity, Docetaxel will be held until recovery to Grade 1 or better. Subsequent doses will be administered at dose level -1. If greater than grade 2 neurotoxicity is observed at the reduced dose, then docetaxel will be stopped and the patient will be removed from protocol.

Non-Hematologic Toxicity
All other non-hematologic toxicities will use the following dose reduction schedule:

Dose reductions for Docetaxel and LDFRT

Grade	Docetaxel Percent of Full Dose	Low Dose Radiation
0 - 1	Full Dose	100%
2 - 3	Decrease 1 Dose Level	100%*

4	HOLD**	HOLD**

*Low-dose radiation will otherwise be given unless grade 3 or greater radiation toxicity occurs as follows: skin reaction, mucositis, esophagitis or other organ toxicity within the radiation port, radiation pneumonitis, decrease in FEV1 < 25% of baseline.

** In the event of a Grade 4 non-hematologic toxicity, **hold all therapy and discuss** with Dr. Susanne Arnold.

8.3 Low-Dose Radiation

Low-dose radiation will otherwise be given unless grade 3 or greater radiation toxicity occurs as follows: skin reaction, mucositis, esophagitis or other organ toxicity within the radiation port, radiation pneumonitis, decrease in FEV1 < 25% of baseline. If the toxicity does not resolve to grade 1 or better, then that port of radiation will be discontinued.

8.4 Colony stimulating factors (CSFs) must be used according to ASCO guidelines (http://www.asco.org). Use of any CSFs must be discontinued at least 48 hours prior to initiation of the next cycle of chemotherapy and must be documented in the patient's record.

8.5 For treatment or dose modification related questions, please contact Dr. Susanne Arnold at (859)323-8043 or (859)257-6011.

8.6 Unexpected or fatal toxicities (including suspected reactions) must be reported to the MCORP, Dr, Susanne Arnold, to the IRB and the KLCRP. The procedure for reporting disease adverse reactions is outlined in Section 16.0.

9.0 STUDY CALENDAR

04-LUN-69-UKY: PHASE I TRIAL OF DOCETAXEL AND LOW-DOSE FRACTIONATED RADIATION (LDFRT) METASTATIC OR RECURRENT NON-SMALL CELL LUNG CANCER

		Cycle 1					Cycle 2				Cycle 3					
REQUIRED STUDIES	PRE	WK	WK	WK	WK	WK	WK	WK	WK	WK	WK	WK	WK	WK	Further Cycles Repeat Previous	∑ Follow
	STUDY	1	2	3	4	5	6	7	8	9	10	11	12			Up
PHYSICAL																
History and Physical Exam	X					X				X					X	X
Weight and Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
Performance Status	X					X				X					X	X
Disease Assessment §*	X								X						X	X
Toxicity Notation						X				X					X	
Pulmonary Function Tests*	X								X						X	
Diagnostic Biopsy	X															
Research Biopsy ⊕		X														
LABORATORY																
CBC/Diff/Platelets	X		X	X	X	X	X	X	X	X	X	X	X		X	
Serum Creatinine	X					X				X					X	
Bilirubin	X					X				X					X	
Alkaline Phosphatase	X					X				X					X	
SGOT or SGPT	X					X				X					X	
X-RAYS AND SCANS																
X-rays and scans for assessment §*	X								X						X	X
CT or MRI of brain	X															
CT of abdomen**	X								X						X	X
Bone scan**	X								X						X	X
TREATMENT																
Dexamethasone #		X	X	X		X	X	X		X	X	X			X	
Docetaxel		X	X	X		X	X	X		X	X	X			X	
Low-Dose Radiation ÿ		X	X	X		X	X	X		X	X	X			X	

Note: Forms submission guidelines are found in Section 14.0.

⊕ For patients who consent to biopsy, obtain between 3 hours and 24 hours after completion of the second fraction of radiation

§ Disease assessment should be performed using the same techniques as for baseline assessment.

* For patients receiving lung radiation, perform these test prestudy, after every two cycles of therapy and the end of study and as clinically indicated during treatment to monitor toxicity. Spirogram w/DLCO required for pre-study and end of study, spirogram alone during study

** If clinically indicated by symptoms

Dexamethasone is to be administered the day prior and day of chemotherapy (see Section 7.2).

∑ Once off ALL protocol treatment, will undergo end of study evaluation (30 days from last dose of study drug and radiation) and then followed every 3 months for first year and then every 6 months for the next two years beginning after registration (see Section 7.5)

ÿ 0.5-0.8 Gy fractions to be given twice a day on Days 1,8, 15 with at least a 3 hour interfraction interval.

10.0 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS

10.1 Measurability of lesions

a. **Measurable disease**: Lesions that can be accurately measured in at least one dimension by 1) medical photograph (skin or oral lesion), palpation, plain x-ray, CT, MRI or other conventional technique with longest diameter 2 cm or greater in the axial plane (bone lesions not included), or 2) spiral CT with longest diameter 1 cm or greater. Ultrasound is suitable only for superficial disease (superficial palpable nodes, subcutaneous lesions, thyroid nodules).

Conventional CT and MRI 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.

b. **Non-measurable disease**: All other lesions including lesions too small to be considered measurable, pleural or pericardial effusions, ascites, bone disease, inflammatory breast disease, leptomeningeal disease, lymphangitis, pulmonitis, abdominal masses not confirmed and followed by imaging techniques, cystic lesions or disease documented by indirect evidence only (e.g., by lab values), previously radiated lesions that have not progressed.

10.2 **Objective status at each evaluation**: Objective Status is to be recorded at each evaluation. 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 at baseline. All measurable lesions not identified as target lesions are non-target lesions and are included as non-measurable disease. Measurements must be provided for target measurable lesions, while presence or absence must be noted for non-target measurable and non-measurable disease.

a. **Complete Response (CR)**: Complete disappearance of all measurable and non-measurable disease. No new lesions. No disease related symptoms. Normalization of markers and other abnormal lab values. All disease must be assessed using the same technique as baseline.

b. **Partial Response (PR)**: Applies only to patients with at least one measurable lesion. Greater than or equal to 30% decrease under baseline of the sum of longest diameters of all target measurable lesions. No unequivocal progression of non-measurable disease. No new lesions. All target measurable lesions must be assessed using the same techniques as baseline.

c. **Stable**: Does not qualify for CR, PR, Progression or Symptomatic Deterioration. All target measurable lesions must be assessed using the same techniques as baseline.

d. **Progression**: One or more of the following must occur: 20% increase in the sum of longest diameters of target measurable lesions over smallest sum observed (over baseline if no decrease during therapy) using the same techniques as baseline. Unequivocal progression of non-measurable disease in the opinion of the treating physician (an explanation must be provided). Appearance of any new lesion/site. Death due to disease without prior documentation of progression and without symptomatic deterioration (see Section 10.2e).

e. **Symptomatic deterioration**: Global deterioration of health status requiring discontinuation of treatment without objective evidence of progression. Efforts should be made to obtain objective evidence of progression after discontinuation.

f. **Assessment inadequate, objective status unknown**: Progression or symptomatic deterioration has not been documented, and one or more target measurable lesions have not been assessed or inconsistent assessment methods were used.

g. Objective status notes:

1. Non-measurable and non-target measurable disease do not affect objective status except in determination of CR (must be absent--a patient who otherwise has a CR, but who has non-measurable or non-target measurable disease present or not assessed, will be classified as having a PR), and in determination of progression (if new sites of disease develop or if unequivocal progression occurs in the opinion of the treating physician).

2. An objective status of PR or stable cannot follow one of CR. Stable can follow PR only in the rare case that tumor increases too little to qualify as progression, but enough that a previously documented 30% decrease no longer holds.

3. In cases for which initial flare reaction is possible (hypercalcemia, increased bone pain, erythema of skin lesions), objective status is not progression unless either symptoms persist beyond 4 weeks or there is additional evidence of progression.

4. Lesions that appear to increase in size due to presence of necrotic tissue will not be considered to have progressed.

5. For bone disease documented on bone scan only, increased uptake does not constitute unequivocal progression.

6. Appearance or worsening of pleural effusions does not constitute unequivocal progression unless cytologically proven of neoplastic origin.

7. If CR determination depends on a lesion for which the status is unclear by the required tests, it is recommended the residual lesion be investigated with biopsy or fine needle aspirate.

10.3 **Best Response**: This is calculated from the sequence of objective statuses.

a. CR: Two or more objective statuses of CR a minimum of four weeks apart documented before progression or symptomatic deterioration.

b. PR: Two or more objective statuses of PR or better a minimum of four weeks apart documented before progression or symptomatic deterioration, but not qualifying as CR.

c. Unconfirmed CR: One objective status of CR documented before progression or symptomatic deterioration but not qualifying as CR or PR.

d. Unconfirmed PR: One objective status of PR documented before progression or symptomatic deterioration but not qualifying as CR, PR or unconfirmed CR.

e. Stable/no response: At least one objective status of stable/no response documented at least 6 weeks after registration and before progression or symptomatic deterioration, but not qualifying as anything else above.

f. Increasing disease: Objective status of progression or symptomatic deterioration within 12 weeks of registration, not qualifying as anything else above.

g. Symptomatic deterioration: objective status of symptomatic deterioration within 12 weeks of registration, not qualifying as anything else above.

h. Inadequate assessment, response unknown: Progression or symptomatic deterioration greater than 12 weeks after registration and no other response category applies.

10.4 **Performance Status**: Patients will be graded according to the Zubrod Performance Status Scale.

POINT	DESCRIPTION
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
2	Ambulatory and capable of self-care but unable to carry out any work activities; up and about more than 50% of waking hours.
3	Capable of limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair.

10.5 **Time to Treatment Failure**: From date of registration to date of first observation of progressive disease (as defined in 10.2d), death due to any cause, symptomatic deterioration (as defined in Section 10.2e), or early discontinuation of treatment.

10.6 **Time to Death**: From date of registration to date of death due to any cause.

11.0 STATISTICAL CONSIDERATIONS

11.1 This phase I study is designed to determine the maximal tolerated dose of LDFRT in combination with Docetaxel for the treatment of metastatic or recurrent NSCLC.

11.2 A maximum of 3-6 patients at each of 4 possible LDFRT dose levels will be evaluated (i.e 50cGy, 60cGy, 70cGy and 80cGy) over a 2 year period. The Docetaxel dose will remain constant. Please see section 7.3 for a description of DLT and escalation decision rules.

11.3 A patient who experiences a DLT should be monitored at least weekly until the DLT resolves or improves to NCI Grade 1or 0. A minimum of 3 patients within each cohort who have been maintained at a given dose level for at least one cycle of chemotherapy is required prior to proceeding with the next dose escalation.

If dose-limiting toxicity (DLT) is not experienced at the 50 cGy dose level, the dose of LDFRT will be escalated to 60 cGy for the next cohort of 3 patients, and then proceed thusly to a maximal dose of 80 cGy of radiation. If a DLT is identified, an additional 3 patients will be accrued to the current dose level. If a second patient enrolled at the same dose level in a cohort of up to six patients experiences a DLT, the maximum tolerated dose (MTD) has been exceeded and the next lower dose will be considered

the MTD. If no DLT is seen, the study will continue until a maximum total dose of 80 cGy of radiation has been evaluated in three patients. Once an MTD has been defined, a total of eight patients will be accrued to that dose level.

This phase I study is not appropriate for power calculations

11.4 Additional objectives are to estimate toxicity and response rate (in a preliminary manner) in this group of NSCLC patients treated with this regimen.

11.5 Molecular Correlative Statistical Considerations

Due to the limited sample size provided in a Phase I setting, these correlative studies will be considered exploratory in nature and will help generate hypotheses for future investigation.

11.6 There is no formal data and safety monitoring committee for Phase I studies. Toxicity, response monitoring and accrual monitoring are done routinely by the Principle Investigator, Study Statistician and the Clinical Research Assistant. Accrual reports and formal toxicity reports are generated every 6 months for the Clinical Care and Research Team. In addition, the Principle Investigator and the Clinical Research Assistant monitor toxicities on an ongoing basis.

12.0 DISCIPLINE REVIEW

This section is not applicable to this study.

13.0 REGISTRATION GUIDELINES

13.1 Patients must be registered prior to initiation of treatment (no more than seven working days prior to planned start of treatment).

13.2 Registration procedures

a. Patients must meet all eligibility requirements.

b. The appropriate IRB-approved and dated consent form must be utilized.

c. Registrations may not be cancelled.

d. Late registrations (after initiation of treatment) will not be accepted.

14.0 DATA SUBMISSION SCHEDULE

14.1 Data must be submitted according to the protocol requirements for **ALL** patients registered, whether or not assigned treatment is administered, including patients deemed to be ineligible. Patients for whom documentation is inadequate to determine eligibility will generally be deemed ineligible.

14.2 Data Submission Procedures

14.3 WITHIN 14 DAYS OF REGISTRATION:

Submit a copy of the following:

a. Section 5.0 Eligibility Criteria and Prestudy Form

b. Baseline Abnormalities Form

c. Baseline Tumor Assessment Form

d. Pathology/Cytology Report(s).

14.4 AFTER COMPLETION OF EACH CYCLE OF TREATMENT:

Submit a copy of the following:

a. Treatment Form

b. Adverse Event Form

14.5 EVERY 2 CYCLES WHILE ON TREATMENT:

Submit a copy of the following:

a. Follow-Up Tumor Assessment Form

b. Radiation Medicine Treatment Flow Sheet.

14.6 WITHIN 14 DAYS OF PROGRESSION OR RELAPSE:

Submit a copy of the following:

a. Follow-Up Tumor Assessment Form

14.7 WITHIN 14 DAYS OF DISCONTINUATION OF TREATMENT:

Submit a copy of the following:

a. Off Treatment Form

b. Follow-Up Tumor Assessment Form

c. Final Adverse Event Form

14.8 ONCE OFF ALL PROTOCOL TREATMENT, SUBMIT EVERY 3 MONTHS FOR THE FIRST YEAR AND THEN EVERY 6 MONTHS FOR 2 YEARS FROM INITIAL REGISTRATION:

Submit a copy of the following:

a. Follow-Up Tumor Assessment Form (until first relapse or progression)

b. Follow-Up Form

14.9 WITHIN 4 WEEKS OF KNOWLEDGE OF DEATH:

Submit a copy of the Notice of Death.

15.0 SPECIAL INSTRUCTIONS

Core needle biopsy will be performed using standard aseptic technique via CT scan guidance or Ultrasound guidance where needed to biopsy viable tumor. Biopsy specimens will be placed in formaldehyde and undergo routine processing to create a paraffin embedded specimen. Patients specimens will be studied for molecular changes as outlined in Kentucky Lung Cancer Grant Proposal "Low-dose fractionated radiation plus Docetaxel as second-line therapy for metastatic or recurrent non-small cell lung cancer." with the patient's consent.

16.0 ETHICAL AND REGULATORY CONSIDERATIONS

The following must be observed to comply with Food and Drug Administration regulations for the conduct and monitoring of clinical investigations; they also represent sound research practice:

Informed Consent

The principles of informed consent are described by Federal Regulatory Guidelines (Federal Register Vol. 46, No. 17, January 27, 1981, part 50) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46). They must be followed to comply with FDA regulations for the conduct and monitoring of clinical investigations.

Institutional Review

This study must be approved by an appropriate institutional review committee as defined by Federal Regulatory Guidelines (Ref. Federal Register Vol. 46, No. 17, January 27, 1981, part 56) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46).

Drug Accountability

Docetaxel is FDA approved for the treatment of non-small cell lung cancer, and is in itself not considered an investigational drug for this study. Standard operating procedures for drug disposition (drug receipt, dispensing, etc) will be maintained by the Markey Cancer Center Clinical Pharmacy.

Adverse Experiences

Any adverse experience greater than or equal to grade 3, if deemed study related, must be reported to the MCORP Office and the Principle Investigator. Any adverse experience which meets protocol-specified reporting guidelines must be reported to the MCORP Office and the Principle Investigator. All serious adverse experiences (as defined below) must also be reported to the Institutional Review Board within 24 hours and documentation of this report sent to the MCORP Office.

All adverse experiences must also be recorded in the appropriate section of the case report form. The report should include, whenever possible, the investigator's written medical judgment as to relationship of the adverse experience to study medication(s) (i.e., "probable", "possible" or "unrelated").

GUIDELINES FOR REPORTING OF
ADVERSE EVENTS (AE) / ADVERSE DRUG REACTIONS (ADR)

1. WITHIN 24 HOURS OF THE EVENT CALL THE MCORP OFFICE AT (859) 257-3379.

2. IN ADDITION, FOLLOW THE GUIDELINES BELOW:

Adverse Event Reporting

Serious adverse events will be reported to University of Kentucky Institutional Review Board. The following definitions of terms are guided by the International Conference on Harmonization and the US Code of Federal Regulations [21 CFR 312.32, effective 06 April 1998] and are included herein. The treating physician should follow all patients with adverse events, regardless of severity, until resolution is satisfactory.

An adverse event is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, which may or may not have a causal relationship with this treatment.

Serious adverse drug experience [serious adverse event] is any adverse drug experience [adverse event] occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious drug experience [serious adverse event] when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Life-threatening is any adverse drug experience [adverse event] that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death. An unexpected or unlabeled event is an adverse event, the nature or severity of which is not consistent with the applicable product information (e.g., package insert for an approved indication or Investigator's Brochure for an unapproved indication).

Unexpected adverse drug experience: Any adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure; or, if an investigator brochure is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigational plan or if the agent is commercially available the specificity or severity of which is not consistent with the risk information described in the package insert (labeling).

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PACLITAXEL, CARBOPLATIN AND RADIOTHERAPY AS INDUCTION THERAPY IN LOCALLY ADVANCED HEAD AND NECK CANCER

00-H&N-11

THE UNIVERSITY OF KENTUCKY

TABLE OF CONTENTS:

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Mansoor Ahmed, Ph.D.

PACLITAXEL, CARBOPLATIN AND RADIOTHERAPY AS INDUCTION THERAPY IN LOCALLY ADVANCED HEAD AND NECK CANCER

Susanne M. Arnold, M.D., William Regine, M.D., and Joseph Valentino, M.D., Mansoor Ahmed, Ph.D., Mohammed Mohuiddin, M.D.

1.0 ABSTRACT

Cancers of the head and neck (H&N) comprise 5% of all cancers, with 40,000 new cases diagnosed annually. Surgery followed by irradiation or irradiation alone has been the standard of care for locally advanced Stage III and IV patients. With this approach, fewer than 30% of patients achieve long-term remission, and most recur locoregionally. Neoadjuvant chemotherapy has been administered prior to definitive therapy with response rates ranging from 60-90%; with pathologic CR rates documented in 30-70% of clinical responders. However, large randomized trials have shown no improvement in overall survival.

Because induction chemotherapy alone does not appear to improve long-term disease free survival in advanced head and neck cancers, concomitant chemotherapy and radiation has been pursued in patients with locally advanced head and neck cancers. Improved disease-free survival has been demonstrated with a variety of agents. The concept of synergy between radiation and chemotherapy is well established in vitro. Various schedules of radiation and chemotherapy have been utilized including weekly chemotherapy during radiation, chemotherapy given every three weeks during hyperfractionated radiation and alternating chemotherapy and radiation.

One exciting new chemotherapeutic agent, Paclitaxel has been shown to radiosensitize cancer cell lines in vitro. Recent studies have added Carboplatin to Paclitaxel in tandem or concurrently with radiation in hopes of improving response rates. From in-vitro data, it appears that the optimum schedule for the combination of Paclitaxel and radiation is to first induce G2/M arrest with Paclitaxel and follow this with radiation therapy. In a recent study by Chendil, et al, a novel radiation scheme appeared to enhance the response of both p53 wild type and p53 mutant cancer cell lines to chemotherapy. In vitro data with Carboplatin also indicates an additive effect when given prior to irradiation using various cell lines. What has not been evaluated, is whether a neoadjuvant regimen of Paclitaxel and Carboplatin followed by 4 small fractions of radiation can be given safely and effect an improved response rate in patients with bulky T2, Stage III and IV H&N cancer. We propose the use of two cycles of Paclitaxel and Carboplatin followed by four small fractions of radiation, prior to definitive treatment (surgery or radiation). It is hoped that using radiation as a chemoenhancer will increase the response rate to induction therapy in this population of patients.

2.0 OBJECTIVES

2.1 To assess the response rate of patients treated with Paclitaxel and Carboplatin followed by four small fractions of radiation given within 36 hours of chemotherapy in patients with bulky T2, Stage III and IV H&N cancer.

2.2 To assess the toxicity of this chemoradiotherapy regimen for the treatment of H&N cancer.

2.3 To assess quality of life issues while undergoing this regimen.

3.0 BACKGROUND AND RATIONALE

3.1 Overview

Cancers of the head and neck (H&N) comprise 5% of all cancers, with 40,000 new cases diagnosed annually. Surgery followed by irradiation or irradiation alone has been the standard of care for locally advanced Stage III and IV patients. With this approach, fewer than 30% of patients achieve long-term remission, and most recur locoregionally (1). Neoadjuvant strategies using Cisplatin and infusional 5-Fluorouracil (5-FU) have been administered prior to definitive therapy with response rates ranging from 60-90%; however, large randomized trials have shown no improvement in overall survival (2,3).

Because induction chemotherapy alone does not appear to improve long-term disease free survival in advanced head and neck cancers, concomitant chemotherapy and radiation has been pursued with a variety of agents including mitomycin-C, bleomycin, 5-FU and Cisplatin. Improved disease-free survival has been demonstrated with each of these agents (4,5,6,7,). The concept of synergy between radiation and chemotherapy is well established in vitro. Radiation appears to recruit more cells into active cell cycle, which, in theory, allows a higher percentage of cells to be susceptible to chemotherapy agents (8). The addition of chemotherapy to radiation, in turn, is thought to alter the intrinsic radioresistance of tumor cells (9). By killing a percentage of cancer cells, chemotherapy also allows reoxygenation of previously hypoxic areas thus enhancing radiotherapy (10). Various schedules of radiation and chemotherapy have been utilized including weekly chemotherapy during radiation, chemotherapy given every three weeks during hyperfractionated radiation and alternating chemotherapy and radiation (7,11,12).

One exciting new chemotherapeutic agent, Paclitaxel, is an inhibitor of microtubule function derived from the Pacific yew, *Taxus brevofolia*. It has been shown to radiosensitize cancer cell lines in vitro (13). Newer regimens have sought to take advantage of this fact, by utilizing Paclitaxel along with Carboplatin in tandem or concurrently with radiation in hopes of improving response rates (14, 15, 16). Investigations into the optimal schedule for delivery of Paclitaxel in combination with radiotherapy have yielded several important tenets:

1. Paclitaxel induces mitotic arrest within two hours after administration and this effect peaks between 8 and 12 hours, while apoptosis peaks between 12 and 24 hours remaining elevated for at least two days (10).
2. Paclitaxel invokes G2/M arrest through its inhibition of microtubule function and G2/M is the most radiosensitive phases of cell cycle (17, 18).
3. Multiple in-vitro studies in head and neck cancer cell lines show supra-additive effect of Paclitaxel and radiation when cells were exposed to Paclitaxel prior to irradiation (19). There appears to be a subadditive effect on cell death when cells were incubated with Paclitaxel after irradiation (20).

One of the most well described molecular determinants of response to ionizing radiation is the status of the tumor suppressor gene p53 within the cancer cell. Wild-type p53 protein expression

confers radiation responsiveness, while p53 mutations result in decreased protein expression and radioresistance (21). In recent work by Chendil, et al, both p53 wild type and mutant colon cancer cell lines were studied to determine the effect of Paclitaxel with radiation. Several novel irradiation schemes were studied to maximize the radiosensitization of Taxanes. A benefit was seen when four small fractions of 50 cGy were given every 8 hours beginning immediately after Paclitaxel exposure, when compared to the effect of a single fraction of 200 cGy. The cells which appeared to benefit most from this schedule were those with p53 mutations (i.e. those cells that were most likely to be radioresistant to radiotherapy alone) (22).

In vitro data with Carboplatin also indicates an additive effect when given prior to irradiation using various cell lines (23, 24). As well, the pharmacokinetics of carboplatin are not altered by pretreatment with Paclitaxel at a standard dose, and this has been confirmed clinically in a multitude of studies in different tumor types (25). What has not been evaluated, is whether a neoadjuvant regimen of Paclitaxel and Carboplatin followed by four fractions of radiation (given within 36 hours of the chemotherapy) can be given safely and effect an improved response rate in patients with bulky Stage II, Stage III and IV H&N cancer.

3.2 Proposal

We propose the use of two cycles of neoadjuvant Paclitaxel and Carboplatin followed by four small fractions of radiation given within 36 hours after chemotherapy, prior to definitive treatment (surgery or radiation) of locally advanced head and neck cancer. Our goal is to increase the response rate to induction therapy by using radiotherapy as a chemoenhancer.

