

# RADIATION THERAPY ONCOLOGY GROUP

## RTOG 99-01

### A PHASE III STUDY TO TEST THE EFFICACY AND SAFETY OF GM-CSF TO REDUCE THE SEVERITY AND DURATION OF MUCOSAL INJURY AND PAIN (*MUCOSITIS*) ASSOCIATED WITH CURATIVE RADIATION THERAPY IN HEAD AND NECK CANCER PATIENTS

**Study Chairman**

Francis LeVeque, D.D.S.  
Harper Hospital/Wayne State Univ.  
3990 John R, 4WS Core  
Detroit, MI 48201  
(313) 745-9300  
FAX (313) 745-9302  
[fleveque@med.wayne.edu](mailto:fleveque@med.wayne.edu)

Radiation Oncology

Charles Scarantino, M.D., Ph.D.  
(919) 784-3018  
FAX (919) 784-3180  
[cscarant@rad.rexhealth.com](mailto:cscarant@rad.rexhealth.com)

Medical Oncology

Roy Baynes, M.D., Ph.D.  
(313) 966-7432  
FAX (313) 966-7656  
[BaynesR@Karmanos.org](mailto:BaynesR@Karmanos.org)

Quality of Life

Darlene Johnson, MBA, CCRA  
(813) 979-3861  
FAX (813) 979-7231  
[johnson@moffitt.usf.edu](mailto:johnson@moffitt.usf.edu)

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#### SCHEMA

<b>S</b>		<b>R</b>	<b><u>Double-Blinded Randomization</u></b>
	<b><u>Concurrent Cisplatin</u></b>		
<b>T</b>		<b>A</b>	Radiation Therapy