4.0 ELIGIBILITY CRITERIA

4.1 Inclusion criteria

4.10 Adult patients greater than 18 years of age.

4.11 ECOG performance status of 0, 1 or 2.

4.12 Patients with pathologically documented bulky T2, III and IV squamous cell cancer of the head and neck (excluding M1 disease), within 2 months of diagnosis. Bulky T2 tumors are defined as those that have a volume of disease greater than 35 cm^3 as measured by CT or MRI scan (26).

4.13 Patients will be medically fit for undergoing chemotherapy. Specifically:

a) no evidence of active angina pectoris or ventricular arrhythmias; no myocardial infarction within the last six months. (Patients with medically controlled hypertension or congestive heart failure are eligible.)

b) an absolute neutrophil count of > 1000/uL and platelet count > 100,000/uL

c) serum total bilirubin < 1.5 mg/dL

d) Creatinine Clearance greater than 50 ml/min
Using an actual or calculated creatinine clearance using the formula:
$\frac{(140 - \text{age}) \times (\text{wgt in kg})}{(\text{serum creatinine}) \times (72)}$ *
*= multiply by 0.85 for females

e) if a pre-existing grade I neuropathy exists, patients must be willing to risk worsening neuropathy secondary to Paclitaxel. Patients with grade II or greater neuropathy will be excluded from study.

f) ability to give written, informed consent to participate in the trial.

4.14 Patients will have measurable disease as determined by MRI or CT scan or evaluable disease determined by panendoscopy to be eligible for enrollment on this study.

4.2 Exclusion criteria

4.21 Pregnant females. Males and women of childbearing potential must use effective contraception in order to prevent pregnancy during therapy.

4.22 Patients with a history of previous or current malignancy at other sites diagnosed within the last 5 years, with the exception of adequately treated carcinoma in-situ of the cervix or basal or squamous cell carcinoma of the skin. Patients with a history of other malignancies, who remain free of recurrence or metastases for greater than five years are eligible.

4.23 Patients with active infection will not be eligible for this protocol until the infection is treated and the symptoms have clinically resolved.

4.24 Patients with a history of allergy to drugs utilizing Cremophor in the formulation.

4.25 Prior induction chemotherapy, prior irradiation or surgery will not be allowed.

4.26 Patients with metastatic disease will not be eligible for this study.

4.27 Patients with grade II or greater peripheral neuropathy will be excluded from study.

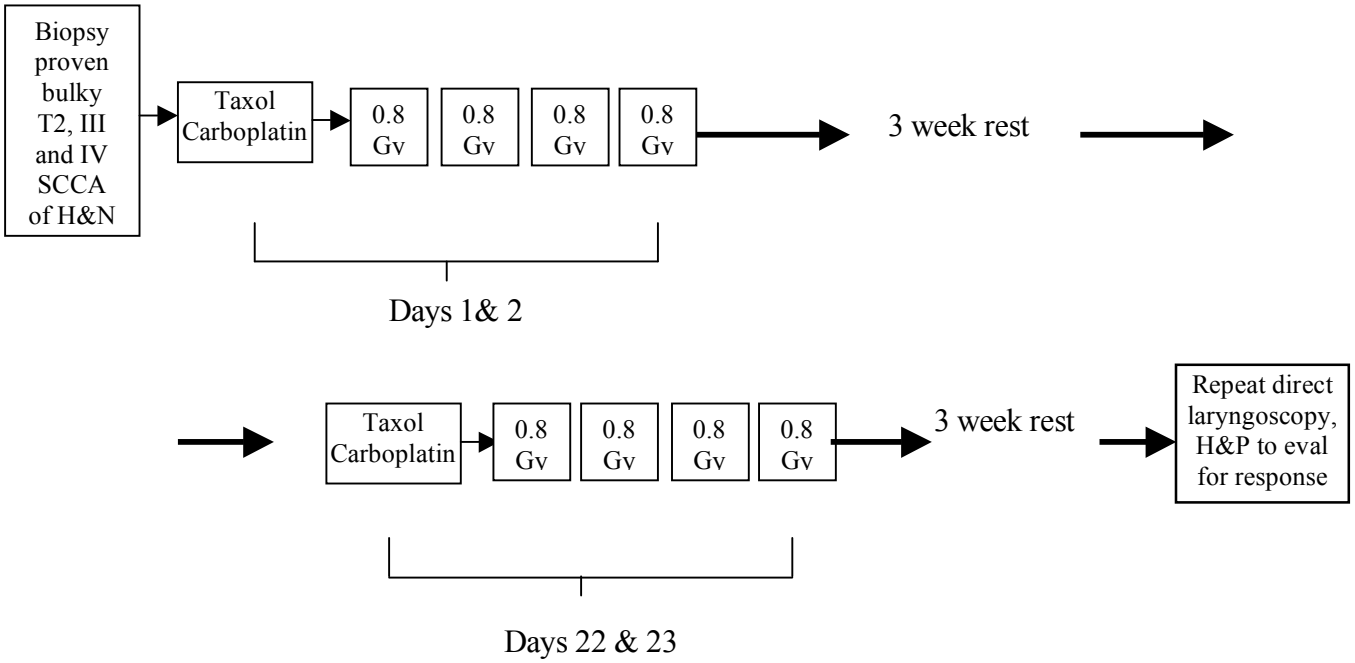
5.0 TREATMENT PLAN

5.1 Pre-treatment Studies

Prior to enrollment, all patients will undergo a history and physical exam, ECOG performance status evaluation, direct laryngoscopy, a CT or MRI scan of the involved area of the head and neck and a chest X-ray or CT of chest within 6 weeks of beginning chemoradiotherapy. A complete blood count with differential and platelets, and serum chemistries (including sodium,

potassium, chloride, bicarbonate, calcium, total protein, albumin, BUN, creatinine, AST, alkaline phosphatase and total bilirubin) within 2 weeks of beginning chemoradiotherapy will also be required.

5.2 Schema:



5.3 Radiation Schedule and Dosage:

Radiation will be given on Day 1 & 2 and 22 & 23 of chemotherapy. The first fraction will be given within 2 hours after completion of chemotherapy and the remaining 3 fractions of each cycle with at least a 6 hr interfraction interval.

5.32 Dosage and fields:

Doses of 80 cGy will be administered with each fraction. The third and fourth fractions will be given the next day, six hours apart. The patient will be treated with shaped fields encompassing gross disease only (including the primary and gross nodal disease) with a maximum 2cm margin. The spinal cord will be excluded from the radiation field and CT based treatment planning will be used as needed and as appropriate.

5.4 Adjuvant chemotherapy.

5.41 Chemotherapy Formulation, Availability and Preparation:

Paclitaxel is commercially available and commercial supplies will be used for this study. Paclitaxel is supplied as a sterile concentrated solution, 6mg/ml, and is available in 5ml and 16.7 ml

multidose vials. Each milliliter contains 6mg paclitaxel 527mg of Cremophor EL (polyoxyethylated caster oil) and 50% dehydrated alcohol, USP, 50%. The contents of the vial must be diluted just prior to clinical use. Paclitaxel at the appropriate dose will be diluted in 5% dextrose injection or 0.9% sodium chloride injection to a final concentration of 0.3 to 1.2mg/ml. Infusions should be mixed as closely as possible to the start of each infusion since paclitaxel stability after 27 hours at room temperature in solution is unknown. Paclitaxel must be prepared in glass, polypropylene or polyolefin containers due to leaching of diethylhexylphthalate (DEHP) plasticizer from polyvinyl chloride (PVC) bags. Paclitaxel will be administered using non-PVC tubing and connectors which are polyethylene lined. In-line filtration should be accomplished by incorporating a hydrophilic, microporous filter of pore size not greater than 0.22 microns. Nothing else should be infused through the lines where paclitaxel is being administered. Solutions exhibiting excessive particulate formation should be discarded.

The Chemo Dispensing Pin^{TM} device or similar devices with spikes should not be used with vials of Paclitaxel since they can cause the stopper to collapse resulting in the loss of sterile integrity of the Paclitaxel solution. Intact vials of Paclitaxel should be stored at room temperature between 2-25^{0}C (36-77^{0}F). Shelf life of the vials stored under appropriate conditions corresponds to the manufacturer's expiration date on each vial. All solutions of Paclitaxel exhibit slight haziness directly proportional to the concentration of drug and time elapsed since preparation. When prepared as above, solutions of Paclitaxel (0.3 – 1.2 mg/ml) are stable for 27 hours.

Carboplatin is commercially available as a sterile lyophilized powder available in single dose vials containing 50 mg, 150 mg, or 450 mg of carboplatin. Each vial contains equal parts by weight of carboplatin and mannitol. Immediately before use the content of each vial must be reconstituted with either sterile water for injection, USP, 5% dextrose in water or 0.9% sodium chloride injection, USP, according to the following schedule:

Vial Strength	Diluent Volume
50 mg	5 ml
150 mg	15 ml
450 mg	45 ml

These dilutions all produce a carboplatin concentration of 10 mg/ml. When prepared as directed, carboplatin solutions are stable for eight hours at room temperature. Since no antibacterial preservative is contained in the formulation, it is recommended that carboplatin solutions be discarded eight hours after dilution. NOTE: Aluminum reacts with carboplatin causing precipitate formation and loss of potency; therefore, needles or intravenous sets containing aluminum parts that may come in contact with the drug must not be used for the preparation or administration of carboplatin.

Unopened vials of carboplatin are stable for the life indicated on the package when stored at controlled room temperature (59-86^{0}F) and protected from light. When prepared, carboplatin solutions are stable for 8 hours at room temperature.

5.42 Chemotherapy Premedication and Dosing:

All chemotherapy will use actual body weight (to a maximum of 2.2 m^2) and will be administered as an i.v. infusion. Paclitaxel will be dosed to the nearest 5mg using a standard body surface area chart. Carboplatin will be dosed using the Calvert formula for calculating the area under the curve (AUC):

$$AUC\ 6=(GFR + 25) \times 6$$

The Glomerular filtration rate (GFR) will be calculated as follows:

$$\frac{(140\text{-age}) \times (\text{wt in kg}) \times 0.85^*}{72 \times \text{serum creatinine}} \qquad ^*\text{for women}$$

To avoid allergic reactions associated with Paclitaxel, the following premedications will be given 30 minutes prior to each dose of Paclitaxel:

- Dexamethasone 20 mg IV
- Cimetidine 300mg IV or Ranitidine 50 mg IV
- Diphenhydramine 25 mg IV

Other premedications including anti-emetics will be at the discretion of the treating physician. Paclitaxel will be given at a dose of 225 mg/m2 intravenously over three hours on Days 1 and 22. Following Paclitaxel infusion, Carboplatin at an AUC of 6 will be given intravenously over 30 minutes.

5.5 Alteration of Schedule:

If a patient has neutropenia (ANC < 1000) or thrombocytopenia (platelets < 100,000) then chemotherapy will be held for 1 week, and restarted when the ANC has increased to >1000 and platelet count > 100,000. Chemotherapy will also be held for febrile neutropenia and will be restarted when neutropenic fever resolves (no temperature > 100.5 ^{0}F, and ANC >1000 cells/mm^3). If a patient has a Grade 4 mucositis, then chemotherapy will be held for one week, and the patient will be reassessed prior to reinstitution of chemotherapy. Grade 3 or greater neuropathy will mandate holding the chemotherapy until the neuropathy returns to Grade 2. Chemotherapy will be discontinued if irreversible, symptomatic cardiac arrhythmia or dysfunction occurs.

Radiotherapy will be held if chemotherapy is held and will restart on the same day as chemotherapy based on the parameters for alteration of schedule listed above.

5.6 Potential Toxicities

Paclitaxel is a microtubule inhibitor derived from the Pacific yew, *Taxus brevifolia.* Its side effects include allergic reactions, arrhythmias, hypotension and heart block. These side effects are reversible with cessation of drug delivery. As well, premedication with steroid, H1

and H2-blockers helps to prevent allergic reactions. Other toxicities include nausea, vomiting, mucositis, diarrhea, seizures, malaise, alopecia, elevated alkaline phosphatase, SGOT and bilirubin, arthralgias, myalgias, peripheral neurotoxicity, myocardial infarction and myelosuppression. Given the risk of anaphylaxis with Paclitaxel, patients will be carefully observed for possible reactions, and supportive equipment and medications to treat these reactions will be immediately available to treat such complications. Cardiac toxicities are rare and continuous cardiac monitoring is not required except for patients with serious conduction abnormalities or other underlying, serious cardiac risk factors.

Reversible skin changes and mucositis are expected side effects of radiotherapy. Combined modality therapy increases the risk for acute toxicities, but with low doses of radiation (640 cGY total) minimal toxicity is expected. The total dose of radiation given as definitive therapy after completion of induction will take into account this initial dose of radiation, and will be at the discretion of the attending radiation oncologist.

Carboplatin is a heavy metal which directly binds to DNA, thus altering the DNA template via the formation of intrastrand cross-links. Major toxicities include nephrotoxicity, myelosuppression, nausea and vomiting, hypersensitivity (including rash, urticaria, erythema, pruritis, bronchospasm, and hypotension), electrolyte imbalance, sensory and motor neuropathy, ototoxicity, hepatic toxicity, decreased electrolyte values, alopecia, pain, gastrointestinal pain, constipation, and diarrhea. The majority of these toxicities are reversible upon discontinuation or completion of the drug.

Performance status will be evaluated based on the ECOG Performance Status Criteria (Appendix B). Toxicities will be graded according to the NCI Toxicity Criteria (Appendix C). There is estimated to be a 1% risk per year of second primary cancers in this population of patients, which is unrelated to treatment.

5.6 Removal of patients from protocol

Protocol therapy will be discontinued at any time if any of the following situations occur:

- Disease progression at any time during therapy or follow-up period
- Unacceptable toxicity
- Patient request to withdraw from study
- Development of intercurrent, non-cancer related illness that prevents continuation of therapy
- Investigator discretion

All patients will be followed regardless of treatment variations until the patient's death or loss to follow-up.

6.0 ANCILLARY MEASURES

6.1 All patients will have electrolyte and complete blood counts monitored prior to each dose of chemotherapy.

6.2 All patients will complete a pre-treatment Head and Neck Quality of Life form (see Appendix D) as well as follow-up forms during and after chemotherapy.

6.3 No prophylactic G-CSF may be given after the first cycle. G-CSF at a dose of 5mcg / kg / day (subcutaneously) may be used for prolonged neutropenia (an ANC < 500/ul for more than 5 days), serious neutropenic fever or prophylaxis of neutropenia after severe neutropenic fever during the second induction cycle.

6.4 Symptomatic treatment of esophagitis or mucositis using magic mouthwash, Lanny's mouthwash or narcotics will be allowed at any time.

7.0 STUDY CALENDAR

Evaluation	Pre-Study	Day 1	Day 2	Day 22	Day 23	Day 36-57	STUDY COMPLETE-DAY 58	Q 3 months
H&P^ PS assessment	X			X		X		X
CBC^	X			X		X		X*
Electrolytes^	X			X		X		X*
Chest X-ray^	X							
MRI or CT scan of H&N^	X**					X		X*
Panendoscopy	X					X		
Creatinine Clearance	X							
QOL form	X					X		
Chemotherapy		X		X				
80 cGy RT		X X	X X	X X	X X			
Toxicities			X	X	X	X		
Surgery or definitive RT								
Survival								X

*until toxicities resolve

**repeated every 6 months until disease progression

^Prestudy H&P, CBC, electrolytes within 14 days of treatment; others within 6 weeks of treatment

QOL = quality of life form prestudy and post study (Day 36-57)

BID = twice a day RT = radiotherapy

Note: to go to surgery or definitive RT days 58-79 as applicable; H&P labs, x-rays and scans to be followed by surgery/RT.

8.0 EVALUATION CRITERIA

8.1 Assessment of tumor response

Patients will have tumor assessment by CT scan or MRI and panendoscopy prior to induction therapy and within three weeks after the completion of chemoradiotherapy. Biopsies of the primary tumor will be taken prior to induction therapy and repeated following induction therapy either at the time of repeat panendoscopy or at the time of definitive surgery. Response to therapy will be described as follows:

- Complete response (CR) is defined as the complete disappearance of all measurable disease.
- Partial response (PR) is defined as a > 50% reduction in the sum of the product of perpendicular diameters of up to five prospectively identified index lesions (prior to treatment on protocol), with no progression in any lesion.
- Stable disease (SD) is defined as less than a partial response but no progression in any lesion.
- Progressive disease (PD)is defined as an increase in any measurable lesion or the appearance of any new lesion, including elevation in serum tumor markers.

Both pathologic and radiographic response to therapy will be assessed where possible.

8.2 Protocol endpoints

The primary endpoint of this study is response rate to induction chemotherapy, prior to definitive therapy (surgery or irradiation). The frequency of severe ($\geq$ Grade 3) toxicities will be examined, and quality of life assessments will be followed.

8.3 Toxicities

Toxicities will be graded using the National Cancer Institute (NCI) scale for acute and subacute toxicity (see Appendix C).

8.4 Adverse Event Reporting

All adverse events regardless of causal relationship will be recorded in the case report forms and source documentation. The PI will determine the intensity of any adverse events according to the CTC and RTOG criteria and their causal relationship. Serious adverse events will be reported to FDA according to the rule of the FDA and IRB.

9.0 STATISTICAL CONSIDERATIONS

9.1 Experimental Design:

This is a Phase II study designed to evaluate the antitumor response and toxicity of the combination of Carboplatin, Paclitaxel and chemosensitizing radiation in locally advanced H&N cancers.

9.2 Accrual and Power Considerations

The primary endpoint for this study is response rate, with secondary endpoints of toxicity and quality of life being followed. For statistical purposes, the response rate (CR +PR) to induction therapy for stage II (bulky), III and IV H&N patients will be considered 50% (15). It is assumed that the response rate for the proposed therapy is at least 70%. A two-stage Phase II trial design is planned, based on a study design by Simon (27). Initially, 23 patients will be enrolled in the study. If twelve or fewer patients show response to therapy (CR + PR) the study will be terminated. If 13 to 22 patients show response, then 14 more will be added to the study (a total of 37 patients). If all 23 patients show response in the initial cohort, then the study will be deemed appropriate for Phase III trial development, and the Phase II trial will be closed. With an alpha level of 0.05 and a beta level of 0.20, this study will have at least 80% power to detect a significant difference between response rate for the proposed regimen and the response rate for induction chemotherapy alone.

10.0 REPORTING PROCEDURES

All eligible patients will be reported to the clinical research office for registration at (606) 257-3379, or Dr. Susanne Arnold at (606) 323-8043.

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APPENDIX A
Staging for Head and Neck Cancer

TNM CATEGORIES

Primary Tumor (T)

All Sites

TX Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy.

T0 No evidence of primary tumor.

Oral Cavity and Oropharynx

Tis Carcinoma *in situ.*

T1 Tumor 2 cm or less

T2 Tumor between 2 and 4 cm in diameter

T3 Tumor greater than 4 cm in greatest diameter

T4 Tumor invades adjacent structures (eg, bone, deep muscle of tongue, skin)

Maxillary Sinus

Tis Carcinoma *in situ.*

T1 Tumor limited to antral mucosa with no erosion or destruction of bone

T2 Tumor with erosion of the infrastructure including the hard palate and/or middle nasal meatus

T3 Tumor invades any of the following: skin of cheek, posterior wall of maxillary sinus, floor or medial wall of orbit, anterior ethmoid sinus

T4 Tumor invades orbital contents and/or any of the following: cribiform plate, posterior ethmoid or sphenoid sinuses, nasopharynx, soft palate, pterygomaxillary or temporal fossae, or base of skull

Nasopharynx

Tis Carcinoma *in situ.*

T1 Tumor limited to one subsite of the nasopharynx

T2 Tumor invades more than one subsite of the nasopharynx

T3 Tumor invades nasal cavity, or oropharynx, or both

T4 Tumor invades skull, or cranial nerves, or both

Larynx

Supraglottis

Tis Carcinoma *in situ.*

T1 Tumor confined to site of origin with normal mobility

T2 Tumor involves adjacent supraglottic site(s) or glottis without fixation

T3 Tumor limited to larynx with fixation or extension to involve postcricoid area, medial wall of pyriform sinus, or preepiglottic space

T4 Massive tumor extending beyond larynx to involve oropharynx, soft tissue of neck, or destruction of thyroid cartilage

Glottis

Tis	Carcinoma *in situ.*
T1	Tumor confined to vocal cord(s) with normal mobility
T2	Supraglottic or subglottis extension of tumor with normal or impaired cord mobility
T3	Tumor confirmed to the larynx with cord fixation
T4	Massive tumor with thyroid cartilage destruction or extension beyond the confines of the larynx

Subglottis

Tis	Carcinoma *in situ.*
T1	Tumor confined to the subglottic region
T2	Tumor extension to vocal cord with normal or impaired cord mobility
T3	Tumor confirmed to the larynx with cord fixation
T4	Massive tumor with cartilage destruction or extension beyond the confines of the larynx, or both

Regional Lymph Nodes (N)

NX	Regional lymph nodes cannot be assessed.
N0	No regional lymph node metastasis.
N1	single ipsilateral node, 3 cm or less
N2a	single ipsilateral node 3-6 cm
N2b	multiple ipsilateral nodes, none > 6cm
N2c	bilateral or contralateral nodes, none > 6cm
N3	metastasis in a node > 6cm

Distant Metastasis (M)

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

Stage Grouping Based on AJCC Criteria

	Classification		
Stage	T	N	M
0	Tis	N0	M0
I	T1	N0	M0
II	T2	N0	M0
III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N0	M0
IV	T4	N0	M0
	Tx	N2, N3	M0
	Tx	Nx	M1

Appendix B
Performance Status Scales/Scores

ECOG or Zubrod scale

0	Asymptomatic and fully active
1	Symptomatic; fully ambulatory; restricted in physically strenuous activity
2	Symptomatic; ambulatory; capable of self-care; more than 50% of waking hours are spent out of bed
3	Symptomatic; limited self-care; spends more than 50% of time in bed, but not bedridden
4	Completely disabled; no self-care; bedridden

Appendix C
COMMON TOXICITY CRITERIA (CTC)

Toxicity	Grade 0	1	2	3	4
ALLERGY/IMMUNOLOGY					
Allergic reaction/ hypersensitivity (including drug fever)	none	transient rash, drug fever < 38°C (<100.4°F)	urticaria, drug fever ≥ 38°C (≥100.4°F), and/or asymptomatic bronchospasm	symptomatic bronchospasm, requiring parenteral medication(s), with or without urticaria; allergy-related edema/angioedema	anaphylaxis
Note: Isolated urticaria, in the absence of other manifestations of an allergic or hypersensitivity reaction, is graded in the DERMATOLOGY/SKIN category.					
Allergic rhinitis (including sneezing, nasal stuffiness, postnasal drip)	none	mild, not requiring treatment	moderate, requiring treatment	-	-
Autoimmune reaction	none	serologic or other evidence of autoimmune reaction but patient is asymptomatic (e.g., vitiligo), all organ function is normal and no treatment is required	evidence of autoimmune reaction involving a non-essential organ or function (e.g., hypothyroidism), requiring treatment other than immunosuppressive drugs	reversible autoimmune reaction involving function of a major organ or other toxicity (e.g., transient colitis or anemia), requiring short-term immunosuppressive treatment	autoimmune reaction causing major grade 4 organ dysfunction; progressive and irreversible reaction; long-term administration of high-dose immuno-suppressive therapy required
Also consider Hypothyroidism, Colitis, Hemoglobin, Hemolysis.					
Serum sickness	none	-	-	present	-
Urticaria is graded in the DERMATOLOGY/SKIN category if it occurs as an isolated symptom. If it occurs with other manifestations of allergic or hypersensitivity reaction, grade as Allergic reaction/hypersensitivity above.					
Vasculitis	none	mild, not requiring treatment	symptomatic, requiring medication	requiring steroids	ischemic changes or requiring amputation
Allergy/Immunology-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
AUDITORY/HEARING					
Conductive hearing loss is graded as Middle ear/hearing in the AUDITORY/HEARING category.					
Earache is graded in the PAIN category.					
External auditory canal	normal	external otitis with erythema or dry desquamation	external otitis with moist desquamation	external otitis with discharge, mastoiditis	necrosis of the canal soft tissue or bone
Note: Changes associated with radiation to external ear (pinnae) are graded under Radiation dermatitis in the					

Toxicity	Grade 0	1	2	3	4
DERMATOLOGY/SKIN category.					
Inner ear/hearing	normal	hearing loss on audiometry only	tinnitus or hearing loss, not requiring hearing aid or treatment	tinnitus or hearing loss, correctable with hearing aid or treatment	severe unilateral or bilateral hearing loss (deafness), not correctable
Middle ear/hearing	normal	serous otitis without subjective decrease in hearing	serous otitis or infection requiring medical intervention; subjective decrease in hearing; rupture of tympanic membrane with discharge	otitis with discharge, mastoiditis or conductive hearing loss	necrosis of the canal soft tissue or bone
Auditory/Hearing-Other (Specify, _____)	normal	mild	moderate	severe	life-threatening or disabling
BLOOD/BONE MARROW					
Hemoglobin (Hgb)	WNL	< LLN - 10.0 g/dl < LLN - 100 g/L < LLN - 6.2 mmol/L	8.0 - < 10.0 g/dl 80 - < 100 g/L 4.9 - < 6.2 mmol/L	6.5 - < 8.0 g/dl 65 - 80 g/L 4.0 - < 4.9 mmol/L	< 6.5 g/dl < 65 g/L < 4.0 mmol/L
Hemolysis (e.g., immune hemolytic anemia, drug-related hemolysis, other) Also consider Haptoglobin, Hgb.	none	only laboratory evidence of hemolysis [e.g., direct antiglobulin test (DAT, Coombs') schistocytes]	evidence of red cell destruction and ≥ 2gm decrease in hemoglobin, no transfusion	requiring transfusion and/or medical intervention (e.g., steroids)	catastrophic consequences of hemolysis (e.g., renal failure, hypotension, bronchospasm, emergency splenectomy)
Leukocytes (total WBC)	WNL	< LLN - 3.0 x 10^9 /L < LLN - 3000/mm^3	≥2.0 - < 3.0 x 10^9 /L ≥2000 - < 3000/mm^3	≥1.0 - < 2.0 x 10^9 /L ≥1000 - < 2000/mm^3	< 1.0 x 10^9 /L < 1000/mm^3
Lymphopenia	WNL	<LLN - 1.0 x 10^9 /L <LLN - 1000/mm^3	≥0.5 - <1.0 x 10^9 /L ≥500 - <1000/mm^3	<0.5 x 10^9 /L <500/mm^3	-
Neutrophils/granulocytes (ANC/AGC)	WNL	≥1.5 - <2.0 x 10^9 /L ≥1500 - <2000/mm^3	≥1.0 - <1.5 x 10^9 /L ≥1000 - <1500/mm^3	≥0.5 - <1.0 x 10^9 /L ≥500 - <1000/mm^3	< 0.5 x 10^9 /L < 500/mm^3
Platelets	WNL	< LLN - <75.0 x 10^9 /L < LLN - 75000/mm^3	≥50.0 - < 75.0 x 10^9 /L ≥50000 - < 75000/mm^3	≥10.0 - < 50.0 x 10^9 /L ≥10000 - < 50000/mm^3	< 10.0 x 10^9 /L < 10000/mm^3
Transfusion: Platelets	none	-	-	yes	platelet transfusions and other measures required to

Toxicity	Grade 0	1	2	3	4
Also consider Hemoglobin.					improve platelet increment; platelet transfusion refractoriness associated with life-threatening bleeding. (e.g., HLA or cross matched platelet transfusions)
Blood/Bone Marrow-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
CARDIOVASCULAR (ARRHYTHMIA)					
Conduction abnormality/ Atrioventricular heart block	none	asymptomatic, not requiring treatment (e.g., Mobitz type I second-degree AV block, Wenckebach)	symptomatic, but not requiring treatment	symptomatic and requiring treatment (e.g., Mobitz type II second-degree AV block, third-degree AV block)	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
Nodal/junctional arrhythmia/dysrhythmia	none	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic and requiring treatment	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
Palpitations Note: Grade palpitations only in the absence of a documented arrhythmia.	none	present	-	-	-
Prolonged QTc interval (QTc > 0.48 seconds)	none	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic and requiring treatment	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
Sinus bradycardia	none	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic and requiring treatment	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
Sinus tachycardia	none	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic and requiring treatment of underlying cause	-
Supraventricular arrhythmias (SVT/atrial fibrillation/ flutter)	none	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic and requiring treatment	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
Syncope (fainting) is graded in the NEUROLOGY category.					
Vasovagal episode	none	-	present without loss of consciousness	present with loss of consciousness	-

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
Ventricular arrhythmia (PVCs/bigeminy/trigeminy/ ventricular tachycardia)	none	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic and requiring treatment	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
Cardiovascular/ Arrhythmia-Other (Specify, _____)	none	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic, and requiring treatment of underlying cause	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
CARDIOVASCULAR (GENERAL)					
Acute vascular leak syndrome	absent	-	symptomatic, but not requiring fluid support	respiratory compromise or requiring fluids	life-threatening; requiring pressor support and/or ventilatory support
Cardiac-ischemia/infarction	none	non-specific T-wave flattening or changes	asymptomatic, ST- and T- wave changes suggesting ischemia	angina without evidence of infarction	acute myocardial infarction
Cardiac left ventricular function	normal	asymptomatic decline of resting ejection fraction of ≥ 10% but < 20% of baseline value; shortening fraction ≥ 24% but < 30%	asymptomatic but resting ejection fraction below LLN for laboratory or decline of resting ejection fraction ≥ 20% of baseline value; < 24% shortening fraction	CHF responsive to treatment	severe or refractory CHF or requiring intubation
CNS cerebrovascular ischemia is graded in the NEUROLOGY category.					
Cardiac troponin I (cTnI)	normal	-	-	levels consistent with unstable angina as defined by the manufacturer	levels consistent with myocardial infarction as defined by the manufacturer
Cardiac troponin T (cTnT)	normal	≥ 0.03 - < 0.05 ng/ml	≥ 0.05 - < 0.1 ng/ml	≥ 0.1 - < 0.2 ng/ml	≥ 0.2 ng/ml
Edema	none	asymptomatic, not requiring therapy	symptomatic, requiring therapy	symptomatic edema limiting function and unresponsive to therapy or requiring drug discontinuation	anasarca (severe generalized edema)
Hypertension	none	asymptomatic, transient increase by >20 mmHg (diastolic) or to > 150/100* if previously WNL; not requiring	recurrent or persistent or symptomatic increase by > 20 mmHg (diastolic) or to > 150/100* if previously WNL;	requiring therapy or more intensive therapy than previously	hypertensive crisis

Toxicity	Grade 0	1	2	3	4
		treatment	not requiring treatment		
**Note: For pediatric patients, use age and sex appropriate normal values > 95th percentile ULN.*					
Hypotension	none	changes, but not requiring therapy (including transient orthostatic hypotension)	requiring brief fluid replacement or other therapy but not hospitalization; no physiologic consequences	requiring therapy and sustained medical attention, but resolves without persisting physiologic consequences	shock (associated with acidemia and impairing vital organ function due to tissue hypoperfusion)
Also consider Syncope (fainting). Note: Angina or MI is graded as Cardiac- ischemia/infarction in the CARDIOVASCULAR (GENERAL) category. *For pediatric patients, systolic BP 65 mmHg or less in infants up to 1 year old and 70 mmHg or less in children older than 1 year of age, use two successive or three measurements in 24 hours.*					
Myocarditis	none	-	-	CHF responsive to treatment	severe or refractory CHF
Operative injury of vein/artery	none	primary suture repair for injury, but not requiring transfusion	primary suture repair for injury, requiring transfusion	vascular occlusion requiring surgery or bypass for injury	myocardial infarction; resection of organ (e.g., bowel, limb)
Pericardial effusion/ pericarditis	none	asymptomatic effusion, not requiring treatment	pericarditis (rub, ECG changes, and/or chest pain)	physiologic consequences resulting from symptoms	tamponade (drainage or pericardial window required)
Peripheral arterial ischemia	none	-	brief episode of ischemia managed non-surgically and without permanent deficit	requiring surgical intervention	life-threatening or with permanent functional deficit (e.g., amputation)
Phlebitis (superficial)	none	-	present	-	-
Note: Injection site reaction is graded in the DERMATOLOGY/SKIN category. Thrombosis/embolism is graded in the CARDIOVASCULAR (GENERAL) category.					
Syncope (fainting) is graded in the NEUROLOGY category.					
Thrombosis/embolism	none	-	deep vein thrombosis, not requiring anticoagulant	deep vein thrombosis, requiring anticoagulant therapy	embolic event including pulmonary embolism
Vein/artery operative injury is graded as Operative injury of vein/artery in the CARDIOVASCULAR (GENERAL) category.					
Visceral arterial ischemia (non-myocardial)	none	-	brief episode of ischemia managed non-surgically and without permanent deficit	requiring surgical intervention	life-threatening or with permanent functional deficit (e.g., resection of ileum)
Cardiovascular/ General-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling

Toxicity	Grade 0	1	2	3	4
COAGULATION					
Note: See the HEMORRHAGE category for grading the severity of bleeding events.					
DIC (disseminated intravascular coagulation) Also grade Platelets. Note: Must have increased fibrin split products or D-dimer in order to grade as DIC.	absent	-	-	laboratory findings present with no bleeding	laboratory findings and bleeding
Partial thromboplastin time (PTT)	WNL	> ULN - ≤ 1.5 x ULN	> 1.5 - ≤ 2 x ULN	>2 x ULN	-
Phelbitis is graded in the CARDIOVASCULAR (GENERAL) category.					
Prothrombin time (PT)	WNL	> ULN - ≤ 1.5 x ULN	> 1.5 - ≤ 2 x ULN	>2 x ULN	-
Thrombosis/embolism is graded in the CARDIOVASCULAR (GENERAL) category.					
Thrombotic microangiopathy (e.g., thrombotic thrombocytopenic purpura/TTP or hemolytic uremic syndrome/HUS) Also consider Hemoglobin (Hgb), Platelets, Creatinine. Note: Must have microangiopathic changes on blood smear (e.g., schistocytes, helmet cells, red cell fragments).	absent	-	-	laboratory findings present without clinical consequences	laboratory findings and clinical consequences, (e.g., CNS hemorrhage/ bleeding or thrombosis/ embolism or renal failure) requiring therapeutic intervention
Coagulation-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
CONSTITUTIONAL SYMPTOMS					
Fatigue (lethargy, malaise, asthenia) Note: See Appendix III for performance status scales.	none	increased fatigue over baseline, but not altering normal activities	moderate (e.g., decrease in performance status by 1 ECOG level or 20% Karnofsky or *Lansky*) or causing difficulty performing some activities	severe (e.g., decrease in performance status by ≥2 ECOG levels or 40% Karnofsky or *Lansky*) or loss of ability to perform some activities	bedridden or disabling
Fever (in the absence of neutropenia, where neutropenia is defined as AGC < 1.0 x 10^9/L) Also consider Allergic reaction/hypersensitivity. Note: The temperature measurements listed above are oral or tympanic.	none	38.0 - 39.0°C (100.4 - 102.2°F)	39.1 - 40.0°C (102.3 - 104.0°F)	> 40.0°C (>104.0°F) for < 24hrs	> 40.0°C (>104.0°F) for > 24hrs
Hot flashes/flushes are graded in the ENDOCRINE category.					
Rigors, chills	none	mild, requiring symptomatic treatment (e.g.,	severe and/or prolonged, requiring narcotic	not responsive to narcotic medication	-

Toxicity	Grade 0	1	2	3	4
		blanket) or non-narcotic medication	medication		
Sweating (diaphoresis)	normal	mild and occasional	frequent or drenching	-	-
Weight gain Also consider Ascites, Edema, Pleural effusion.	< 5%	5 - <10%	10 - <20%	≥ 20%	-
Weight loss Also consider Vomiting, Dehydration, Diarrhea.	< 5%	5 - <10%	10 - <20%	≥20%	-
Constitutional Symptoms-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
DERMATOLOGY/SKIN					
Alopecia	normal	mild hair loss	pronounced hair loss	-	-
Bruising (in absence of grade 3 or 4 thrombocytopenia)	none	localized or in dependent area	generalized	-	-
Note: Bruising resulting from grade 3 or 4 thrombocytopenia is graded as Petechiae/purpura and Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia in the HEMORRHAGE category, not in the DERMATOLOGY/SKIN category.					
Dry skin	normal	controlled with emollients	not controlled with emollients	-	-
Erythema multiforme (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis)	absent	-	scattered, but not generalized eruption	severe or requiring IV fluids (e.g., generalized rash or painful stomatitis)	life-threatening (e.g., exfoliative or ulcerating dermatitis or requiring enteral or parenteral nutritional support)
Flushing	absent	present	-	-	-
Hand-foot skin reaction	none	skin changes or dermatitis without pain (e.g., erythema, peeling)	skin changes with pain, not interfering with function	skin changes with pain, interfering with function	-
Injection site reaction	none	pain or itching or erythema	pain or swelling, with inflammation or phlebitis	ulceration or necrosis that is severe or prolonged, or requiring surgery	-
Nail changes	normal	discoloration or ridging (koilonychia) or pitting	partial or complete loss of nail(s) or pain in nailbeds	-	-
Petechiae is graded in the HEMORRHAGE category.					
Photosensitivity	none	painless erythema	painful erythema	erythema with desquamation	-
Pigmentation changes (e.g., vitiligo)	none	localized pigmentation changes	generalized pigmentation changes	-	-

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
Pruritus	none	mild or localized, relieved spontaneously or by local measures	intense or widespread, relieved spontaneously or by systemic measures	intense or widespread and poorly controlled despite treatment	-
Purpura is graded in the HEMORRHAGE category.					
Radiation dermatitis	none	faint erythema or dry desquamation	moderate to brisk erythema or a patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	confluent moist desquamation, ≥1.5 cm diameter, not confined to skin folds; pitting edema	skin necrosis or ulceration of full thickness dermis; may include bleeding not induced by minor trauma or abrasion
Note: Pain associated with radiation dermatitis is graded separately in the PAIN category as Pain due to radiation.					
Radiation recall reaction (reaction following chemotherapy in the absence of additional radiation therapy that occurs in a previous radiation port)	none	faint erythema or dry desquamation	moderate to brisk erythema or a patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	confluent moist desquamation, ≥1.5 cm diameter, not confined to skin folds; pitting edema	skin necrosis or ulceration of full thickness dermis; may include bleeding not induced by minor trauma or abrasion
Rash/desquamation	none	macular or papular eruption or erythema without associated symptoms	macular or papular eruption or erythema with pruritus or other associated symptoms covering <50% of body surface or localized desquamation or other lesions covering <50% of body surface area	symptomatic generalized erythroderma or macular, papular or vesicular eruption or desquamation covering ≥50% of body surface area	generalized exfoliative dermatitis or ulcerative dermatitis
Also consider Allergic reaction/hypersensitivity. Note: Erythema multiforme (Stevens-Johnson syndrome) is graded separately as Erythema multiforme.					
Urticaria (hives, welts, wheals)	none	requiring no medication	requiring PO or topical treatment or IV medication or steroids for <24 hours	requiring IV medication or steroids for ≥24 hours	-
Wound- infectious	none	cellulitis	superficial infection	infection requiring IV antibiotics	necrotizing fascitis
Wound- non-infectious	none	incisional separation	incisional hernia	fascial disruption without evisceration	fascial disruption with evisceration
Dermatology/Skin- Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling

Toxicity	Grade 0	1	2	3	4
ENDOCRINE					
Cushingoid appearance (e.g., moon face with or without buffalo hump, centripetal obesity, cutaneous striae) Also consider Hyperglycemia, Hypokalemia.	absent	-	present	-	-
Feminization of male	absent	-	-	present	-
Gynecomastia	none	mild	pronounced or painful	pronounced or painful and requiring surgery	-
Hot flashes/flushes	none	mild or no more than 1 per day	moderate and greater than 1 per day	-	-
Hypothyroidism	absent	asymptomatic,TSH elevated, no therapy given	symptomatic or thyroid replacement treatment given	patient hospitalized for manifestations of hypothyroidism	myxedema coma
Masculinization of female	absent	-	-	present	-
SIADH (syndrome of inappropriate antidiuretic hormone)	absent	-	-	present	-
Endocrine-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
GASTROINTESTINAL					
Amylase is graded in the METABOLIC/LABORATORY category.					
Anorexia	none	loss of appetite	oral intake significantly decreased	requiring IV fluids	requiring feeding tube or parenteral nutrition
Ascites (non-malignant)	none	asymptomatic	symptomatic, requiring diuretics	symptomatic, requiring therapeutic paracentesis	life-threatening physiologic consequences
Colitis Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia, Melena/GI bleeding, Rectal bleeding/hematochezia, Hypotension.	none	-	abdominal pain with mucus and/or blood in stool	abdominal pain, fever, change in bowel habits with ileus or peritoneal signs, and radiographic or biopsy documentation	perforation or requiring surgery or toxic megacolon
Constipation	none	requiring stool softener or dietary modification	requiring laxatives	obstipation requiring manual evacuation or enema	obstruction or toxic megacolon
Dehydration	none	dry mucous	requiring IV fluid	requiring IV fluid	physiologic

Toxicity	Grade 0	1	2	3	4
		membranes and/or diminished skin turgor	replacement (brief)	replacement (sustained)	consequences requiring intensive care; hemodynamic collapse
Also consider Hypotension, Diarrhea, Vomiting, Stomatitis/pharyngitis (oral/pharyngeal mucositis).					
Diarrhea Patients without colostomy:	none	increase of < 4 stools/day over pre-treatment	increase of 4-6 stools/day, or nocturnal stools	increase of ≥7 stools/day or incontinence; or need for parenteral support for dehydration	physiologic consequences requiring intensive care; or hemodynamic collapse
Patients with a colostomy:	none	mild increase in loose, watery colostomy output compared with pretreatment	moderate increase in loose, watery colostomy output compared with pretreatment, but not interfering with normal activity	severe increase in loose, watery colostomy output compared with pretreatment, interfering with normal activity	physiologic consequences, requiring intensive care; or hemodynamic collapse
Duodenal ulcer (requires radiographic or endoscopic documentation)	none	-	requiring medical management or non-surgical treatment	uncontrolled by outpatient medical management; requiring hospitalization	perforation or bleeding, requiring emergency surgery
Dyspepsia/heartburn	none	mild	moderate	severe	-
Dysphagia, esophagitis, odynophagia (painful swallowing)	none	mild dysphagia, but can eat regular diet	dysphagia, requiring predominantly pureed, soft, or liquid diet	dysphagia, requiring IV hydration	complete obstruction (cannot swallow saliva) requiring enteral or parenteral nutritional support, or perforation
Note: If toxicity is radiation-related, grade either under Dysphagia- esophageal related to radiation or Dysphagia- pharyngeal related to radiation.					
Dysphagia- esophageal related to radiation	none	mild dysphagia, but can eat regular diet	dysphagia, requiring predominantly liquid, pureed or soft diet	dysphagia requiring feeding tube, IV hydration or hyperalimentation	complete obstruction (cannot swallow saliva); ulceration with bleeding not induced by minor trauma or abrasion or perforation
Also consider Pain due to radiation, Mucositis due to radiation. Note: Fistula is graded separately as Fistula- esophageal.					
Dysphagia - pharyngeal related to radiation	none	mild dysphagia, but can eat regular diet	dysphagia, requiring predominantly pureed, soft, or liquid diet	dysphagia, requiring feeding tube, IV hydration or hyperalimentation	complete obstruction (cannot swallow saliva); ulceration with bleeding not induced by minor trauma or abrasion or perforation
Also consider Pain due to radiation, Mucositis due to radiation.					

Toxicity	Grade 0	1	2	3	4
Note: Fistula is graded separately as Fistula- pharyngeal.					
Fistula- esophageal	none	-	-	present	requiring surgery
Fistula- pharyngeal	none	-	-	present	requiring surgery
Flatulence	none	mild	moderate	-	-
Gastric ulcer (requires radiographic or endoscopic documentation)	none	-	requiring medical management or non-surgical treatment	bleeding without perforation, uncontrolled by outpatient medical management; requiring hospitalization or surgery	perforation or bleeding, requiring emergency surgery
Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia.					
Gastritis	none	-	requiring medical management or non-surgical treatment	uncontrolled by out-patient medical management; requiring hospitalization or surgery	life-threatening bleeding, requiring emergency surgery
Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia.					
Hematemesis is graded in the HEMORRHAGE category.					
Hematochezia is graded in the HEMORRHAGE category as Rectal bleeding/hematochezia.					
Ileus (or neuroconstipation)	none	-	intermittent, not requiring intervention	requiring non-surgical intervention	requiring surgery
Mouth dryness	normal	mild	moderate	-	-
Mucositis Note: Mucositis not due to radiation is graded in the GASTROINTESTINAL category for specific sites: Colitis, Esophagitis, Gastritis, Stomatitis/pharyngitis (oral/pharyngeal mucositis), and Typhlitis; or the RENAL/GENITOURINARY category for Vaginititis. Radiation-related mucositis is graded as Mucositis due to radiation.					
Mucositis due to radiation	none	erythema of the mucosa	patchy pseudomembranous reaction (patches generally ≤ 1.5 cm in diameter and non-contiguous)	confluent pseudomembranous reaction (contiguous patches generally > 1.5 cm in diameter)	necrosis or deep ulceration; may include bleeding not induced by minor trauma or abrasion
Also consider Pain due to radiation. Note: Grade radiation mucositis of the larynx here. Dysphagia related to radiation is also graded as either Dysphagia- esophageal related to radiation or Dysphagia- pharyngeal related to radiation, depending on the site of treatment.					
Nausea	none	able to eat	oral intake significantly decreased	no significant intake, requiring IV fluids	-
Pancreatitis	none	-	-	abdominal pain with pancreatic enzyme elevation	complicated by shock (acute circulatory failure)
Also consider Hypotension. Note: Asymptomatic amylase and Amylase are graded in the METABOLIC/LABORATORY category.					

Toxicity	Grade 0	1	2	3	4
Salivary gland changes	none	slightly thickened saliva/may have slightly altered taste (e.g., metallic); additional fluids may be required	thick, ropy, sticky saliva; markedly altered taste; alteration in diet required	-	acute salivary gland necrosis
Sense of smell	normal	slightly altered	markedly altered	-	-
Stomatitis/pharyngitis (oral/pharyngeal mucositis)	none	painless ulcers, erythema, or mild soreness in the absence of lesions	painful erythema, edema, or ulcers, but can eat or swallow	painful erythema, edema, or ulcers requiring IV hydration	severe ulceration or requires parenteral or enteral nutritional support or prophylatic intubation
Note: Radiation-related mucositis is graded as Mucositis due to radiation.					
Taste disturbance (dysgeusia)	normal	slightly altered	markedly altered	-	-
Typhlitis (inflammation of the cecum)	none	-	-	abdominal pain, diarrhea, fever, or radiographic documentation	perforation, bleeding or necrosis or other life-threatening complication requiring surgical intervention (e.g., colostomy)
Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia, Hypotension, Febrile/neutropenia.					
Vomiting	none	1 episode in 24 hours over pretreatment	2-5 episodes in 24 hours over pretreatment	≥6 episodes in 24 hours over pretreatment; or need for IV fluids	Requiring parenteral nutrition; or physiologic consequences requiring intensive care; hemodynamic collapse
Also consider Dehydration.					
Weight gain is graded in the CONSTITUTIONAL SYMPTOMS category.					
Weight loss is graded in the CONSTITUTIONAL SYMPTOMS category.					
Gastrointestinal-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling

HEMORRHAGE

Note: Transfusion in this section refers to pRBC infusion.

For any bleeding with grade 3 or 4 platelets (< 50,000), always grade Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia. Also consider platelets, transfusion- pRBCS, and transfusion-platelets in addition to the grade that incorporates the site or type of bleeding.

If the site or type of hemorrhage/bleeding is listed, also use the grading that incorporates the site of bleeding: CNS hemorrhage/bleeding, Hematuria, Hematemesis, Hemoptysis, Hemorrhage/bleeding with surgery, Melena/lower GI bleeding, Petechiae/purpura (Hemorrhage/bleeding into skin), Rectal bleeding/hematochezia, Vaginal bleeding.

If the platelet count is ≥50,000 and the site or type of bleeding is listed, grade the specific site. If the site or type is not listed and the platelet count is ≥50,000, grade Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia and specify the site or

Toxicity	Grade 0	1	2	3	4
type in the OTHER category.					
Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia	none	mild without transfusion		requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Also consider Platelets, Hemoglobin, Transfusion-platelet, Transfusion-pRBCs. Note: This toxicity must be graded for any bleeding with grade 3 or 4 thrombocytopenia. Also grade the site or type of hemorrhage/bleeding. If the site is not listed, grade as Other in the HEMORRHAGE category.					
Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia	none	mild without transfusion		requiring transfusion	catastrophic bleeding requiring major non-elective intervention
Also consider Platelets, Hemoglobin, Transfusion-platelet, Transfusion-pRBCs. Note: Bleeding in the absence of grade 3 or 4 thrombocytopenia is graded here only if the specific site or type of bleeding is not listed elsewhere in the HEMORRHAGE category. Also grade as Other in the HEMORRHAGE category.					
CNS hemorrhage/bleeding	none	-	-	bleeding noted on CT or other scan with no clinical consequences	hemorrhagic stroke or hemorrhagic vascular event (CVA) with neurologic signs and symptoms
Epistaxis	none	mild without transfusion	-	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Hematemesis	none	mild without transfusion	-	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Hematuria (in the absence of vaginal bleeding)	none	microscopic only	intermittent gross bleeding, no clots	persistent gross bleeding or clots; may require catheterization or instrumentation, or transfusion	open surgery or necrosis or deep bladder ulceration
Hemoptysis	none	mild without transfusion	-	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Hemorrhage/bleeding associated with surgery Note: Expected blood loss at the time of surgery is not graded as a toxicity.	none	mild without transfusion	-	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Melena/GI bleeding	none	mild without transfusion	-	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Petechiae/purpura (hemorrhage/bleeding into skin or mucosa)	none	rare petechiae of skin	petechiae or purpura in dependent areas of skin	generalized petechiae or purpura of skin or petechiae of any	-

Toxicity	Grade 0	1	2	3	4
				mucosal site	
Rectal bleeding/ hematochezia	none	mild without transfusion or medication	persistent, requiring medication (e.g., steroid suppositories) and/or break from radiation treatment	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Vaginal bleeding	none	spotting, requiring < 2 pads per day	requiring ≥ 2 pads per day, but not requiring transfusion	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Hemorrhage-Other (Specify site, _____)	none	mild without transfusion	-	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
HEPATIC					
Alkaline phosphatase	WNL	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
Bilirubin	WNL	> ULN - 1.5 x ULN	> 1.5 - 3.0 x ULN	> 3.0 - 10.0 x ULN	> 10.0 x ULN
GGT (γ - Glutamyl transpeptidase)	WNL	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
Hepatic enlargement	absent	-	-	present	-
Note: Grade Hepatic enlargement only for changes related to VOD or other treatment related toxicity.					
Hypoalbuminemia	WNL	<LLN - 3 g/dl	≥2 - <3 g/dl	<2 g/dl	-
Liver dysfunction/failure (clinical)	normal	-	-	asterixis	encephalopathy or coma
Note: Documented viral hepatitis is graded in the INFECTION category.					
Portal vein flow	normal	-	decreased portal vein flow	reversal/retrograde portal vein flow	-
SGOT (AST) (serum glutamic oxaloacetic transaminase)	WNL	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
SGPT (ALT) (serum glutamic pyruvic transaminase)	WNL	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
Hepatic-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
INFECTION/FEBRILE NEUTROPENIA					
Catheter-related infection	none	mild, no active treatment	moderate, localized infection, requiring local or oral treatment	severe, systemic infection, requiring IV antibiotic or antifungal treatment or hospitalization	life-threatening sepsis (e.g., septic shock)

Toxicity	Grade 0	1	2	3	4
Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection) (ANC < 1.0 x 10^9/L, fever ≥38.5°C)	none	-	-	Present	Life-threatening sepsis (e.g., septic shock)
Note: Hypothermia instead of fever may be associated with neutropenia and is graded here.					
Infection (documented clinically or microbiologically) with grade 3 or 4 neutropenia (ANC < 1.0 x 10^9/L)	none	-	-	present	life-threatening sepsis (e.g., septic shock)
Note: Hypothermia instead of fever may be associated with neutropenia and is graded here. In the absence of documented infection with grade 3 or 4 neutropenia, grade as Febrile neutropenia.					
Infection with unknown ANC	none	-	-	present	life-threatening sepsis (e.g., septic shock)
Note: This toxicity criterion is used in the rare case when ANC is unknown.					
Infection without neutropenia	none	mild, no active treatment	moderate, localized infection, requiring local or oral treatment	severe, systemic infection, requiring IV antibiotic or antifungal treatment, or hospitalization	life-threatening sepsis (e.g., septic shock)
Infection/Febrile Neutropenia-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
Wound-infectious is graded in the DERMATOLOGY/SKIN category.					
LYMPHATICS					
Lymphatics	normal	mild lymphedema	moderate lymphedema requiring compression; lymphocyst	severe lymphedema limiting function; lymphocyst requiring surgery	severe lymphedema limiting function with ulceration
Lymphatics-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
METABOLIC/LABORATORY					
Acidosis (metabolic or respiratory)	normal	pH < normal, but ≥7.3	-	pH < 7.3	pH < 7.3 with life-threatening physiologic consequences
Alkalosis (metabolic or respiratory)	normal	pH > normal, but ≤7.5	-	pH > 7.5	pH > 7.5 with life-threatening physiologic consequences
Amylase	WNL	> ULN - 1.5 x ULN	> 1.5 - 2.0 x ULN	> 2.0 - 5.0 x ULN	>5.0 x ULN

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
Bicarbonate	WNL	< LLN - 16 mEq/dl	11 - 15 mEq/dl	8 - 10 mEq/dl	< 8 mEq/dl
CPK (creatine phosphokinase)	WNL	> ULN - 2.5 x ULN	> 2.5 - 5 x ULN	> 5 - 10 x ULN	> 10 x ULN
Hypercalcemia	WNL	> ULN - 11.5 mg/dl > ULN - 2.9 mmol/L	>11.5 - 12.5 mg/dl > 2.9 - 3.1 mmol/L	>12.5 - 13.5 mg/dl > 3.1 - 3.4 mmol/L	> 13.5 mg/dl > 3.4 mmol/L
Hypercholesterolemia	WNL	> ULN - 300 mg/dl > ULN - 7.75 mmol/L	> 300 - 400 mg/dl > 7.75 - 10.34 mmol/L	> 400 - 500 mg/dl >10.34 - 12.92 mmol/L	> 500 mg/dl > 12.92 mmol/L
Hyperglycemia	WNL	> ULN - 160 mg/dl > ULN - 8.9 mmol/L	> 160 - 250 mg/dl > 8.9 - 13.9 mmol/L	> 250 - 500 mg/dl > 13.9 - 27.8 mmol/L	> 500 mg/dl > 27.8 mmol/L or ketoacidosis
Hyperkalemia	WNL	> ULN - 5.5 mmol/L	> 5.5 - 6.0 mmol/L	> 6.0 - 7.0 mmol/L	> 7.0 mmol/L
Hypermagnesemia	WNL	> ULN - 3.0 mg/dl > ULN - 1.23 mmol/L	-	> 3.0 - 8.0 mg/dl > 1.23 - 3.30 mmol/L	> 8.0 mg/dl > 3.30 mmol/L
Hypernatremia	WNL	> ULN - 150 mmol/L	>150 - 155 mmol/L	>155 - 160 mmol/L	>160 mmol/L
Hypertriglyceridemia	WNL	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 10 x ULN	> 10 x ULN
Hyperuricemia	WNL	> ULN - ≤ 10 mg/dl ≤ 0.59 mmol/L without physiologic consequences	-	> ULN - ≤ 10 mg/dl ≤ 0.59 mmol/L with physiologic consequences	> 10 mg/dl > 0.59 mmol/L
Also consider Tumor lysis syndrome, Renal failure, Creatinine, Potassium.					
Hypocalcemia	WNL	<LLN - 8.0 mg/dl <LLN - 2.0 mmol/L	7.0 - < 8.0 mg/dl 1.75 - < 2.0 mmol/L	6.0 - < 7.0 mg/dl 1.5 - < 1.75 mmol/L	<6.0 mg/dl < 1.5 mmol/L
Hypoglycemia	WNL	<LLN - 55 mg/dl <LLN - 3.0 mmol/L	40 - < 55 mg/dl 2.2 - < 3.0 mmol/L	30 - < 40 mg/dl 1.7 - < 2.2 mmol/L	< 30 mg/dl < 1.7 mmol/L
Hypokalemia	WNL	<LLN - 3.0 mmol/L	-	2.5 - <3.0 mmol/L	<2.5 mmol/L
Hypomagnesemia	WNL	<LLN - 1.2 mg/dl <LLN - 0.5 mmol/L	0.9 - <1.2 mg/dl 0.4 - < 0.5 mmol/L	0.7 - < 0.9 mg/dl 0.3 - < 0.4 mmol/L	< 0.7 mg/dl < 0.3 mmol/L
Hyponatremia	WNL	<LLN - 130 mmol/L	-	120 - <130 mmol/L	<120 mmol/L
Hypophosphatemia	WNL	<LLN -2.5 mg/dl <LLN - 0.8 mmol/L	≥2.0 - <2.5 mg/dl ≥0.6 - <0.8 mmol/L	≥1.0 - <2.0 mg/dl ≥0.3 - <0.6 mmol/L	< 1.0 mg/dl <0.3 mmol/L
Hypothyroidism is graded in the ENDOCRINE category.					
Lipase	WNL	> ULN - 1.5 x ULN	> 1.5 - 2.0 x ULN	> 2.0 - 5.0 x ULN	> 5.0 x ULN
Metabolic/Laboratory-Other (Specify,	none	mild	moderate	severe	life-threatening or disabling

Toxicity	Grade 0	1	2	3	4
_____)					
MUSCULOSKELETAL					
Arthralgia is graded in the PAIN category.					
Arthritis	none	mild pain with inflammation, erythema or joint swelling but not interfering with function	moderate pain with inflammation, erythema, or joint swelling interfering with function, but not interfering with activities of daily living	severe pain with inflammation, erythema, or joint swelling and interfering with activities of daily living	disabling
Muscle weakness (not due to neuropathy)	normal	asymptomatic with weakness on physical exam	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	bedridden or disabling
Myalgia is graded in the PAIN category.					
Myositis (inflammation/damage of muscle) Also consider CPK. Note: Myositis implies muscle damage (i.e., elevated CPK).	none	mild pain, not interfering with function	pain interfering with function, but not interfering with activities of daily living	pain interfering with function and interfering with activities of daily living	bedridden or disabling
Osteonecrosis (avascular necrosis)	none	asymptomatic and detected by imaging only	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	symptomatic; or disabling
Musculoskeletal-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
NEUROLOGY					
Aphasia, receptive and/or expressive, is graded under Speech impairment in the NEUROLOGY category.					
Arachnoiditis/meningismus/ radiculitis Also consider Headache, Vomiting, Fever.	absent	mild pain not interfering with function	moderate pain interfering with function, but not interfering with activities of daily living	severe pain interfering with activities of daily living	unable to function or perform activities of daily living; bedridden; paraplegia
Ataxia (incoordination)	normal	asymptomatic but abnormal on physical exam, and not interfering with function	mild symptoms interfering with function, but not interfering with activities of daily living	moderate symptoms interfering with activities of daily living	bedridden or disabling
CNS cerebrovascular ischemia	none	-	-	transient ischemic event or attack	permanent event (e.g., cerebral

Toxicity	Grade 0	1	2	3	4
				(TIA)	vascular accident)
CNS hemorrhage/bleeding is graded in the HEMORRHAGE category.					
Cognitive disturbance/ learning problems	*none*	*cognitive disability; not interfering with work/school performance; preservation of intelligence*	*cognitive disability; interfering with work/school performance; decline of 1 SD (Standard Deviation) or loss of developmental milestones*	*cognitive disability; resulting in significant impairment of work/school performance; cognitive decline > 2 SD*	*inability to work/frank mental retardation*
Confusion	normal	confusion or disorientation or attention deficit of brief duration; resolves spontaneously with no sequelae	confusion or disorientation or attention deficit interfering with function, but not interfering with activities of daily living	confusion or delirium interfering with activities of daily living	harmful to others or self; requiring hospitalization
Cranial neuropathy is graded in the NEUROLOGY category as Neuropathy-cranial.					
Delusions	normal	-	-	present	toxic psychosis
Depressed level of consciousness Note: Syncope (fainting) is graded in the NEUROLOGY category.	normal	somnolence or sedation not interfering with function	somnolence or sedation interfering with function, but not interfering with activities of daily living	obtundation or stupor; difficult to arouse; interfering with activities of daily living	coma
Dizziness/lightheadedness	none	not interfering with function	interfering with function, but not interfering with activities of daily living	interfering with activities of daily living	bedridden or disabling
Dysphasia, receptive and/or expressive, is graded under Speech impairment in the NEUROLOGY category.					
Extrapyramidal/ involuntary movement/ restlessness	none	mild involuntary movements not interfering with function	moderate involuntary movements interfering with function, but not interfering with activities of daily living	severe involuntary movements or torticollis interfering with activities of daily living	bedridden or disabling
Hallucinations	normal	-	-	present	toxic psychosis
Headache is graded in the PAIN category.					
Insomnia	normal	occasional difficulty sleeping not interfering with function	difficulty sleeping interfering with function, but not interfering with activities of daily living	frequent difficulty sleeping, interfering with activities of daily living	-

Toxicity	Grade 0	1	2	3	4
Note: This toxicity is graded when insomnia is related to treatment. If pain or other symptoms interfere with sleep do NOT grade as insomnia.					
Irritability *(children <3 years of age)*	*normal*	*mild; easily consolable*	*moderate; requiring increased attention*	*severe; inconsolable*	-
Leukoencephalopathy associated radiological findings	*none*	*mild increase in SAS (subarachnoid space) and/or mild ventriculomegaly; and/or small (+/- multiple) focal T2 hyperintensities, involving periventricular white matter or < 1/3 of susceptible areas of cerebrum*	*moderate increase in SAS; and/or moderate ventriculomegaly; and/or focal T2 hyperintensities extending into centrum ovale; or involving 1/3 to 2/3 of susceptible areas of cerebrum*	*severe increase in SAS; severe ventriculomegaly; near total white matter T2 hyperintensities or diffuse low attenuation (CT); focal white matter necrosis (cystic)*	*severe increase in SAS; severe ventriculomegaly; diffuse low attenuation with calcification (CT); diffuse white matter necrosis (MRI)*
Memory loss	normal	memory loss not interfering with function	memory loss interfering with function, but not interfering with activities of daily living	memory loss interfering with activities of daily living	amnesia
Mood alteration-anxiety agitation	normal	mild mood alteration not interfering with function	moderate mood alteration interfering with function, but not interfering with activities of daily living	severe mood alteration interfering with activities of daily living	suicidal ideation or danger to self
Mood alteration-depression	normal	mild mood alteration not interfering with function	moderate mood alteration interfering with function, but not interfering with activities of daily living	severe mood alteration interfering with activities of daily living	suicidal ideation or danger to self
Mood alteration-euphoria	normal	mild mood alteration not interfering with function	moderate mood alteration interfering with function, but not interfering with activities of daily living	severe mood alteration interfering with activities of daily living	danger to self
Neuropathic pain is graded in the PAIN category.					
Neuropathy- cranial	absent	-	present, not interfering with activities of daily living	present, interfering with activities of daily living	life-threatening, disabling
Neuropathy- motor	normal	subjective weakness but no	mild objective weakness	objective weakness interfering with	paralysis

Toxicity	Grade 0	1	2	3	4
		objective findings	interfering with function, but not interfering with activities of daily living	activities of daily living	
Neuropathy-sensory	normal	loss of deep tendon reflexes or paresthesia (including tingling) but not interfering with function	objective sensory loss or paresthesia (including tingling), interfering with function, but not interfering with activities of daily living	sensory loss or paresthesia interfering with activities of daily living	permanent sensory loss that interferes with function
Nystagmus Also consider Vision-double vision.	absent	present	-	-	-
Personality/behavioral	normal	change, but not disruptive to patient or family	disruptive to patient or family	disruptive to patient and family; requiring mental health intervention	harmful to others or self; requiring hospitalization
Pyramidal tract dysfunction (e.g., ↑ tone, hyperreflexia, positive Babinski, ↓ fine motor coordination)	normal	asymptomatic with abnormality on physical examination	symptomatic or interfering with function but not interfering with activities of daily living	interfering with activities of daily living	bedridden or disabling; paralysis
Seizure(s)	none	-	seizure(s) self-limited and consciousness is preserved	seizure(s) in which consciousness is altered	seizures of any type which are prolonged, repetitive, or difficult to control (e.g., status epilepticus, intractable epilepsy)
Speech impairment (e.g., dysphasia or aphasia)	normal	-	awareness of receptive or expressive dysphasia, not impairing ability to communicate	receptive or expressive dysphasia, impairing ability to communicate	inability to communicate
Syncope (fainting) Also consider CARDIOVASCULAR (ARRHYTHMIA), Vasovagal episode, CNS cerebrovascular ischemia.	absent	-	-	present	-
Tremor	none	mild and brief or intermittent but not interfering with function	moderate tremor interfering with function, but not interfering with activities of daily living	severe tremor interfering with activities of daily living	-
Vertigo	none	not interfering with function	interfering with function, but not	interfering with activities of daily	bedridden or disabling

Toxicity	Grade 0	1	2	3	4
			interfering with activities of daily living	living	
Neurology-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
OCULAR/VISUAL					
Cataract	none	asymptomatic	symptomatic, partial visual loss	symptomatic, visual loss requiring treatment or interfering with function	-
Conjunctivitis	none	abnormal ophthalmologic changes, but asymptomatic or symptomatic without visual impairment (i.e., pain and irritation)	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	-
Dry eye	normal	mild, not requiring treatment	moderate or requiring artificial tears	-	-
Glaucoma	none	increase in intraocular pressure but no visual loss	increase in intraocular pressure with retinal changes	visual impairment	unilateral or bilateral loss of vision (blindness)
Keratitis (corneal inflammation/ corneal ulceration)	none	abnormal ophthalmologic changes but asymptomatic or symptomatic without visual impairment (i.e., pain and irritation)	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	unilateral or bilateral loss of vision (blindness)
Tearing (watery eyes)	none	mild: not interfering with function	moderate: interfering with function, but not interfering with activities of daily living	interfering with activities of daily living	-
Vision- blurred vision	normal	-	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	-
Vision- double vision (diplopia)	normal	-	symptomatic and interfering with function, but not interfering with activities of daily	symptomatic and interfering with activities of daily living	-

Toxicity	Grade 0	1	2	3	4
			living		
Vision- flashing lights/floaters	normal	mild, not interfering with function	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	-
Vision- night blindness (nyctalopia)	normal	abnormal electro-retinography but asymptomatic	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	-
Vision- photophobia	normal	-	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	-
Ocular/Visual-Other (Specify, _____)	normal	mild	moderate	severe	unilateral or bilateral loss of vision (blindness)
PAIN					
Abdominal pain or cramping	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Arthralgia (joint pain)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Arthritis (joint pain with clinical signs of inflammation) is graded in the MUSCULOSKELETAL category.					
Bone pain	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Chest pain (non-cardiac and non-pleuritic)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily	severe pain: pain or analgesics severely interfering with activities of daily living	disabling

Toxicity	Grade 0	1	2	3	4
			living		
Dysmenorrhea	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Dyspareunia	none	mild pain not interfering with function	moderate pain interfering with sexual activity	severe pain preventing sexual activity	-
Dysuria is graded in the RENAL/GENITOURINARY category.					
Earache (otalgia)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Headache	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Hepatic pain	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Myalgia (muscle pain)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Neuropathic pain (e.g., jaw pain, neurologic pain, phantom limb pain, post-infectious neuralgia, or painful neuropathies)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Pain due to radiation	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with	severe pain: pain or analgesics severely interfering with activities of daily living	disabling

Toxicity	Grade 0	1	2	3	4
			activities of daily living		
Pelvic pain	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Pleuritic pain	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Rectal or perirectal pain (proctalgia)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Tumor pain (onset or exacerbation of tumor pain due to treatment)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Tumor flair is graded in the SYNDROME category.					
Pain-Other (Specify, _____)	none	mild	moderate	severe	disabling
PULMONARY					
Adult Respiratory Distress Syndrome (ARDS)	absent	-	-	-	present
Apnea	none	-	-	present	requiring intubation
Carbon monoxide diffusion capacity (DL_{CO})	≥ 90% of pretreatment or normal value	≥75 - <90% of pretreatment or normal value	≥50 - <75% of pretreatment or normal value	≥25 - <50% of pretreatment or normal value	< 25% of pretreatment or normal value
Cough	absent	mild, relieved by non-prescription medication	requiring narcotic antitussive	severe cough or coughing spasms, poorly controlled or unresponsive to treatment	-
Dyspnea (shortness of breath)	normal	-	dyspnea on exertion	dyspnea at normal level of activity	dyspnea at rest or requiring ventilator support
FEV_1	≥ 90% of	≥75 - <90% of	≥50 - <75% of	≥25 - <50% of	< 25% of

Toxicity	Grade 0	1	2	3	4
	pretreatment or normal value	pretreatment or normal value	pretreatment or normal value	pretreatment or normal value	pretreatment or normal value
Hiccoughs (hiccups, singultus)	none	mild, not requiring treatment	moderate, requiring treatment	severe, prolonged, and refractory to treatment	-
Hypoxia	normal	-	decreased O_2 saturation with exercise	decreased O_2 saturation at rest, requiring supplemental oxygen	decreased O_2 saturation, requiring pressure support (CPAP) or assisted ventilation
Pleural effusion (non-malignant)	none	asymptomatic and not requiring treatment	symptomatic, requiring diuretics	symptomatic, requiring O_2 or therapeutic thoracentesis	life-threatening (e.g., requiring intubation)
Pleuritic pain is graded in the PAIN category.					
Pneumonitis/pulmonary infiltrates	none	radiographic changes but asymptomatic or symptoms not requiring steroids	radiographic changes and requiring steroids or diuretics	radiographic changes and requiring oxygen	radiographic changes and requiring assisted ventilation
Pneumothorax	none	no intervention required	chest tube required	sclerosis or surgery required	life-threatening
Pulmonary embolism is graded as Thrombosis/embolism in the CARDIOVASCULAR (GENERAL) category.					
Pulmonary fibrosis	none	radiographic changes, but asymptomatic or symptoms not requiring steroids	requiring steroids or diuretics	requiring oxygen	requiring assisted ventilation
Note: Radiation-related pulmonary fibrosis is graded in the RTOG/EORTC Late Radiation Morbidity Scoring Scheme- Lung. (See Appendix IV)					
Voice changes/stridor/larynx (e.g., hoarseness, loss of voice, laryngitis)	normal	mild or intermittent hoarseness	persistent hoarseness, but able to vocalize; may have mild to moderate edema	whispered speech, not able to vocalize; may have marked edema	marked dyspnea/stridor requiring tracheostomy or intubation
Note: Cough from radiation is graded as cough in the PULMONARY category. Radiation-related hemoptysis from larynx/pharynx is graded as Grade 4 Mucositis due to radiation in the GASTROINTESTINAL category. Radiation-related hemoptysis from the thoracic cavity is graded as Grade 4 Hemoptysis in the HEMORRHAGE category.					
Pulmonary-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
RENAL/GENITOURINARY					
Bladder spasms	absent	mild symptoms, not requiring intervention	symptoms requiring antispasmotic	severe symptoms requiring narcotic	-
Creatinine	WNL	> ULN - 1.5 x ULN	> 1.5 - 3.0 x ULN	> 3.0 - 6.0 x ULN	> 6.0 x ULN
Note: Adjust to age-appropriate levels for pediatric patients.					
Dysuria (painful urination)	none	mild symptoms requiring no intervention	symptoms relieved with therapy	symptoms not relieved despite therapy	-

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
Fistula or GU fistula (e.g., vaginal, vesicovaginal)	none	-	-	requiring intervention	requiring surgery
Hemoglobinuria	-	present	-	-	-
Hematuria (in the absence of vaginal bleeding) is graded in the HEMORRHAGE category.					
Incontinence	none	with coughing, sneezing, etc.	spontaneous, some control	no control (in the absence of fistula)	-
Operative injury to bladder and/or ureter	none	-	injury of bladder with primary repair	sepsis, fistula, or obstruction requiring secondary surgery; loss of one kidney; injury requiring anastomosis or re-implantation	septic obstruction of both kidneys or vesicovaginal fistula requiring diversion
Proteinuria	normal or < 0.15 g/24 hours	1+ or 0.15 - 1.0 g/24 hours	2+ to 3+ or 1.0 - 3.5 g/24 hours	4+ or > 3.5 g/24 hours	nephrotic syndrome
Note: If there is an inconsistency between absolute value and uristix reading, use the absolute value for grading.					
Renal failure	none	-	-	requiring dialysis, but reversible	requiring dialysis and irreversible
Ureteral obstruction	none	unilateral, not requiring surgery	-	bilateral, not requiring surgery	stent, nephrostomy tube, or surgery
Urinary electrolyte wasting (e.g., Fanconi's syndrome, renal tubular acidosis)	none	asymptomatic, not requiring treatment	mild, reversible and manageable with oral replacement	reversible but requiring IV replacement	irreversible, requiring continued replacement
Also consider Acidosis, Bicarbonate, Hypocalcemia, Hypophosphatemia.					
Urinary frequency/urgency	normal	increase in frequency or nocturia up to 2 x normal	increase > 2 x normal but < hourly	hourly or more with urgency, or requiring catheter	-
Urinary retention	normal	hesitancy or dribbling, but no significant residual urine; retention occurring during the immediate postoperative period	hesitancy requiring medication or occasional in/out catheterization (<4 x per week), or operative bladder atony requiring indwelling catheter beyond immediate postoperative period but for < 6 weeks	requiring frequent in/out catheterization (≥ 4 x per week) or urological intervention (e.g., TURP, suprapubic tube, urethrotomy)	bladder rupture
Urine color change (not related to other dietary or physiologic cause e.g., bilirubin, concentrated urine, hematuria)	normal	asymptomatic, change in urine color	-	-	-
Vaginal bleeding is graded in the HEMORRHAGE category.					
Vaginitis	none	mild, not requiring	moderate, relieved	severe, not relieved	ulceration

Toxicity	Grade 0	1	2	3	4
(not due to infection)		treatment	with treatment	with treatment, or ulceration not requiring surgery	requiring surgery
Renal/Genitourinary-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
SECONDARY MALIGNANCY					
Secondary Malignancy-Other (Specify type, _____) excludes metastastic tumors	none	-	-	-	present
SEXUAL/REPRODUCTIVE FUNCTION					
Dyspareunia is graded in the PAIN category.					
Dysmenorrhea is graded in the PAIN category.					
Erectile impotence	normal	mild (erections impaired but satisfactory)	moderate (erections impaired, unsatisfactory for intercourse)	no erections	-
Female sterility	normal	-	-	sterile	-
Femininization of male is graded in the ENDOCRINE category.					
Irregular menses (change from baseline)	normal	occasionally irregular or lengthened interval, but continuing menstrual cycles	very irregular, but continuing menstrual cycles	persistent amenorrhea	-
Libido	normal	decrease in interest	severe loss of interest	-	-
Male infertility	-	-	Oligospermia (low sperm count)	Azoospermia (no sperm)	-
Masculinization of female is graded in the ENDOCRINE category.					
Vaginal dryness	normal	mild	requiring treatment and/or interfering with sexual function, dyspareunia	-	-
Sexual/Reproductive Function-Other (Specify, _____)	none	mild	moderate	severe	disabling
SYNDROMES (not included in previous categories)					
Acute vascular leak syndrome is graded in the CARDIOVASCULAR (GENERAL) category.					
ARDS (Adult Respiratory Distress Syndrome) is graded in the PULMONARY category.					
Autoimmune reactions are graded in the ALLERGY/IMMUNOLOGY category.					
DIC (disseminated intravascular coagulation) is graded in the COAGULATION category.					
Fanconi's syndrome is graded as Urinary electrolyte wasting in the RENAL/GENITOURINARY category.					
Renal tubular acidosis is graded as Urinary electrolyte wasting in the RENAL/GENITOURINARY category.					
Stevens-Johnson syndrome (erythema multiforme) is graded in the DERMATOLOGY/SKIN category.					

Toxicity	Grade 0	1	2	3	4
SIADH (syndrome of inappropriate antidiuretic hormone) is graded in the ENDOCRINE category.					
Thrombotic microangiopathy (e.g., thromboitic thrombocytopenic purpura/TTP or hemolytic uremic syndrom/HUS) is graded in the COAGULATION category.					
Tumor flare Also consider Hypercalcemia. Note: Tumor flare is characterized by a constellation of symptoms and signs in direct relation to initiation of therapy (e.g., anti-estrogens/androgens or additional hormones). The symptoms/signs include tumor pain, inflammation of visible tumor, hypercalcemia, diffuse bone pain, and other electrolyte disturbances.	none	mild pain not interfering with function	moderate pain; pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain; pain or analgesics interfering with function and interfering with activities of daily living	Disabling
Tumor lysis syndrome Also consider Hyperkalemia, Creatinine.	absent	-	-	present	-
Urinary electrolyte wasting (e.g., Fanconi's syndrome, renal tubular acidosis) is graded under the RENAL/GENITOURINARY category.					
Syndromes-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling

Toxicity Module

To be implemented at the request of the study sponsor or principal investigator in the protocol or by protocol amendment when more detailed information is considered pertinent.

Toxicity:	Date of Treatment:		Course Number:
Date of onset:			Grade at onset:
Date of first change in grade:			Grade:
Date of next change in grade:			Grade:
Date of next change in grade:			Grade:
Date of next change in grade:			Grade:
Date of next change in grade:			Grade:
Date of next change in grade:			Grade:
Did toxicity resolve? If so, date of resolution of toxicity:	Yes_____	No_____	
Date of last observation (if prior to recovery):			
Reason(s) observations stopped (if prior to recovery):			
Was patient retreated?	Yes_____	No_____	
If yes, was treatment delayed for recovery? Date of next treatment?	Yes_____ No_____		
Dose reduced for next treatment?	Yes_____	No_____	

Additional Comments:

_____

_____

If module is being activated for new toxicity, not currently in CTC, please provide definitions for toxicity grading:

Grade 0 = _____

Grade 1 = _____

Grade 2 = _____

Grade 3 = _____

Grade 4 = _____

RTOG/EORTC Late Radiation Morbidity Scoring Scheme
Use for toxicities occuring greater than 90 days after radiation therapy.

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
Bladder- Late RT Morbidity Scoring	No change from baseline	Slight epithelial atrophy/minor telangiectasia (microscopic hematuria)	Moderate frequency/ generalized telangiectasia/ intermittent macroscopic hematuria	Severe frequency and dysuria/severe generalized telangiectasia (often with petechiae); frequent hematuria; reduction in bladder capacity (< 150 cc)	Necrosis/contracted bladder (capacity < 100 cc)/severe hemorrhagic cystitis
Bone- Late RT Morbidity Scoring	No change from baseline	Asymptomatic; no growth retardation; reduced bone density	Moderate pain or tenderness; growth retardation; irregular bone sclerosis	Severe pain or tenderness; complete arrest of bone growth; dense bone sclerosis	Necrosis/ spontaneous fracture
Brain- Late RT Morbidity Scoring	No change from baseline	Mild headache; slight lethargy	Moderate headache; great lethargy	Severe headaches; severe CNS dysfunction (partial loss of power or dyskinesia)	Seizures or paralysis; coma
Esophagus- Late RT Morbidity Scoring	No change from baseline	Mild fibrosis; slight difficulty in swallowing solids; no pain on swallowing	Unable to take solid food normally; swallowing semi-solid food; dilatation may be indicated	Severe fibrosis; able to swallow only liquids; may have pain on swallowing; dilation required	Necrosis/ perforation; fistula
Heart- Late RT Morbidity Scoring	No change from baseline	Asymptomatic or mild symptoms; transient T wave inversion and ST changes; sinus tachycardia > 110 (at rest)	Moderate angina on effort; mild pericarditis; normal heart size; persistent abnormal T wave and ST changes; low QRS	Severe angina; pericardial effusion; constrictive pericarditis; moderate heart failure; cardiac enlargement; EKG abnormalities	Tamponade/severe heart failure/severe constrictive pericarditis
Joint- Late RT Morbidity Scoring	No change from baseline	Mild joint stiffness; slight limitation of movement	Moderate stiffness; intermittent or moderate joint pain; moderate limitation of movement	Severe joint stiffness; pain with severe limitation of movement	Necrosis/complete fixation
Kidney- Late RT Morbidity Scoring	No change from baseline	Transient albuminuria; no hypertension; mild impairment of renal function; urea 25 - 35 mg%;	Persistent moderate albuminuria (2+); mild hypertension; no related anemia; moderate impairment of	Severe albuminuria; severe hypertension; persistent anemia (< 10 g%); severe	Malignant hypertension; uremic coma/urea > 100%

Toxicity	Grade 0	1	2	3	4
		creatinine 1.5 - 2.0 mg%; creatinine clearance > 75%	renal function; urea > 36 - 60 mg%; creatinine clearance > 50 - 74%	renal failure; urea > 60 mg%; creatinine > 4 mg%; creatinine clearance < 50%	
Larynx- Late RT Morbidity Scoring	No change from baseline	Hoarseness; slight arytenoid edema	Moderate arytenoid edema; chondritis	Severe edema; severe chondritis	Necrosis
Liver- Late RT Morbidity Scoring	No change from baseline	Mild lassitude; nausea; dyspepsia; slightly abnormal liver function	Moderate symptoms; some abnormal liver function tests; serum albumin normal	Disabling hepatic insufficiency; liver function tests grossly abnormal; low albumin; edema or ascites	Necrosis/hepatic coma or encephalopathy
Lung- Late RT Morbidity Scoring	No change from baseline	Asymptomatic or mild symptoms (dry cough); slight radiographic appearances	Moderate symptomatic fibrosis or pneumonitis (severe cough); low grade fever; patchy radiographic appearances	Severe symptomatic fibrosis or pneumonitis; dense radiographic changes	Severe respiratory insufficiency/ continuous O_2/assisted ventilation
Mucous membrane- Late RT Morbidity Scoring	No change from baseline	Slight atrophy and dryness	Moderate atrophy and telangiectasia; little mucus	Marked atrophy with complete dryness; severe telangiectasia	Ulceration
Salivary glands- Late RT Morbidity Scoring	No change from baseline	Slight dryness of mouth; good response on stimulation	Moderate dryness of mouth; poor response on stimulation	Complete dryness of mouth; no response on stimulation	Fibrosis
Skin- Late RT Morbidity Scoring	No change from baseline	Slight atrophy; pigmentation change; some hair loss	Patchy atrophy; moderate telangiectasia; total hair loss	Marked atrophy; gross telangiectasia	Ulceration
Small/Large intestine- Late RT Morbidity Scoring	No change from baseline	Mild diarrhea; mild cramping; bowel movement 5 x daily slight rectal discharge or bleeding	Moderate diarrhea and colic; bowel movement > 5 x daily; excessive rectal mucus or intermittent bleeding	Obstruction or bleeding, requiring surgery	Necrosis/ perforation fistula
Spinal cord- Late RT Morbidity Scoring	No change from baseline	Mild Lhermitte's syndrome	Severe Lhermitte's syndrome	Objective neurological findings at or below cord level treatment	Mono-, para-, quadriplegia
Subcutaneous tissue- Late RT Morbidity Scoring	No change from baseline	Slight induration (fibrosis) and loss of subcutaneous fat	Moderate fibrosis but asymptomatic; slight field contracture; < 10%	Severe induration and loss of subcutaneous tissue; field	Necrosis

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
			linear reduction	contracture > 10% linear measurement	
Eye- Late RT Morbidity Scoring	No change from baseline	Asymptomatic cataract; minor corneal ulceration or keratitis	Symptomatic cataract; moderate corneal ulceration; minor retinopathy or glaucoma	Severe keratitis; severe retinopathy or detachment; severe glaucoma	Panophthalmitis; blindness
Radiation-Other (Specify, _____)	None	Mild	Moderate	Severe	Life-threatening or disabling

Appendix D
Quality of Life Forms
Fact-G and Fact-H&N

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

PHYSICAL WELL-BEING

		not at all	a little bit	some-what	quite a bit	very much
1.	I have a lack of energy…….	0	1	2	3	4
2.	I have nausea……	0	1	2	3	4
3.	Because of my physical condition, I have trouble meeting the needs of my family……..	0	1	2	3	4
4.	I have pain……	0	1	2	3	4
5.	I am bothered by side effects of treatment……...	0	1	2	3	4
6.	I feel ill…….	0	1	2	3	4
7.	I am forced to spend time in bed……..	0	1	2	3	4

8. Looking at the above 7 questions, how much would you say your PHYSICAL WELL-BEING affects your quality of life? (circle one number)

0 1 2 3 4 5 6 7 8 9 10
Not at all Very much

SOCIAL/FAMILY WELL-BEING

		not at all	a little bit	some-what	quite a bit	very much
9.	I feel distant from my friends…….	0	1	2	3	4
10.	I get emotional support from my family…….	0	1	2	3	4
11.	I get support from my friends and neighbors……..	0	1	2	3	4
12.	My family has accepted my illness..……	0	1	2	3	4
13.	Family communication about my illness is poor..……...	0	1	2	3	4
14.	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
15.	Have you been sexually active during the past year? No___ Yes____ If yes, I am satisfied with my sex life..	0	1	2	3	4

16. Looking at the above 7 questions, how much would you say your SOCIAL/FAMILY WELL-BEING affects your quality of life? (circle one number)

0 1 2 3 4 5 6 7 8 9 10
Not at all Very much

RELATIONSHIP WITH DOCTOR

		not at all	a little bit	some-what	quite a bit	very much
17.	I have confidence in my doctor(s)..…….	0	1	2	3	4
18.	My doctor is available to answer my questions...……	0	1	2	3	4

19. Looking at the above 2 questions, how much would you say your RELATIONSHIP WITH THE DOCTOR affects your quality of life? (circle one number)

0 1 2 3 4 5 6 7 8 9 10
Not at all Very much

EMOTIONAL WELL-BEING

		not at all	a little bit	some-what	quite a bit	very much
20.	I FEEL SAD…….	0	1	2	3	4
21.	I am proud of how I'm coping with my illness..……..	0	1	2	3	4
22.	I am losing hope in the fight against my illness……...	0	1	2	3	4
23.	I feel nervous……	0	1	2	3	4
24.	I worry about dying……..……...	0	1	2	3	4
25.	I worry that my condition will get worse…….	0	1	2	3	4

26. Looking at the above 6 questions, how much would you say your EMOTIONAL WELL-BEING affects your quality of life? (circle one number)

0 1 2 3 4 5 6 7 8 9 10
Not at all Very much

FUNCTIONAL WELL-BEING

		not at all	a little bit	some-what	quite a bit	very much
27.	I am able to work (include work in home)…….	0	1	2	3	4
28.	My work (include work in home) is fulfilling……	0	1	2	3	4
29.	I am able to enjoy life……..	0	1	2	3	4
30.	I have accepted my illness……	0	1	2	3	4
31.	I am sleeping well…….……...	0	1	2	3	4
32.	I am enjoying the things I usually do for fun……...	0	1	2	3	4
33.	I am content with the quality of my life right now……..	0	1	2	3	4

34. Looking at the above 7 questions, how much would you say your FUNCTIONAL WELL-BEING affects your quality of life? (circle one number)

0 1 2 3 4 5 6 7 8 9 10
Not at all Very much

ADDITIONAL CONCERNS

		not at all	a little bit	some-what	quite a bit	very much
35.	I am able to eat the foods that I like…….	0	1	2	3	4
36.	My mouth is dry……	0	1	2	3	4
37.	I have trouble breathing……	0	1	2	3	4
38.	My voice has its usual quality and strength..……	0	1	2	3	4
39.	I am able to eat as much food as I want…..……...	0	1	2	3	4
40.	I am self-conscious about how my face and neck look….	0	1	2	3	4
41.	I can swallow naturally and easily...……..	0	1	2	3	4
42.	I smoke cigarettes or other tobacco products……	0	1	2	3	4
43.	I drink alcohol (e.g. beer, wine, etc.)…….	0	1	2	3	4
44.	I am able to communicate with others……..	0	1	2	3	4
45.	I can eat solid foods……..	0	1	2	3	4

46. Looking at the above 7 questions, how much would you say your PHYSICAL WELL-BEING affects your quality of life? (circle one number)

0 1 2 3 4 5 6 7 8 9 10

Not at all Very much

PACLITAXEL, CARBOPLATIN AND LOW DOSE RADIATION AS INDUCTION THERAPY IN LOCALLY ADVANCED HEAD AND NECK CANCER

02-H&N-15BMS (CRG-0043-02)
THE UNIVERSITY OF KENTUCKY

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1.0 ABSTRACT

Squamous cell cancers of the head and neck (SCCHN) comprise 5% of all cancers, with 40,000 new cases diagnosed annually. Surgery followed by irradiation or irradiation alone has been the standard of care for locally advanced Stage III and IV patients. With this approach, fewer than 30% of patients achieve long-term remission, and most recur locoregionally. Neoadjuvant chemotherapy has been administered prior to definitive therapy with response rates ranging from 60-90%, with pathologic CR rates documented in 30-70% of clinical responders. However, large randomized trials have shown no improvement in overall survival. Because induction chemotherapy alone does not appear to improve long-term disease free survival in advanced head and neck cancers, concomitant chemotherapy and radiation has been pursued in patients with locally advanced head and neck cancers. The concept of synergy between radiation and chemotherapy is well established in vitro. Various schedules of radiation and chemotherapy have been utilized including weekly chemotherapy during radiation, chemotherapy given every three weeks during radiation and alternating chemotherapy and radiation.

One novel approach to capitalizes on the synergy between radiation and chemotherapy is the use of low doses fractionated radiation (LDFRT) as a chemotherapy enhancer. In vitro data suggests that LDFRT enhances the response of both p53 wild type and p53 mutant cancer cell lines to chemotherapy. Not only was the cell death fraction increased, but there was no development of radioresistance in the cell lines studies when low doses of radiation were utilized. This strategy was translated into a clinical trial using four 80-cGy fractions of radiation with Carboplatin and Paclitaxel. Preliminary results have produced an impressive 85% response rate and this neoadjuvant regimen was safe and easy to deliver in patients with locally advanced SCCHN patients. In recently published work by Belani, a regimen using Carboplatin every four weeks combined with weekly Paclitaxel improved response rates in non-small cell lung cancer. The delivery of chemotherapy on a weekly schedule would be of particular benefit when adding LDFRT, because tumor cells could be exposed to LDFRT on multiple occasions per cycle of induction therapy, without the theoretic development of radioresistance. We propose to expand our understanding of LDFRT and chemotherapy by using two cycles of Paclitaxel and Carboplatin in a modification of the Belani regimen, plus LDFRT as induction therapy prior to definitive treatment (surgery or radiation). It is hoped that using LDFRT as a chemoenhancer will further increase the response rate seen with induction therapy in this population of patients.

2.0 OBJECTIVES

2.1 To assess the response rate of patients treated with Paclitaxel, Carboplatin and LDFRT in patients with bulky T2, Stage III and IV H&N cancer.

2.2 To assess the number of pathologic complete responses seen with this regimen.

2.2 To assess the toxicity of this chemoradiotherapy regimen for the treatment of H&N cancer.

2.3 To assess quality of life issues while undergoing this regimen.

2.4 To assess the overall survival of patients treated with this regimen.

3.0 BACKGROUND AND RATIONALE

3.1 Background

Squamous cell cancer of the head and neck (SCCHN) comprise 5% of all cancers, with 40,000 new cases diagnosed annually. Surgery followed by irradiation or irradiation alone has been the standard of care for locally advanced Stage III and IV patients. With this approach, fewer than 30% of patients achieve long-term remission, and most recur locoregionally (1). Neoadjuvant strategies using Cisplatin and infusional 5-Fluorouracil (5-FU) have been administered prior to definitive therapy with response rates ranging from 60-90%; however, large randomized trials have shown no improvement in overall survival (2,3).

While induction chemotherapy alone does not appear to improve long-term disease free survival in advanced SCCHN, concomitant chemotherapy and radiation has demonstrated an improved response rate both in the neoadjuvant (4,5) and adjuvant setting (6). The concept of synergy between radiation and chemotherapy is well established in vitro. Radiation recruits more cells into active cell cycle, which, in theory, allows a higher percentage of cells to be susceptible to chemotherapy agents (7). The addition of chemotherapy to radiation, in turn, is thought to alter the intrinsic radioresistance of tumor cells (8). By killing a percentage of cancer cells, chemotherapy also allows reoxygenation of previously hypoxic areas thus enhancing radiotherapy (9). Various schedules of radiation and chemotherapy have been utilized including weekly chemotherapy during radiation, chemotherapy given every three weeks during hyperfractionated radiation and alternating chemotherapy and radiation (4-6,10).

3.2 Preclinical Studies using LDFRT

Until recently, the initial slope of the radiation cell-survival curve (doses of 0-100 cGy) was presumed to be an ineffective dose range for human tumor therapy. However, as techniques to adequately study low dose radiation have improved, quite the opposite effect has been described. Joiner revolutionized thinking about low doses of radiation (<100 cGy) by demonstrating an initial phase of hypersensitivity to radiation using doses from 0 to 50 cGy (11,12). In work from the University of Kentucky, Ahmed and colleagues (13,14) have expanded our understanding of this synergy by combining LDFRT and various chemotherapeutic agents. Using very low doses of radiation in combination with chemotherapy, they have demonstrated enhanced cell death compared to chemotherapy or radiation alone. More importantly, in cell culture, pro-apoptotic pathways were enhanced without the induction of pro-survival pathways; both in p53 mutant and wild-type cell lines. Significantly, LDFRT avoids the development of one type of radiation resistance (the upregulation of pro-survival pathways) seen with higher dose radiation. This may provide one way to overcome radiation resistance, a major cause of treatment failure in SCCHN, while still enhancing cell death.

3.3 Clinical Studies using LDFRT

These pre-clinical studies suggest a unique synergistic effect between LDFRT and taxane-based chemotherapy. In novel work from the University of Kentucky, a protocol of Paclitaxel and Carboplatin coupled with low-dose radiation (4 doses of 80 cGy given as a chemotherapy potentiator) has been evaluated in advanced head and neck cancer as an induction prior to surgery. The published results of this trial indicate no increased toxicity, and a response rate of 85% (15 complete responses (CR) with 9 pathologic CR's, 18 partial responses (PR), 4 stable disease (SD) in the first 39 patients studied (15) (clinical protocol completed, manuscript in preparation). Following this protocol, the majority of patients received hyperfractionated radiation although five underwent surgery. No patients had side effects that limited the delivery of standard therapy (radiation or surgical resection). There have been no adverse long-term effects in those patients greater than 1 year of follow-up (n=15), although this study has a short median follow-up and conclusions regarding late toxicities is premature. Because of the excellent clinical response seen with this regimen in SCCHN, we felt that further study of this novel strategy was warranted. Specifically, this protocol examines whether the number of pathologic CR's can be increased by maximizing the amount of chemotherapy and enhancing radiation given.

3.4 Rationale for Paclitaxel and Carboplatin

Paclitaxel, an inhibitor of microtubule function derived from the Pacific yew, *Taxus brevofolia*, has been shown to radiosensitize cancer cell lines in vitro (16, 17). Newer regimens have sought to take advantage of this fact, by utilizing Paclitaxel along with Carboplatin in tandem or concurrently with radiation in hopes of improving response rates (15,18-20). Investigations into the optimal schedule for delivery of Paclitaxel in combination with radiotherapy have yielded several important tenets:

1. Paclitaxel induces mitotic arrest within two hours after administration and this effect peaks between 8 and 12 hours, while apoptosis peaks between 12 and 24 hours remaining elevated for at least two days (21).
2. Paclitaxel invokes G2/M arrest through its inhibition of microtubule function and G2/M is the most radiosensitive phases of cell cycle (21,22).
3. Multiple in-vitro studies in head and neck cancer cell lines show supra-additive effect of Paclitaxel and radiation when cells were exposed to Paclitaxel prior to irradiation (16). There appears to be a subadditive effect on cell death when cells were incubated with Paclitaxel after irradiation (17).

One of the most well described molecular determinants of response to ionizing radiation is the status of the tumor suppressor gene p53 within the cancer cell. Wild-type p53 protein expression confers radiation responsiveness, while p53 mutations result in decreased protein expression and radioresistance (23). In recent work by Chendil, et al, both p53 wild type and mutant colon cancer (13) and SCCHN (14) cell lines were studied to determine the effect of Paclitaxel with radiation. Several novel irradiation schemes were studied to maximize the radiosensitization of Taxanes. A benefit was seen when four small fractions of 50 cGy were given every 8 hours beginning immediately after Paclitaxel exposure, when compared to the effect of a single fraction of 200 cGy. The cells which appeared to benefit most from this schedule were those with p53 mutations (i.e. those cells that were most likely to be radioresistant to radiotherapy alone) (13,14).

In vitro data with Carboplatin also indicates an additive effect when given prior to irradiation using various cell lines (24, 25). As well, the pharmacokinetics of carboplatin are not altered by pretreatment with Paclitaxel at a standard dose, and this has been confirmed clinically in a multitude of studies in different tumor types (26). We propose to expand our understanding of LDFRT and chemotherapy by using two cycles of Paclitaxel and Carboplatin with LDFRT as induction therapy in patients with bulky Stage II, Stage III and IV H&N cancer.

3.5 Rationale for LDFRT Dosing and Schedule

In recently published work by Belani et al (27), a regimen using Carboplatin every four weeks combined with weekly Paclitaxel (three out of four weeks) improved response rates in non-small cell lung cancer. This approach maximized the dose intensity of chemotherapy without increasing toxicity to any measurable extent. The delivery of chemotherapy on a weekly schedule would be of particular benefit when adding LDFRT, because tumor cells could be exposed to LDFRT on multiple occasions per cycle of induction therapy, without the theoretic development of radioresistance.

In designing this second protocol, LDFRT fractions were lowered from 80cGy to 50 cGy for several reasons. As Paclitaxel is delivered weekly, the dose was decreased to allow multiple LDFRT fractions to be delivered without compromising the total dose of radiation given to the head and neck. The total dose of LDFRT given in the initial study by Arnold, et al, (15) was 640 cGy. Any further radiation given to patient (i.e. definitive radiation) took into account this 640 cGy, in calculating total standard doses of radiation to the tumor. The authors felt that doses over 800 cGy given in a neoadjuvant fashion would compromise the dose of definitive radiation given to patients following our neoadjuvant strategy. Therefore, dose de-escalation allows maximum exposure to LDFRT during chemotherapy without attenuating the delivery of definitive radiation. In addition, initial data by Joiner indicates the effective range of LDFRT may be less than 50 cGy (and is less likely to induce radiation resistance), while our preclinical studies indicated efficacy from 50 to 80 cGy.

3.6 Future Plans for Biologic Correlative Studies

Tissues will be collected pre-therapy and immediately after the first dose of chemotherapy and LDFRT, as listed in section 5.6. Planned investigation (not included in the funding of this clinical protocol) will include (but is not limited to) the analysis of protein expression of cell death genes: p53, p21 $^{waf1/cip1}$, TGF-β receptors, bcl-x_L, bcl-2 and bax in pre- and post-treated tumor biopsy specimens. These genes are representative of different pathways affecting growth inhibition and apoptosis in SCCHN. Based on preliminary findings (13, 14), we theorize that the dysregulation of these pathways (p53, TGF-β or cross-point regulators of apoptosis) will cause an impact on treatment response. However, it is unknown which pathways are affected by LDFRT and therefore, this biologic correlate will be undertaken to further define the molecular mechanism of LDFRT's effect on tumor cells.

4.0 ELIGIBILITY CRITERIA

4.1 Inclusion criteria

4.10 Adult patients greater than 18 years of age.

4.11 ECOG performance status of 0, 1 or 2.

4.12 Patients with pathologically documented bulky T2, III and IV SCCHN (excluding M1 disease), within 2 months of diagnosis. Bulky T2 tumors are defined as those that have a volume of disease greater than 35 cm^3 as measured by CT or MRI scan (28).

4.13 Patients will be medically fit for undergoing chemotherapy. Specifically:

a) no evidence of active angina pectoris or ventricular arrhythmia's; no myocardial infarction within the last six months. (Patients with medically controlled hypertension or congestive heart failure are eligible.)

b) an absolute neutrophil count of > 1000/uL and platelet count > 100,000/uL

c) serum total bilirubin < 1.5 mg/dL

d) Creatinine Clearance greater than 60 ml/min
Using an actual or calculated creatinine clearance using the formula:
$\frac{(140 - \text{age}) \times (\text{wgt in kg})}{(\text{serum creatinine}) \times (72)}$ *
* multiply by 0.85 for females

e) if a pre-existing grade I neuropathy exists, patients must be willing to risk worsening neuropathy secondary to Paclitaxel. Patients with grade II or greater neuropathy will be excluded from study.

f) ability to give written, informed consent to participate in the trial.

4.14 Patients will have measurable disease as determined by MRI or CT scan or evaluable disease determined by panendoscopy to be eligible for enrollment on this study.

4.2 Exclusion criteria

4.21 Pregnant females. Males and women of childbearing potential must use effective contraception in order to prevent pregnancy during therapy.

4.22 Patients with a history of previous or current malignancy at other sites diagnosed within the last 5 years, with the exception of adequately treated carcinoma in-situ of the cervix or basal or squamous cell carcinoma of the skin. Patients with a history of other malignancies, who remain free of recurrence or metastases for greater than five years are eligible.

4.23 Patients with active infection will not be eligible for this protocol until the infection is treated and the symptoms have clinically resolved.

4.24 Patients with a history of allergy to drugs utilizing Cremophor in the formulation.

4.25 Prior chemotherapy, prior irradiation or surgery for SCCHN will not be allowed.

4.26 Patients with metastatic disease will not be eligible for this study.

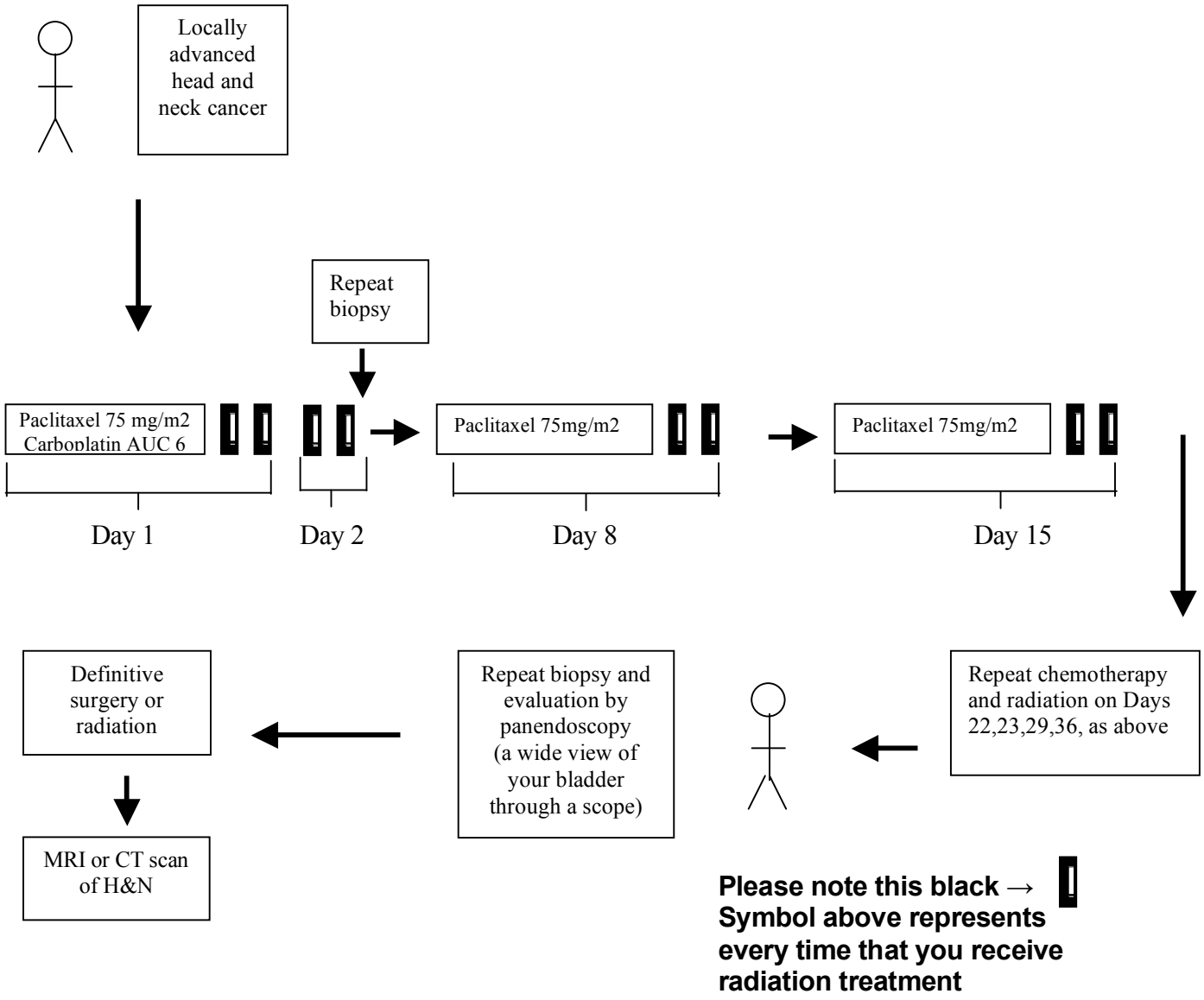
4.27 Patients with grade II or greater peripheral neuropathy will be excluded from study.

5.0 TREATMENT PLAN

5.1 Pre-treatment Studies

Prior to enrollment, all patients will undergo a history and physical exam, ECOG performance status evaluation, direct laryngoscopy, a CT or MRI scan of the involved area of the head and neck and a chest X-ray within 1 month of beginning chemoradiotherapy. A complete blood count with differential and platelets, and serum chemistries (including sodium, potassium, chloride, bicarbonate, calcium, total protein, albumin, BUN, creatinine, AST, alkaline phosphatase and total bilirubin) within 2 weeks of beginning chemoradiotherapy will also be required.

5.2 Schema: Revised 1-07-03 Amendment #1



Radiation will be given on Days 1, 2, 8, 15, 22, 23, 29 & 36 of chemotherapy. The first fraction will be given within 1 hours after completion of chemotherapy while the remaining fractions of each cycle will have at least a 4 to 6 hr interfraction interval.

5.32 Dosage and fields:

Doses of 50 cGy will be administered with each fraction (to a total of 800 cGy for the entire induction scheme). The patient will be treated with shaped fields encompassing gross disease only (including the primary and gross nodal disease) with a maximum 2cm margin. The spinal cord will be excluded from the radiation field and CT based treatment planning will be used as needed and as appropriate. The accepted standard total dose of radiation used for definitive therapy ranges from

66-72Gy when once-daily RT is used at 1.8-2.0Gy/fraction and from 74.4-81.6Gy when twice-daily RT is used at 1.2Gy/fraction. In calculating the planned total dose of radiation to be used for subsequent, definitive therapy the radiation oncologist will incorporate the induction dose used into the final calculation for a maximum total dose of approximately 74Gy if once-daily fractionation is used or approximately 82.4Gy if twice-daily fractionation is used. Since the 800 cGy used in the induction regimen is delivered at a very low dose/fraction (ie 50cGy), it is expected that the incorporation of this dose into the calculated total doses should not be associated with any significant increase in late radiation damage/effect.

5.4 Neoadjuvant chemotherapy.

5.41 Chemotherapy Formulation, Availability and Preparation:

Paclitaxel is commercially available and commercial supplies will be used for this study. Paclitaxel is supplied as a sterile concentrated solution, 6mg/ml, and is available in 5ml, 16.7 ml and 50 ml multidose vials. Each milliliter contains 6mg paclitaxel 527mg of polyoxyethylated caster oil and 49.75% dehydrated alcohol, USP, sodium metabisulfite and sterile water for injection, USP. The contents of the vial must be diluted just prior to clinical use. Paclitaxel at the appropriate dose will be diluted in 5% dextrose injection or 0.9% sodium chloride injection to a final concentration of 0.3 to 1.2mg/ml. Infusions should be mixed as closely as possible to the start of each infusion since paclitaxel stability after 27 hours at room temperature in solution is unknown. Paclitaxel must be prepared in glass, polypropylene or polyolefin containers due to leaching of diethylhexylphthalate (DEHP) plasticizer from polyvinyl chloride (PVC) bags. Paclitaxel will be administered using non-PVC tubing and connectors which are polyethylene lined. In-line filtration should be accomplished by incorporating a hydrophilic, microporous filter of pore size not greater than 0.22 microns. Nothing else should be infused through the lines where paclitaxel is being administered. Solutions exhibiting excessive particulate formation should be discarded.

The Chemo Dispensing Pin^{TM} device or similar devices with spikes should not be used with vials of Paclitaxel since they can cause the stopper to collapse resulting in the loss of sterile integrity of the Paclitaxel solution. Intact vials of Paclitaxel should be stored at room temperature between 20-25^{0}C (68-77^{0}F). Shelf life of the vials stored under appropriate conditions corresponds to the manufacturer's expiration date on each vial. All solutions of Paclitaxel exhibit slight haziness directly proportional to the concentration of drug and time elapsed since preparation. When prepared as above, solutions of Paclitaxel (0.3 – 1.2 mg/ml) are stable for 27 hours.

Carboplatin is commercially available as a sterile lyophilized powder available in single dose vials containing 50 mg, 150 mg, or 450 mg of carboplatin. Each vial contains equal parts by weight of carboplatin and mannitol. Immediately before use the content of each vial must be reconstituted with either sterile water for injection, USP, 5% dextrose in water or 0.9% sodium chloride injection, USP, according to the following schedule:

Vial Strength	Diluent Volume
50 mg	5 ml
150 mg	15 ml
450 mg	45 ml

These dilutions all produce a carboplatin concentration of 10 mg/ml. When prepared as directed, carboplatin solutions are stable for eight hours at room temperature. Since no antibacterial preservative is contained in the formulation, it is recommended that carboplatin solutions be discarded eight hours after dilution. NOTE: Aluminum reacts with carboplatin causing precipitate formation and loss of potency; therefore, needles or intravenous sets containing aluminum parts that may come in contact with the drug must not be used for the preparation or administration of carboplatin.

Unopened vials of carboplatin are stable for the life indicated on the package when stored at controlled room temperature (59-86^{0}F) and protected from light. When prepared, carboplatin solutions are stable for 8 hours at room temperature.

5.42 Chemotherapy Premedication and Dosing:

All chemotherapy will use actual body weight (to a maximum of 2.2 m^2) and will be administered as an i.v. infusion. Paclitaxel will be given at a dose of 75 mg/m2 intravenously over one hour on Days 1, 8, 15, 22, 29 and 36. Paclitaxel will be dosed to the nearest 5mg using a standard body surface area chart. Carboplatin will be dosed using the Calvert formula for calculating the area under the curve (AUC) on Days 1 & 22:

$$\text{AUC } 6=(\text{GFR} + 25) \times 6$$

The Glomerular filtration rate (GFR) will be calculated as follows using the Cockcroft-Gault equation on Days 1 & 22:

$$\frac{(140\text{-age}) \times (\text{wt in kg}) \times 0.85^*}{72 \times \text{serum creatinine}} \qquad *\text{for women}$$

Following Paclitaxel infusion on Days 1 & 22, Carboplatin at an AUC of 6 will be given intravenously over 30 minutes on Days 1 & 22.

To avoid allergic reactions associated with Paclitaxel, the following premedications will be given 30 minutes prior to each dose of Paclitaxel:

- Dexamethasone 20 mg IV
- Cimetidine 300mg IV or Ranitidine 50 mg IV
- Diphenhydramine 25 mg IV

Other premedications including anti-emetics will be at the discretion of the treating physician.

5.5 Dose Modifications:

Assessment for dose modification will be conducted prior to each dose. Dose escalation will not be allowed during this study. Chemotherapy dose s may be reduced for hematological and non-hematological effects. Treatment may be delayed nor more than two weeks to allow recovery from

toxicity. A patient will be allowed a maximum of two dose reductions. Dose adjustments will be made according to the following guidelines:

Dose Modification Table		
Modification Episode	Carboplatin (AUC)	Paclitaxel (mg/m2)
0	6	75
-1	5	65
-2	4	55

Hematologic Toxicity

Hematologic toxicity is based on interval laboratory results offuring within one day of treatment or on the day of treatment.

ANC		Platelet Count	Dose Modification
>800/uL	And/or	>50,000/uL	No change, give previous dose
≤ 800/uL	And/or	≤ 50,000/uL	Decrease 1 level

If ANC ≤ 800/uL or ≤ 50,000/uL at the start of the second cycle of chemotherapy (Day 22), hold chemotherapy and radiation for 1 week and resume at prior dose level (no dose re-escalation will be allowed). IF ANC ≤ 800 is accompanied by a temperature > 100.5 ^{0}F, therapy will be held until ANC > 800/uL and patient is afebrile.

Non-hematologic Toxicity

Modifications or withholding of chemotherapy and radiation will occur if the toxicity is considered to be related to study drug. Non-hematologic toxicities will be based on any interval observations between treatments or at the time of each dose.

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Mucositis	No change	No change	No change	Hold until ≤ grade 2, then reduce 1 dose level
Motor and Sensory Neuropathy	No change	No change	Hold until≤ grade 2, then reduce 1 dose level	Off study
Arthralgias Myalgias Fatigue	No Change	No Change	Hold until≤ grade 2, then reduce Paclitaxel by 1 dose level	Off study
Hepatic Dysfucntion	No Change	Decrease Paclitaxel by 1 dose level	Hold until≤ grade 2, then reduce Paclitaxel by 1 dose level	Off study

For any grade 3 or 4 toxicity not mentioned above (excluding alopecia), treatment should be withheld until resolution to grade ≤ 2. Treatment should resume at a one dose level reduction. For grade 1 or 2 toxicities, no dose reductions will occur. Chemotherapy will be discontinued if irreversible, symptomatic cardiac arrhythmia/dysfunction occurs.

Radiotherapy will be held if chemotherapy is held and will restart on the same day as chemotherapy based on the parameters for alteration of schedule listed above.

5.6 Post-Treatment Biopsies and Definitive Therapy

No earlier than four hours after completion of the fourth fraction of radiation (Day 2), and no later than 24 hours after (Day 3), patients will undergo repeat biopsy of their primary tumors (or nodal disease). This biopsy is optional and is for research purposes only, and will be strictly outlined as such in the consent form.

Within one to two weeks of completion of the second cycle of chemotherapy and radiation (Day 36), a panendoscopy will be performed. At that time, the initial site will be evaluated and biopsied, and an assessment of tumor response will be made by the otolaryngologist performing the procedure. Even in cases of apparent complete response, biopsies of the primary tumor area will be taken for pathologic response assessment. This is considered part of routine care of patients undergoing neoadjuvant therapy.

Definitive surgery will be based on the initial extent of disease and stage of the cancer. Definitive radiation will incorporate the induction dose used into the final dose calculation, at the discretion of the treating radiation oncologist.

5.7 Potential Toxicities

Paclitaxel is a microtubule inhibitor derived from the Pacific yew, *Taxus brevifolia.* Its side effects include allergic reactions, arrhythmia's, hypotension and heart block. These side effects are reversible with cessation of drug delivery. As well, premedication with steroid, H1 and H2-blockers helps to prevent allergic reactions. Other toxicities include nausea, vomiting, mucositis, diarrhea, seizures, malaise, alopecia, elevated alkaline phosphatase, SGOT and bilirubin, arthralgias, myalgias, peripheral neurotoxicity, myocardial infarction and myelosuppression. Given the risk of anaphylaxis with Paclitaxel, patients will be carefully observed for possible reactions, and supportive equipment and medications to treat these reactions will be immediately available to treat such complications. Cardiac toxicities are rare and continuous cardiac monitoring is not required except for patients with serious conduction abnormalities or other underlying, serious cardiac risk factors.

Paraplatin is a heavy metal that directly binds to DNA, thus altering the DNA template via the formation of intrastrand cross-links. Major toxicities include: 1) Myelosuppression (with thrombocytopenia, neutropenia, leukopenia, or anemia), that typically resolves by Day 28 when Paraplatin is given as a single agent; 2) Allergic reactions (including rash, urticaria, erythema, pruritus, and rarely bronchospasm and hypotension) that can be successfully managed with standard epinephrine, corticosteroid, and antihistamine therapy; 3) Neurologic symptoms including

peripheral neuropathies and mild paresthesias; 4) Gastrointestinal symptoms including nausea and vomiting, diarrhea, weight loss, constipation, and gastrointestinal pain; 5) Hepatic toxicity including elevation of the alkaline phosphatase, total bilirubin, and SGOT; 6) Pain, asthenia and alopecia. The majority of these toxicities are reversible upon discontinuation or completion of the drug. Incidence rates of adverse events associated with Paraplatin are provided in the product package insert.

Reversible skin changes and mucositis are expected side effects of radiotherapy. Combined modality therapy increases the risk for acute toxicities, but with low doses of radiation (640 cGy total) minimal toxicity is expected. The total dose of radiation given as definitive therapy after completion of induction will take into account this initial dose of radiation, and will be at the discretion of the attending radiation oncologist.

There is estimated to be a 1% risk per year of second primary cancers in this population of patients, which is unrelated to treatment.

Performance status will be evaluated based on the ECOG Performance Status Criteria (Appendix B). Toxicities will be graded using the National Cancer Institute (NCI) scale for acute and subacute toxicity: http://ctep.cancer.gov/reporting/ctc.html. As well, the Radiation Therapy Oncology Group's late toxicity scale will be used http://www.rtog.org/members/toxicity/late.html.

5.8 Removal of patients from protocol

Protocol therapy will be discontinued at any time if any of the following situations occur:

- Disease progression at any time during therapy or follow-up period
- Unacceptable toxicity
- Patient request to withdraw from study
- Development of intercurrent, non-cancer related illness that prevents continuation of therapy
- Investigator discretion

All patients will be followed regardless of treatment variations until the patient's death or loss to follow-up.

6.0 ANCILLARY MEASURES

6.1 All patients will have electrolytes and complete blood counts monitored prior to each dose of chemotherapy.

6.2 All patients will complete a pre-treatment Head and Neck Quality of Life form (see Appendix C) as well as a follow-up form at the completion of this study.

6.3 No prophylactic G-CSF may be given after the first cycle. G-CSF at a dose of 5mcg / kg / day (subcutaneously) may be used for prolonged neutropenia (an ANC < 500/ul for more than 5 days), serious neutropenic fever or prophylaxis of neutropenia after severe neutropenic fever during the second induction cycle, as per published ASCO guidelines: http://www.jco.org/cgi/content/abstract/17/11/3676.

6.4 Symptomatic treatment of esophagitis or mucositis using magic mouthwash, Lanny's mouthwash or narcotics will be allowed at any time.

7.0 STUDY CALENDAR

Evaluation	Pre-Study	Day 1	Day 2	Day 8	Day 15	Day 22	Day 23	Day 29	Day 36	Day 42-56	STUDY COMPLETED DAY 56	Q 3 months
H&P PS assessment	X					X				X		X
CBC	X			X	X	X		X	X	X		X*
Electrolytes	X					X				X		X*
Chest X-ray	X											X**
MRI or CT scan of H&N	X**									X		X**
Panendoscopy	X									X		
Repeat biopsy			X^									
Creatinine Clearance	X					X						
QOL form	X									X		
Chemotherapy		X		X	X	X		X	X			
50 cGy RT		X X	X X	X X	X X	X X	X X	X X	X X			
Surgery or definitive RT										X		

*until toxicities resolve
**repeated q6 months until disease progression
^between 4 and 24 hours after the last dose of radiation (Cycle 1 only)

BID = twice a day
QOL = quality of life form
RT = radiotherapy

8.0 EVALUATION CRITERIA

8.1 Assessment of tumor response

Both pathologic and radiographic response to therapy will be assessed where possible. Primary tumors will be assessed by the attending otolaryngologist by panendoscopy, with biopsies taken in the case of a question of response. Nodal disease response will be assessed by radiographic means. At least one measurable lesion is required for enrollment on this study. CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. All patients will be assessed for response at the end of LDFRT and chemotherapy. Evaluation will follow the RECIST criteria (29), as outlined below.

Response Criteria	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 dimension (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

Response	Evaluation of non-target lesions
Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level
Incomplete Response/ Stable Disease (SD):	Persistence of one or more non-target lesion(s) or/and 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 (1)

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

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 PD the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria

Target lesions	Non-Target lesions	Evaluation of non-target lesions	Overall response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic

deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment. In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

8.2 Protocol endpoints

The primary endpoint of this study is pathologic CR rate to induction chemotherapy, prior to definitive therapy (surgery or irradiation). Secondary endpoints of severe (≥ Grade 3) toxicities will be examined, overall survival, response rate and quality of life will be followed.

8.3 Toxicities

Toxicities will be graded using the National Cancer Institute's (NCI) Common Toxicity Scale (CTC) for acute and subacute toxicity: http://ctep.cancer.gov/reporting/ctc.html. As well, the Radiation Therapy Oncology Group's late toxicity scale will be used http://www.rtog.org/members/toxicity/late.html.

8.4 Adverse Event Reporting

8.4.1 Definitions of adverse events

Adverse event (AE)

Any untoward medical occurrence in a clinical investigation patient administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An adverse event (AE) can, therefore, be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product.

Serious adverse event (SAE)

A serious adverse event is any untoward medical occurrence that at any dose:

- Results in death;
- Is life-threatening (defined as an event in which the patient or subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity;
- Is a congenital anomaly or birth defect;
- Results in the development of drug dependency or drug abuse;
- Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgement, may jeopardize the patient/subject or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency

room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.

For reporting purposes, BMS also considers the occurrences of pregnancy, cancer, or overdose (regardless of adverse outcome) as events that must be reported as important medical events.

In addition to the above requirements, death, regardless of cause, that occurs within 30 days of the last dose of study drug (industry standard) or that occurs after 30 days and is a result of delayed toxicity due to administration of the study drug, should be reported as a serious adverse event.

Unexpected adverse event
An adverse event that is not mentioned in the Investigator's Brochure or package insert or the specificity or severity of which is not consistent with the Investigator's brochure or package insert.

8.4.2 Reporting adverse events

Adverse events
Adverse events will be recorded for the duration of a patient's participation in the trial. All adverse events (except grade 1 and 2 laboratory abnormalities unless a dose treatment modification, delay or therapeutic intervention is required), regardless of causal relationship, are to be recorded in the source documentation. Pre-existing conditions at baseline will be recorded. If a pre-existing condition does not change, it does not have to be reported on subsequent cycles.

The investigator must determine the toxicity of adverse events according to the CTC version 2.0 and their causal relationship.

Serious adverse events
Adverse events classified as serious require expeditious handling and reporting to comply with regulatory requirements.

All serious adverse events, whether considered to be drug-related or not, require that a Serious Adverse Event Report Form be completed within 24 hours of the investigator becoming aware of the event. The investigator must immediately report all unexpected serious adverse events to the Institutional Review Board in writing.

Serious adverse events will be reported to:

Susanne M. Arnold, MD Markey Cancer Center, cc445 800 Rose Street Lexington, KY 40536
Phone number: (859)323-8043 (8-5) and (859)323-5234 (after hours) Fax number: (859)257-7715

For studies conducted under an Investigator IND, any event that is both serious and unexpected must be reported to the FDA as soon as possible and, in no event, later than 7 days (death or life-threatening event) or 15 days (all other SAEs) after the investigator's or institution's initial receipt of the information. Bristol-Myers Squibb will be provided with a simultaneous copy via facsimile of all adverse events filed with the FDA. SAEs should be reported on the MedWatch Form 3500 which can be accessed at:

https://www.accessdata.fda.gov/scripts/MedWatch.

MedWatch forms should be sent to the FDA online at the above internet address or at:

MEDWATCH
5600 Fishers Lane
Rockville, MD 20852-9787
Fax: 1-800-FDA-0178 (1-800-332-0178)

All SAEs should simultaneously be faxed to Bristol-Myers Squibb at:

Ken Kassler-Taub, M.D.
Drug Safety & Pharmacovigilance
Bristol-Myers Squibb Company
P.O. Box 5400
Mail Stop HW19-1.01
Princeton, NJ 08543-5400
Phone Number: 609-818-3737
Fax Number: 609-818-3804

All adverse events regardless of causal relationship will be recorded in the case report forms and source documentation. The PI will determine the intensity of any adverse events according to the CTC and RTOG criteria and their causal relationship. Serious adverse events will be reported to FDA according to the rule of the FDA and IRB.

9.0 STATISTICAL CONSIDERATIONS

9.1 Experimental Design:

This is a Phase II study designed to evaluate the antitumor response and toxicity of the combination of Carboplatin, Paclitaxel and chemosensitizing radiation in locally advanced H&N cancers.

9.2 Accrual and Power Considerations

The primary endpoint for this study is pathologic complete response rate, with secondary endpoints of overall response rate, toxicity and quality of life. For statistical purposes, the response rate (CR +PR) to induction therapy for stage II (bulky), III and IV H&N patients will be considered 85%

with a pathologic complete response rate of 24% as documented in our recently reported study (15). It is assumed that the pathologic complete response rate for the proposed therapy is at least 50%. A Phase II trial design is planned, therefore 24 patients will be enrolled in the study. With an alpha level of 0.05 and a beta level of 0.20, this study will have at least 80% power to detect a significant difference between the complete pathologic response rate for the proposed regimen and that of the prior reference regimen (15).

10.0 REPORTING PROCEDURES

All eligible patients will be reported to the clinical research office for registration at (606) 257-3379, or Dr. Susanne Arnold at (606) 323-8043.

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APPENDIX A
Staging for Head and Neck Cancer

TNM CATEGORIES

Primary Tumor (T)

All Sites

TX Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy.

T0 No evidence of primary tumor.

Oral Cavity and Oropharynx

Tis Carcinoma *in situ.*

T1 Tumor 2 cm or less

T2 Tumor between 2 and 4 cm in diameter

T3 Tumor greater than 4 cm in greatest diameter

T4 Tumor invades adjacent structures (eg, bone, deep muscle of tongue, skin)

Maxillary Sinus

Tis Carcinoma *in situ.*

T1 Tumor limited to antral mucosa with no erosion or destruction of bone

T2 Tumor with erosion of the infrastructure including the hard palate and/or middle nasal meatus

T3 Tumor invades any of the following: skin of cheek, posterior wall of maxillary sinus, floor or medial wall of orbit, anterior ethmoid sinus

T4 Tumor invades orbital contents and/or any of the following: cribiform plate, posterior ethmoid or sphenoid sinuses, nasopharynx, soft palate, pterygomaxillary or temporal fossae, or base of skull

Nasopharynx

Tis Carcinoma *in situ.*

T1 Tumor limited to one subsite of the nasopharynx

T2 Tumor invades more than one subsite of the nasopharynx

T3 Tumor invades nasal cavity, or oropharynx, or both

T4 Tumor invades skull, or cranial nerves, or both

Larynx

Supraglottis

Tis Carcinoma *in situ.*

T1 Tumor confined to site of origin with normal mobility

T2 Tumor involves adjacent supraglottic site(s) or glottis without fixation

T3 Tumor limited to larynx with fixation or extension to involve postcricoid area, medial wall of pyriform sinus, or preepiglottic space

T4 Massive tumor extending beyond larynx to involve oropharynx, soft tissue of neck, or destruction of thyroid cartilage

Glottis

Tis Carcinoma *in situ.*

T1 Tumor confined to vocal cord(s) with normal mobility
T2 Supraglottic or subglottis extension of tumor with normal or impaired cord mobility
T3 Tumor confirmed to the larynx with cord fixation
T4 Massive tumor with thyroid cartilage destruction or extension beyond the confines of the larynx

Subglottis
Tis Carcinoma *in situ.*
T1 Tumor confined to the subglottic region
T2 Tumor extension to vocal cord with normal or impaired cord mobility
T3 Tumor confirmed to the larynx with cord fixation
T4 Massive tumor with cartilage destruction or extension beyond the confines of the larynx, or both

Regional Lymph Nodes (N)
NX Regional lymph nodes cannot be assessed.
N0 No regional lymph node metastasis.
N1 single ipsilateral node, 3 cm or less
N2a single ipsilateral node 3-6 cm
N2b multiple ipsilateral nodes, none > 6cm
N2c bilateral or contralateral nodes, none > 6cm
N3 metastasis in a node > 6cm

Distant Metastasis (M)
MX Distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis present

Stage Grouping Based on AJCC Criteria

	Classification		
Stage	T	N	M
0	Tis	N0	M0
I	T1	N0	M0
II	T2	N0	M0
III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N0	M0
IV	T4	N0	M0
	Tx	N2, N3	M0
	Tx	Nx	M1

Appendix B

Performance Status Scales/Scores

ECOG or Zubrod scale

0	Asymptomatic and fully active
1	Symptomatic; fully ambulatory; restricted in physically strenuous activity
2	Symptomatic; ambulatory; capable of self-care; more than 50% of waking hours are spent out of bed
3	Symptomatic; limited self-care; spends more than 50% of time in bed, but not bedridden
4	Completely disabled; no self-care; bedridden

Appendix C
Quality of Life Forms
Fact-G and Fact-H&N

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

PHYSICAL WELL-BEING

		not at all	a little bit	some-what	quite a bit	very much
1.	I have a lack of energy…….	0	1	2	3	4
2.	I have nausea……	0	1	2	3	4
3.	Because of my physical condition, I have trouble meeting the needs of my family……..	0	1	2	3	4
4.	I have pain……	0	1	2	3	4
5.	I am bothered by side effects of treatment……...	0	1	2	3	4
6.	I feel ill…….	0	1	2	3	4
7.	I am forced to spend time in bed……..	0	1	2	3	4

8. Looking at the above 7 questions, how much would you say your PHYSICAL WELL-BEING affects your quality of life? (circle one number)

0 1 2 3 4 5 6 7 8 9 10
Not at all Very much

SOCIAL/FAMILY WELL-BEING

		not at all	a little bit	some-what	quite a bit	very much
9.	I feel distant from my friends…….	0	1	2	3	4
10.	I get emotional support from my family…….	0	1	2	3	4
11.	I get support from my friends and neighbors……..	0	1	2	3	4
12.	My family has accepted my illness..……	0	1	2	3	4
13.	Family communication about my illness is poor..……...	0	1	2	3	4
14.	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
15.	Have you been sexually active during the past year? No___ Yes____ If yes, I am satisfied with my sex life..	0	1	2	3	4

16. Looking at the above 7 questions, how much would you say your SOCIAL/FAMILY WELL-BEING affects your quality of life? (circle one number)

0 1 2 3 4 5 6 7 8 9 10
Not at all Very much

RELATIONSHIP WITH DOCTOR

		not at all	a little bit	some-what	quite a bit	very much
17.	I have confidence in my doctor(s)..…….	0	1	2	3	4
18.	My doctor is available to answer my questions...……	0	1	2	3	4

19. Looking at the above 2 questions, how much would you say your RELATIONSHIP WITH THE DOCTOR affects your quality of life? (circle one number)

0 1 2 3 4 5 6 7 8 9 10
Not at all Very much

EMOTIONAL WELL-BEING

		not at all	a little bit	some-what	quite a bit	very much
20.	I FEEL SAD…….	0	1	2	3	4
21.	I am proud of how I'm coping with my illness..……..	0	1	2	3	4
22.	I am losing hope in the fight against my illness……...	0	1	2	3	4
23.	I feel nervous……	0	1	2	3	4
24.	I worry about dying……..……...	0	1	2	3	4
25.	I worry that my condition will get worse…….	0	1	2	3	4

26. Looking at the above 6 questions, how much would you say your EMOTIONAL WELL-BEING affects your quality of life? (circle one number)

0 1 2 3 4 5 6 7 8 9 10
Not at all Very much

FUNCTIONAL WELL-BEING

		not at all	a little bit	some-what	quite a bit	very much
27.	I am able to work (include work in home)…….	0	1	2	3	4
28.	My work (include work in home) is fulfilling.……	0	1	2	3	4
29.	I am able to enjoy life……..	0	1	2	3	4
30.	I have accepted my illness……	0	1	2	3	4
31.	I am sleeping well……..……...	0	1	2	3	4
32.	I am enjoying the things I usually do for fun……...	0	1	2	3	4
33.	I am content with the quality of my life right now……..	0	1	2	3	4

34. Looking at the above 7 questions, how much would you say your FUNCTIONAL WELL-BEING affects your quality of life? (circle one number)

0 1 2 3 4 5 6 7 8 9 10
Not at all Very much

ADDITIONAL CONCERNS

		not at all	a little bit	some-what	quite a bit	very much
35.	I am able to eat the foods that I like…….	0	1	2	3	4
36.	My mouth is dry……	0	1	2	3	4
37.	I have trouble breathing……	0	1	2	3	4
38.	My voice has its usual quality and strength..……	0	1	2	3	4
39.	I am able to eat as much food as I want…..……...	0	1	2	3	4
40.	I am self-conscious about how my face and neck look….	0	1	2	3	4
41.	I can swallow naturally and easily...……..	0	1	2	3	4
42.	I smoke cigarettes or other tobacco products……	0	1	2	3	4
43.	I drink alcohol (e.g. beer, wine, etc.)…….	0	1	2	3	4
44.	I am able to communicate with others……..	0	1	2	3	4
45.	I can eat solid foods……..	0	1	2	3	4

46. Looking at the above 7 questions, how much would you say your PHYSICAL WELL-BEING affects your quality of life? (circle one number)

0 1 2 3 4 5 6 7 8 9 10

Not at all Very much

A PHASE I STUDY USING LOW DOSE ABDOMINAL RADIOTHERAPY AS A TAXOTERE CHEMOSENSITIZER FOR RECURRENT/PERSISTENT OR ADVANCED OVARIAN CANCER

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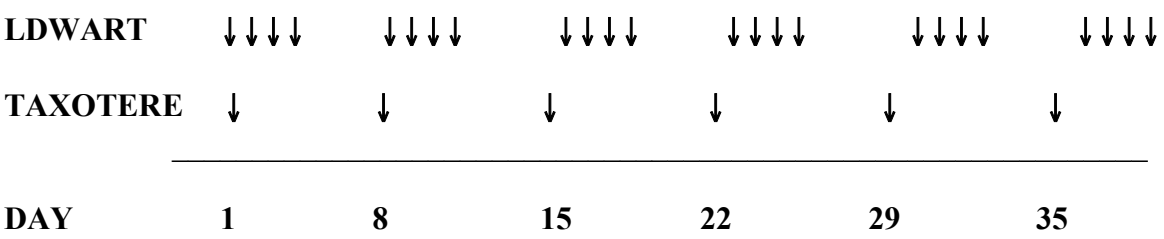
STATISTICIAN: Richard Krysio, Ph.D

Revision 000.001 March 3, 2003

Continuation Review March 10, 2004

SCHEMA

Patient population: Recurrent Ovarian Cancer



Taxotere: 20 mg/m2 in 1 hr infusion q wkly x 6 weeks

LDWART- Low Dose Whole Abdominal Radiation Therapy (60 cGy bid x 2 days)

The dose of taxotere infusion will be increased in increments of 5 mg/m2 per groups of three patients at each dose level to establish the MTD.

SCHEDULE OF EVALUATIONS / STUDY CALENDAR

Parameter	Prestudy	Weekly	Every 2 Weeks	Study Termi-nation	Follow - Up
History	X	X		X	X
Physical examination	X	X	X	X	X
Weight	X	X	X	X	X
Vital signs	X	X	X	X	X
Measurement of tumor	X			X	X
Performance status (ECOG)	X	X	X	X	X
CBC, differential, platelet count	X	X	X	X	X
Creatinine, Serum bilirubin, glucose, alkaline phosphatase, SGOT	X	X	X		X
Electrolytes (Na, K, C1, CO_2)	X	X	X		X
Serum HCG	****				****
Chest x-ray	X				X
Chest CT scan	X				****
Bone scan/bone films	****				****
Liver scan or abdominal CT	X			X	X
Brain CT or MRI scan	****				****
EKG	X				****

**** as indicated

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1.0 OBJECTIVES

This is a Phase I Dose escalation study of Radiation induced Chemosensitization in recurrent/persistent or advanced stage (suboptimally debulked III/IV) ovarian carcinoma.

Primary Objective:

1.1 To establish the maximal tolerated dose of weekly Taxotere and hyperfractionated low dose whole abdominal radiation

Secondary Objectives:

1.2 To assess the toxicity of combined weekly Taxotere and low dose whole abdominal radiation.

1.3 To assess the response and time to progression.

2.0 BACKGROUND AND RATIONALE:

2.1 Three modalities of therapy have established roles in the treatment of ovarian carcinoma: surgery, chemotherapy, and radiation therapy (XRT). The choice of which modality to use depends upon many factors. In general, stage I-II ovarian carcinoma is effectively treated with surgical excision, with or without adjuvant chemotherapy or radiotherapy, whereas more advanced disease (stage II/III) is best treated with combined surgery and chemotherapy (1). The introduction of combined modality therapy using surgery and Cisplatin based chemotherapy represented an important advancement in the treatment of this disease. The subsequent introduction of Paclitaxel plus Cisplatin further improved survival rates (2). However, even when surgery and chemotherapy are used together only a small fraction of patients with advanced disease (stage III) are cured, approximately 15%. The majority of these patients will develop intraperitoneal recurrence of their tumors. An especially poor outcome is seen in those patients unable to undergo optimal debulking of their disease (> 1 cm residual disease).(3,4,5)

The Gynecology Oncology Group (GOG) has conducted a randomized Phase III study comparing Paclitaxel (Taxol) and Cisplatin with Cyclophosphamide and Cisplatin in suboptimally debulked (>1 cm residual mass) stage III and IV patients who had no prior chemotherapy.(2) There was a statistically significant improvement in the clinical response rate in the Taxol arm (73%) versus 60%. Median survival was also significantly better in the TP arm (38 months versus 24 months, p=.001). However, the differences in surgically documented

complete responses were low in both arms and not statistically different (20% for CP versus 26% for TP) underlining the fact that there is a need for further improvement in therapeutic strategies to raise the pathological complete response rate.

Recent results from the GOG 132 trial show that in suboptimal stage III or IV disease as defined by at least one mass greater than one centimeter after the initial cytoreductive surgery, the results of Cisplatin/ Taxol chemotherapy have been less than satisfactory.(6) In 648 patients entered into the study comparing cisplatin alone, Taxol alone or the combination of Cisplatin and Taxol, the clinical complete response was 43% and the partial response was 23% with 33% showing no response. However, on second-look laparotomy only 24% of patients had no evidence of disease and 76% of patients had either persistent disease (63% gross disease and 13% microscopic disease). Overall survival in these patients at two years was 50% but the progression free survival was only 20% at 24 months. Most of these patients continued to fail progressively in spite of salvage chemotherapy with a 5-yr survival of only 12%.

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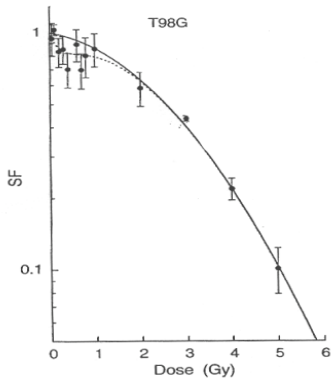
Several strategies for salvage therapy have been attempted but the response to salvage therapy has been poor (13-20%) and progression free survival rates for salvage therapy are reported as 12-15% at two years.(7-10)

Ovarian carcinoma is known to be a radiosensitive tumor, which has prompted the study of whole abdominal radiotherapy (WART) used in a palliative or in an adjuvant setting in an attempt to decrease intrabdominal recurrence of this disease(11-14). Unfortunately, treatment of the entire abdomen necessarily results in a limitation of the total dose of radiotherapy able to be delivered, and whole abdominal radiotherapy in an adjuvant setting. The traditional approach to radiation therapy for Stage III ovarian cancers has been to use total abdominal and pelvic radiation in conventional doses of 150-200 cGy per day for total doses of 2500-3000 cGy. The major shortcoming with this approach has been the toxicity of treatment and the inability to combine this with full dose chemotherapy which is a significant drawback especially in an era when chemotherapy is recognized as the primary treatment strategy. (15-18)

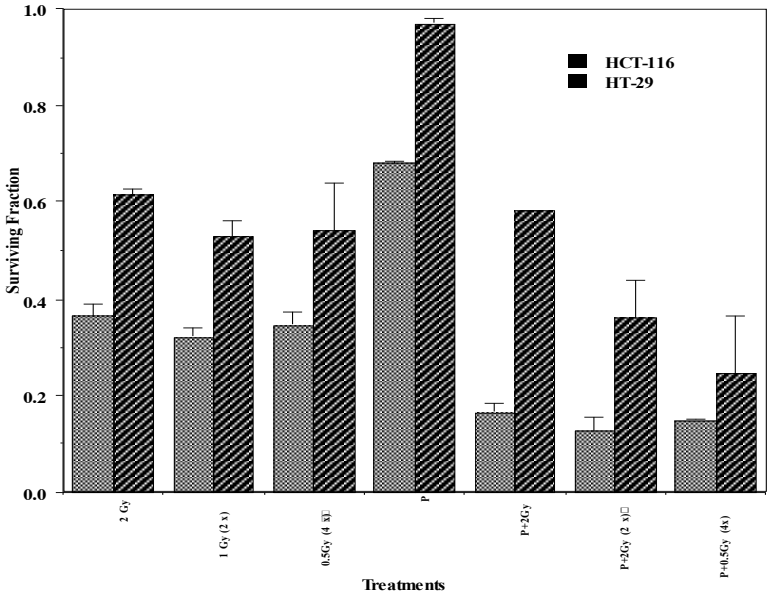
Exciting new data from Michael Joiner at the Gray Laboratories of England have redefined our understanding of the radiation cell survival curve. The traditional thinking that the initial slope of the radiation cell survival was defined by a shoulder followed by steep straight line segment was a result of our inability to study the effects of very low doses of radiation on cell survival function and was derived from extrapolation of data obtained at higher doses (>100 cGy) of radiation. The data from the Gray Laboratories suggested instead that the initial slope of the survival curve is much more complex and is defined by an initial phase of hypersensitivity to radiation with a steep cell killing effect between 0-50 cGy followed by a plateau effect between 50-120 cGy and a subsequent straight line portion of the survival curve, (see Figure 1).



This survival curve seems to be consistently reproduced in 14 of 14 tumor cell lines that have been examined indicating that this might be far more real than the traditional cell survival curve (Figure 1)

Systemic chemotherapy has successfully been used in combination with radiation to treat a wide variety of tumors. Recent data suggests that improved survival, reduced local recurrence and increased organ preservation has been achieved for a wide variety of cancers. One of the fundamental problems, however, is that combined modality treatments are often associated with some enhanced toxicity and therefore the strategy is rarely applicable when wide field radiation is required, (i.e. whole abdomen). A novel strategy of combining fractionated low dose radiation as a chemosensitizer with full dose chemotherapy may off-set the limitations due to normal tissue toxicity and yet improve on the efficacy of chemotherapy. Our preliminary data using colon cancer cell lines show that fractionated low dose radiation 50 cGy x 4 given following a 24-hour exposure to Taxol can reduce cell survival by a factor of 2 as compared to a single fraction of 200 cGy given after Taxol exposure. This is especially true in cells with p53 mutations which are usually considered both drug and radiation resistant. (Figure 2)

Figure 2.



There is laboratory and clinical evidence that Cisplatin and radiotherapy,(21,22) as well as Taxol and radiotherapy,(23) act in a synergistic fashion when given concurrently. This effect has been used to improve the response rate, control rate, and survival in carcinomas of the head and neck, esophagus, lung, cervix, rectum, and anal canal (24). The general treatment approach in these settings has been to deliver full courses of high dose radiotherapy (4500-7000 cGy over several weeks) combined with chemotherapy used as a radiosensitizer, given in a daily, weekly, or monthly fashion. This approach is unlikely to be successful in the treatment of ovarian carcinoma as the hematologic toxicity resulting from standard dose irradiation of the whole abdomen prohibits delivery of full dose chemotherapy. An alternative approach would be to not rely on the Cisplatin containing chemotherapy as the primary treatment agent, but to use whole abdominal radiotherapy in much lower than standard doses as a chemosensitizer with Taxotere. The toxicity of whole abdominal radiotherapy would thus be greatly reduced. To our knowledge, low dose chemosensitizing WART has not previously been studied.

Recent experiments have also shown that functional intranuclear P53 is required for sensitivity of cancer cells to a variety of chemotherapy drugs and radiation. P53 mutations of even one allele predispose cell to the loss of function of P53 and to the development of Cisplatin resistance.(25-28) Over 90% of Ovarian cancer cells that express P53 have been shown to have mutations.(29) Our experiments have shown that in P53 mutated cell lines, low dose (0.5 Gy) fractionated radiation added to Taxol increased cell killing by a factor of 2.(20)

We have undertaken a Phase I dose escalation study of low dose fractionated whole abdominal radiation with standard full dose Cisplatin (75 mg/m2)/ Taxol (135 mg/m2 over 24 hrs.) every three weeks x 3. In the first 3 patients treated, 80 cGy per fraction x 4 was well tolerated without significant bowel or bone marrow toxicity. This protocol was stopped because most salvage regimens for Ovarian cancer have now shifted to either Carboplatin/ Taxol (1 hour infusion) or single agent weekly Taxol.(30-32) Our data from low dose fractionated whole abdominal radiation with weekly 5 FU for GI carcinomatosis also shows that 80 cGy bid for two days with chemotherapy was well tolerated (MTD 100 cGy bid x 2 days). In our current protocol we have used the standard approach to salvage chemotherapy with weekly Taxol and 60 cGy bid of Low dose fractionated whole abdominal radiation as the chemosensitizer based on our in vitro data.

This protocol is designed to exploit the sensitization effects of low dose radiation in a multifractionated approach concurrently with chemotherapy to induce sensitivity of tumor cells. At the same time the lower doses of radiation should minimize any normal tissue toxicity.

Weekly Taxotere with Radiation Therapy has been used for the treatment of a wide variety of cancers. Koukourakis and colleagues conducted a Phase II trial

of Taxotere and radiation therapy in patients with locally advanced NSCLC, using the recommended Taxotere dose (30mg/m^{2}week) as a 30-minuts infusion weekly for 6 weeks. Concurrent radiation therapy was administered as 2 Gy/day for 5 days/week for a total dose of 64 Gy over 6.5 weeks. The 35 patients entered in this study were evaluable for toxicity. No grade 3-4 neutropenia, anemia, or thrombocytopenia was observed. Lymphocytopenia was universal, with 5 (14%) and 30 (86%) patients experiencing grade 3 and 4 lymphocytopenia, respectively. Twelve of the 35 patients (34%) had a CR and 16 (46%) had a PR, for an ORR of 80%. Of the remaining 7 patients, 4 had minimal response (11%) and 3 had stable disease (9%). The overall median survival was 12 months. After 1 year, 48% of patients were alive. (33)

Similar results have been obtained by Aamdal et al and Sistermanns with Taxotere with Concurrent Radiotherapy. Patients received Taxotere 30mg/m^2 on days 1, 8, 22, and 29 of a 5-week schedule. Concurrent thoracic radiation was administered 2 Gy/day, 5 days/week for a total dose of 50 Gy. (34-35)

This Phase I study is a dose escalation of the Taxotere dose to establish the MTD of Taxotere in conjunction with weekly low dose radiation.

The treatment approach outlined in this protocol has not been evaluated, to our knowledge, in the treatment of ovarian carcinoma with concurrent use of chemotherapy and radiotherapy. If low dose fractionated radiation can achieve the same level of enhanced tumor cell kill in patients with ovarian cancer as seen in the in vitro laboratory studies, significant improvements can be achieved in the treatment of not only recurrent ovarian cancers but it may be useful in the primary treatment since 70% of patients with advanced ovarian cancer fail in spite of aggressive primary treatment with chemotherapy and surgery.

Docetaxel has become well established as an effective regimen in the treatment of Epithelial Ovarian cancers (39). It may be more effective than Paclitaxel because of a more favorable tissue pharmacology and a longer physiological half life (38). However Docetaxel (Taxotere) has generally been used as a short (1 hour) infusion on a three weekly schedule. Since most salvage regimens use weekly Taxotere this protocol will assess and establish the safe dose of Taxotere infusion in conjunction with LDFRT starting using an established safe dose of 10 mg/m2 weekly (37).

3.0 ELIGIBILITY CRITERIA:

3.1 Eligible Patients

3.11 Patients with recurrent ovarian carcinoma following prior 1st line chemotherapy , any relapse.

3.12 Patients must be older than 18 years and younger than 80 years

3.13 Patients should have adequate bone marrow, renal and hepatic function

3.13.1 WBC $\geq$ 3000 cells/mcl
3.13.2 Granulocytes $\geq$ 1500/mcl
3.13.3 Platelets $\geq$ 100,000/mcl
3.13.4 Creatinine < 2.0 mg/dcl
3.13.4 Bilirubin must be WNL
3.13.5 SGOT and/or SGPT may be up to 2.5 x institutional ULN if alkaline phoshatase is < ULN

3.14 Patients who have signed an approved informed consent

3.15 Peripheral neuropathy must be $\leq$ grade 1

3.16 Hgb $\geq$ 8.0 g/dl

3.2 Ineligible Patients

3.21 Patients that have distant metastatic disease, outside abdomen and pelvis.

3.22 Patients that have received prior radiation to the whole abdomen

3.23 Patients with anticipated survival less than 3 months

3.24 Patients that have a Karnofsky Performance of < 60%.

3.25 Patients with histories of other invasive malignancies, with the exception of Non-melanoma skin cancer, who had (or have) any evidence of the other cancer present within 5 years or whose previous cancer treatment contraindicates this protocol therapy.

3.26 Patients with a history of severe hypersensitivity reaction to Taxotere or other drugs formulated with polysorbate 80.

3.27 Patients who have received prior Taxotere treatment.

4.0 STUDY MODALITIES

4.1 Radiation Therapy

4.11 All patients will receive radiation therapy

4.12 All treatment will be delivered by megavoltage equipment (6-25 Mev). The minimum source skin distance (SSD) will be 80 cm, dose rates of 200-300 cGy per minute at the midplane will be used.

4.13 Treatment plan and dose specification:
All doses will be calculated at the midplane in the center of the target volume for opposed fields.

4.14 Low Dose Whole Abdominal Radiation (LDWART)

4.141 LDWART will be given starting on day 1 of each week of treatment. Treatment will given as follows: 60 cGy fractions, given twice daily x 2 days, with a minimum of 4 hours interfraction interval. The first fraction of radiotherapy will be given 3 hours after the initiation of Taxotere.

4.142 Abdominal field borders for RT planning are as follows:

Inferior borders - inferior border of the obturator foramina or 2 cm below the lowest extent of the disease
Superior borders - one centimeter above the dome of the diaphragm at the patient's maximum comfortable expiration

4.2 Chemotherapy

4.21 Weekly - Premedication with Dexamethasone 10mg IV, 30 minutes prior to infusion, is recommended for all patients receiving weekly Taxotere therapy to reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions. Antimetics will be prescribed and repeated at the discretion of the physician.

4.22 Taxotere: 20 mg/m2, 1 hour infusion day 1 and repeated each week for a total of 6 treatment courses.

4.23 Taxotere Dose Escalation: The Taxotere dose will be escalated by increments of 5 mg/m2 to establish the MTD. A dose limiting toxicity (DLT) is defined as Gr.3 or Gr. 4 Non-Hematologic NCI CTCV.2 Toxicity.

Cohorts of 3-6 patients will be treated according to the schedule described in Table 1. If no DLT is encountered in patients

treated at a dose level, subsequent patients will be treated at the next higher dose level. Intrapatient dose escalation is not permitted. If one patient experiences DLT, then the dose level will be expanded to a minimum of 6 patients. If two of these six patients experience DLT, it will be determined that the MTD has been exceeded and the preceding dose level will be declared the MTD. If 2 or more out of 6 patients develop a DLT at Dose Level 1, patients will be treated at Dose Level-1. If 2 or more out of 6 patients experience a DLT at Dose Level-1, accrual to this study will cease. (See Table 1 below as reference).

After initial assignment to a dose level, a patient will not have her dose of Taxotere escalated.

Table 1

Number of Patients with DLT at a Given Dose Level	**Escalation Decision Rule**
0 out of 3	Enter 3 patients at the next dose level.
$\geq$2	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
1 out of 3	Enter at least 3 more patients at this dose level. • If 0 of these 3 patients experience DLT, proceed to the next dose level. • If 1 or more of this group suffer DLT, then dose escalation is stopped and this dose is declared the maximally administered dose. Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were
	• treated previously at that dose.
$\leq$1 out of 6 at highest dose level below the maximally administered dose	This is generally the recommended phase 2 dose. At least 6 patients must be entered at the recommended phase 2 dose.

4.24 The only research portion of the study is the use of WART in conjunction with Taxotere as opposed to chemotherapy alone. Taxotere will be initiated within 6 weeks of laparotomy or documented evidence of recurrence. A total of 6 courses will be planned. All the following procedures described are part of the patient's routine clinical care.

5.0 ENTRY PROCEDURES

5.1 Patient Entry

When a suitable candidate has been obtained for protocol entry, the following steps should be taken:

5.11 A Consent Form must be signed by the patient or guardian.

5.12 Make certain all eligibility requirements according to section 3.0 have been met.

5.13 The institution will enter the patient's initials, protocol number, name, and assigned regimen in the appropriate place in their Log Book to verify the patient's entry.

6.0 TAXOTERE DOSE MODIFICATIONS

No more than two dose modifications should be allowed for any patient. If a patient requires a third dose-reduction of Taxotere, she should be removed from the study If such a patient is clinically benefiting from treatment, and, if the physician believes the toxicity will be alleviated sufficiently with dose modification, further treatment will be permitted at the discretion of the Principal Investigator in consultation with Aventis Pharmaceuticals, U.S. Medical Affairs.

If a patient develops a Grade 3/4 Non-hematologic toxicity, the patient will be removed from study. This DOES NOT INCLUDE Grade ¾ nausea and vomiting or one episode of a Grade 3 Hypersensitivity Reaction. Please refer to Section 6.2 for clarification of these exemptions.

6.1 HEMATOLOGIC TOXICITY

TREATMENT-DAY PARAMETERS

Prior to receiving any dose of Taxotere, patients must have an absolute neutrophil count $\geq$ 1,000/mm^3.

6.2 INTRA-CYCLE TOXICITY

Thrombocytopenia. Grade 4 thrombocytopenia requires a 25% dose reduction.

Anemia. There are no specific recommendations for the management of anemia.

Neutropenia. If ANC < 1000/mm^3 on day of treatment, should decrease Taxotere one dose level after recovery to $\geq$ 1000/mm^3. Patients with afebrile grade 4 neutropenia ≥7 days should be dose reduced 25%, after recovery.

Patients with grade 4 neutropenia associated with fever (one reading of oral temperature > 38.5° C, or three readings of oral temperature > 38.0° C in a 24-hour period) will be considered a DLT, and WILL be removed from study.

Dose Modifications for Neutropenia

Dose Level	% Taxotere® Dose (mg/m^2)
Dose Given That Cycle	100%
Level –1	75%
Level – 2	50%

Hepatic Dysfunction. Liver function tests will be evaluated between Baseline and prior to dose 4.

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

Dose Modifications for Abnormal Liver Function (Taxotere®)

Bilirubin	Alkaline phosphatase	SGOT	Action
1.1-1.5 x ULN	NA	NA	Wait ≤ 3 weeks. If recovered*, reduce Taxotere® dose by 25%. If not, off study.
≤ ULN	and ≤ 5 x ULN	and 2.6 – 5 x ULN	Reduce Taxotere® dose by 25% without treatment delay.

*Bilirubin ≤ ULN *and* alkaline phosphatase ≤ 5 x ULN *and* SGOT ≤ 5 x ULN.

Note: A maximum of two dose reductions per patient are allowed.

ULN = upper limit of normal for institution

Bilirubin >1.5 X ULN or Alkaline Phosphatase >5X ULN or SGOT > 5X ULN is considered a DLT requiring patient to come off study.

Stomatitis If stomatitis is present on day 1 of any cycle, treatment should be withheld until stomatitis has resolved. If Grade 3/4 stomatitis occurs, the patient should be removed from study.

Peripheral Neuropathy The Taxotere dose should be reduced by 25% without treatment delay for Grade 2 neuropathies. Treatment should be discontinued for Grade 3/4 neuropathies.

Hypersensitivity Reactions
See Appendix I for treatment of hypersensitivity reactions . Treatment should be discontinued for two episodes of Grade 3 hypersensitivity reactions or any Grade 4 hypersensitivity reactions. There are no dose reductions for hypersensitivity reactions.

Fluid Retention
See Appendix II for the treatment template for fluid retention. There are no dose reductions for fluid retention.

Hyperlacrimation
See Appendix III for management template.

Nausea/Vomiting
Grade 3/4 nausea/vomiting that is treated successfully with antiemetics WILL NOT be considered a DLT.

Other Non-Hematologic Toxicities
For Grade ¾ toxicities, patient will be removed from study.

7.0 RADIATION TREATMENT MODIFICATIONS

7.1 Treatments will be modified due to the following toxicities:

7.11 Hematologic Adverse Effects

A decline in the WBC and platelet counts to Grade 2 level may frequently occur. A CBC should be obtained weekly, and if the WBC falls below 2000 or platelet count below 100,000, a CBC should be obtained twice weekly.

Chemotherapy will be interrupted for Grade 3 or 4 hematological toxicity. Radiation will be held if the platelet counts are $\leq$ 20,000 or the absolute neutrophil count is $\leq$ 500 for more than 7 days. If this occurs, counts will be obtained twice weekly and chemotherapy will be resumed when ANC $\geq$ 500 and platelets $\geq$ 50,000.

7.12 Gastrointestinal Adverse Effects

Nausea, vomiting, and diarrhea during the course of radiation therapy may be treated symptomatically by anti-emetic, anti-diarrhea medication, and dietary modification.

8.0 ADVERSE EVENTS

Evaluating and Reporting Adverse Experiences

Adverse experiences will be monitored throughout this study and such events will be reported to the IRB on Adverse Experiences Report Forms.

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

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

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

SAE Reporting

In IND-exempt studies, All serious, related adverse events will be reported and documented on Form FDA 3500 A **(**MedWatch Form) and *and simultaneously* faxed to the FDA and to Aventis Pharmaceuticals Global Pharmacovigilance and Epidemiology. This includes serious, related, labeled (expected) and serious, related, unlabeled (unexpected) adverse experiences. Dr. Mohouiddin will be notified immediately by phone (859)323-6486 or by pager at (859) 323-3000 X 1614.

These reports should be sent by **FAX** or **E-MAIL** to:
Aventis Pharmaceuticals
Global Pharmacovigilance and Epidemiology
101 Mettler's Road
Mail Code EM-C1-E
East Millstone, NJ 08873

By FAX: (908)-231-4827, within 24 hours of receipt by investigator / sponsor. FAX transmission should include Grant-In-Aid Study Number, Study Title, and name of Principal Investigator.

By E-MAIL: GPEmailbox@aventis.com , within 24 hours of receipt by investigator / sponsor E-Mail transmission should include Grant-In-Aid Study Number, Study Title, and name of Principal Investigator.

For Comparator Drugs / Secondary Suspects (Concomitant Medications), all serious adverse experiences will be forwarded to the product manufacturer.

9.0 CRITERIA FOR REMOVAL OF PATIENTS FROM STUDY

Patients may discontinue their participation in the study at any time by withdrawal of their informed consent. They will continue treatment using a standard of care regiment. Patients requiring a third dose modification will be removed from the study by the principle investigator.

10.0 SAFETY AND EFFICACY

Patients will be monitored throughout the clinical trial. The safety and efficacy will be evaluated by assessing the patients for adverse events. Patients will have laboratory evaluation and physical examinations performed as standard-of-care and as clinically indicated. Investigational site staff will record any clinically significant abnormalities

in laboratory results or physical findings as adverse events. Toxicity will be graded according to NCI CTC Toxicity Grading, V2.0. (Appendix V)

11.0 STUDY MONITORING AND REPORTING PROCEDURES

11.1 A patient consent form must be signed by the patient or guardian prior to study entry.

11.2 The following forms must be completed for all patients that are entered onto this protocol, and placed in the patient's case report folder.

FOUR WEEKS AFTER ENTRY

- Form A (Patient Registration)
- Form D (Pre-Treatment Summary Sheet)
- Form E (Anatomical Diagram of Clinical Tumor Location)

SIX WEEKS AFTER ENTRY

Form C (Surgical Reporting Form)

Operative Report- One copy of the institution's dictated operative report.

Discharge Summary- One copy of the discharge summary which clearly summarizes the clinical, surgical, and pathologic findings, as well as documenting post-operation recovery with specific documentation of presence or absence of wound complications, other morbidity, and mortality information.

Form F (Pathology Form)

Pathology Report- One copy of the institution's dictated pathology report.

TWO WEEKS AFTER RADIOTHERAPY ENDS

- Form G (Radiation Therapy Form)
- One copy of the daily treatment record
- One copy of the dosimetry calculation
- One copy of the isodose distribution curves, except for patients treated via AP-PA portals alone
- One copy of the portal film for each external field (i.e., AP, PA, Left Lateral, Right Lateral, etc.)

Form T- (Toxicity Reporting Form)
-must be completed and submitted for entry into the protocol binder.

Form Q- (Follow-up Form)
must be completed and submitted for entry into the protocol binder

12.0 STATISTICAL CONSIDERATIONS

This is a Phase I study.

This study has is a dose finding study. The primary endpoint for the first part is assessment of acute toxicity to identify the maximum tolerated dose (MTD) of Taxotere when given concurrently with whole abdominal radiation. For the second part of the study further assessment of acute and chronic treatment toxicity will be accomplished at the established MTD/recommended Phase II dose.

For the purpose of this study, acute toxicity will be defined as events that have onset during or within 30 days of completing radiation therapy.

All events with onset beyond 30 days of completing radiation therapy will be considered as chronic. The late effects of therapy may have onset delayed as much as 6 months after completing therapy, and may persist indefinitely.

The primary objective of this study is to determine the maximally tolerated dose of Taxotere given as a one hour infusion for six weekly doses.

A minimum of three patients at each of the dose levels are to be evaluated (i.e. 10 mg/m^2, 15 mg/m^2, 20 mg/m^2, and 25 mg/m^2.) If none of the three patients develop a DLT then the next three patients will be escalated to the next dose level. If one out of three patients develop a DLT, three out of 6 additional patients will be treated at that same dose level. If no more than one out of six patients develops a DLT then the dose will be increased to the next dose level. If 2 of 6 patients develop a DLT then the dose level below will be considered as the Maximum Tolerated Dose (MTD).

The variables to be collected, analyzed and reported to determine the safe and maximum tolerated dose (MTD) of Taxotere when given concurrent with whole abdominal radiation are:

1) Dose of each drug and number of courses received.

2) Site (local/distant) of treatment failure (secondary endpoint)

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APPENDIX I

HYPERSENSITIVITY REACTIONS

MANAGEMENT OF ACUTE HYPERSENSITIVITY

Severity of Symptoms	Treatment Guidelines
Mild symptoms: localized cutaneous reactions such as mild pruritus, flushing, rash	· consider decreasing the rate of infusion until recovery from symptoms, stay at bedside and monitor patient · then, complete Taxotere infusion at the initial planned rate
Moderate symptoms: any symptom that is not listed above (mild symptoms) or below (severe symptoms) such as generalized pruritus, flushing, rash, dyspnea, hypotension with systolic BP > 80 mm Hg	· interrupt Taxotere infusion · give diphenhydramine 50 mg IV with or without dexamethasone 10 mg IV; monitor patient until resolution of symptoms · resume Taxotere infusion after recovery of symptoms; depending on the physician's assessment of the patient, Taxotere infusion should be resumed at a slower rate, then increased incrementally to the initial planned rate*, (eg. infuse at an 8 hour rate for 5 minutes, then at a 4-h rate for 5 minutes, then at a 2-h rate for 5 minutes, then finally, resume at the 1-h infusion rate)* · depending on the intensity of the reaction observed, additional oral or IV premedication with an antihistamine should also be given for the **next cycle** of treatment, and the rate of infusion should be decreased initially and then increased back to the recommended 1-hour infusion, *(eg. infuse at an 8 hour rate for 5 minutes, then at a 4-h rate for 5 minutes, then at a 2-h rate for 5 minutes, and finally, administer at the 1-h infusion rate)*
Severe symptoms: any reaction such as bronchospasm, generalized urticaria, systolic BP ≤ 80mm Hg, angioedema	· immediately discontinue Taxotere infusion · give diphenhydramine 50 mg IV with or without dexamethasone 10 mg IV and/or epinephrine as needed; monitor patient until resolution of symptoms · the same treatment guidelines outlined under moderate symptoms (i.e. the third and fourth bullets) should be followed.
Anaphylaxis (NCI grade 4 reaction)	· NO FURTHER STUDY DRUG THERAPY

APPENDIX II

MANAGEMENT OF EDEMA / FLUID RETENTION

No dose reduction is required. Patients developing new onset edema, progression of existing edema, or another sign of fluid retention (eg. 2 pound weight gain) are to be treated with oral diuretics. Regimens found to be effective in the management of fluid retention due to Taxotere are listed below.

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

Further therapy should be customized depending upon the clinical situation. The clinical tolerance of the patient, the overall tumor response and the medical judgment of the investigator will determine if it is in the patient's best interest to continue or discontinue treatment.

APPENDIX III

MANAGEMENT OF HYPERLACRIMATION IN PATIENTS RECEIVING WEEKLY TAXOTERE

The excessive lacrimation (epiphora) seen in some patients receiving weekly Taxotere appears to be related to cumulative dose (median~300 mg/m^2) and resolves rapidly after treatment cessation.

Excessive lacrimation seems to be the result of a chemical conjunctivitis and/or chemical inflammation (with edema) of the lacrimal duct epithelium (producing a reversible lacrimal duct stenosis). Consequently, investigators in clinical trials have treated such patients with (a) artificial tears and/or (b) saline eye wash and/or (c) steroid based eye drops.

It is suggested that the following approach be taken to patients experiencing clinically significant hyperlacrimation:

1. Withhold Taxotere treatment for up to 2 weeks,
2. Recommend frequent instillation of artificial tears,
3. Reinstitute "weekly" Taxotere on a 3 out of every 4 week schedule, and
4. Prescribe a steroid ophthalmic solution (eg. prednisolone acetate) 2 gtts each eye bid for 3 days starting the day before Taxotere administration in patients **without** a history of herpetic eye disease.

APPENDIX IV

STUDY MEDICATION

TAXOTERE

PREPARATION AND ADMINISTRATION PRECAUTIONS

TAXOTERE is a cytotoxic anticancer drug and, as with other potentially toxic compounds, caution should be exercised when handling and preparing TAXOTERE solutions. The use of gloves is recommended. Please refer to **Handling and Disposal** section.

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

TAXOTERE for Injection Concentrate requires <u>two</u> dilutions prior to administration. Please follow the preparation instructions provided below. **Note:** Both the TAXOTERE 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 TAXOTERE 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 TAXOTERE for Injection Concentrate. **<u>If the procedure is followed as described, an initial diluted solution of 10mg docetaxel/mL will result.</u>**
3. Gently rotate the initial diluted solution for approximately 15 seconds to assure full mixture of the concentrate and diluent.
4. The initial diluted TAXOTERE solution (10 mg docetaxel/mL) should be clear; however, there may be some foam on top of the solution due to the polysorbate 80. Allow the solution to stand for a few minutes to allow any foam to dissipate. It is not required that all foam dissipate prior to continuing the preparation process.

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

B. Preparation of the Final Dilution for Infusion

1. Aseptically withdraw the required amount of initial diluted TAXOTERE solution (10 mg docetaxel/mL) with a calibrated syringe and inject into a 100 mL infusion bag or bottle of either 0.9% Sodium Chloride solution or 5% Dextrose solution to produce a final concentration of 0.3 to 0.74 mg/mL.

   If a dose greater than 80 mg of TAXOTERE is required, use a larger volume of the infusion vehicle so that a concentration of 0.74 mg/mL TAXOTERE is not exceeded.
2. Thoroughly mix the infusion by manual rotation.
3. As with all parenteral products, TAXOTERE should be inspected visually for particulate matter or discoloration prior to administration whenever the solution and container permit. If the TAXOTERE for Injection initial diluted solution or

final dilution for infusion is not clear or appears to have precipitation, these should be discarded.

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

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

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

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

HOW SUPPLIED

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

TAXOTERE 80 MG (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.

Storage: Store between 2 and 25°C (36 and 77ºF). Retain in the original package to protect from bright light. Freezing does not adversely affect the product.

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

Weekly Dosing

Protocols involving the weekly administration of Taxotere are currently utilizing 30-minute or 15-minute infusion times in addition to a 1-hour infusion period. This is due to the fact that the infusion solution volume (100 mL) for weekly Taxotere is generally less than that for every 3-week treatment (250 mL). However, a patient with a large BSA may require an infusion volume greater than 100 mL in order to stay within the Taxotere concentration guidelines given above.

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Radiation Therapy to the Abdomen Plus Docetaxel in Treating Patients With Recurrent or Persistent Advanced Ovarian, Peritoneal, or Fallopian Tube Cancer

This study is currently recruiting patients.

Sponsors and Collaborators: Gynecologic Oncology Group
National Cancer Institute (NCI)

Information provided by: National Cancer Institute (NCI)

Purpose

RATIONALE: Radiation therapy uses high-energy x-rays to damage tumor cells. Drugs used in chemotherapy, such as docetaxel, work in different ways to stop tumor cells from dividing so they stop growing or die. Combining chemotherapy with radiation therapy may kill more tumor cells.

PURPOSE: Phase I trial to study the effectiveness of low-dose radiation therapy to the abdomen combined with docetaxel in treating patients who have recurrent or persistent advanced ovarian, peritoneal, or fallopian tube cancer.

Condition	Treatment or Intervention	Phase
recurrent ovarian epithelial cancer peritoneal cavity cancer Fallopian Tube Cancer stage III ovarian epithelial cancer stage IV ovarian epithelial cancer	Drug: docetaxel Procedure: chemosensitization/potentiation Procedure: chemotherapy Procedure: radiation therapy	Phase I

MedlinePlus related topics: Cancer;
Cancer Alternative Therapy; Ovarian Cancer; Reproductive Health

Study Type: Interventional
Study Design: Treatment

Official Title: Phase I Study of Low-Dose Abdominal Radiotherapy and Docetaxel in Patients With Recurrent or Persistent Advanced Ovarian, Peritoneal, or Fallopian Tube Cancer

Further Study Details:

OBJECTIVES:

- Determine the maximum tolerated dose of docetaxel in combination with low-dose abdominal radiotherapy in patients with recurrent or persistent advanced ovarian, peritoneal, or fallopian tube cancer.
- Determine the safety and toxicity of this regimen in these patients.

OUTLINE: This is a multicenter, dose-escalation study of docetaxel.

Patients receive docetaxel IV over 30 minutes once daily on days 1, 8, 15, 22, 29, and 35. Within 3 hours after beginning docetaxel, patients also receive low-dose abdominal radiotherapy twice daily (at least 4 hours apart) on days 1, 2, 8, 9, 15, 16, 22, 24, 29, 30, 35, and 36. Treatment continues in the absence of unacceptable toxicity.

Cohorts of 3-6 patients receive escalating doses of docetaxel until the maximum tolerated dose (MTD) is determined. The MTD is defined as the dose preceding that at which 2 of 6 patients experience dose-limiting toxicity.

Patients are followed every 3 months for 2 years, every 6 months for 3 years, and then annually thereafter.

PROJECTED ACCRUAL: A total of 3-30 patients will be accrued for this study within 0.25-2.5 years.

Eligibility

Ages Eligible for Study: 18 Years and above, Genders Eligible for Study: Both

Criteria

DISEASE CHARACTERISTICS:

- Diagnosis of ovarian, peritoneal, or fallopian tube carcinoma
- Radiographic, clinical, or pathologic evidence of relapse
- Recurrent or persistent disease after chemotherapy (may be enrolled at first or subsequent relapse)
- Received prior taxane OR platinum agent

PATIENT CHARACTERISTICS: Age

- 18 and over

Performance status

- GOG 0-2

Life expectancy

- Not specified

Hematopoietic

- WBC at least 3,000/mm^3
- Absolute neutrophil count at least 1,500/mm^3
- Platelet count at least 100,000/mm^3

Hepatic

- Bilirubin no greater than 1.5 times upper limit of normal (ULN)
- SGOT/SGPT no greater than 2.5 times ULN
- Alkaline phosphatase no greater than 2.5 times ULN

Renal

- Creatinine no greater than 1.5 times ULN

Other

- Not pregnant
- Negative pregnancy test
- Fertile patients must use effective contraception
- No grade 2 or greater neuropathy (sensory or motor)
- No septicemia
- No severe infection
- No circumstance that would preclude study completion

PRIOR CONCURRENT THERAPY: Biologic therapy

- Not specified

Chemotherapy

- See Disease Characteristics

Endocrine therapy

- Not specified

Radiotherapy

- No prior radiotherapy to the abdomen or pelvis

Surgery

- Not specified

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More Information

Clinical trial summary from the National Cancer Institute's PDQ® database

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Record last reviewed: December 2004
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ClinicalTrials.gov Identifier: NCT00066456
Health Authority: United States: Federal Government
ClinicalTrials.gov processed this record on 2005-02-04

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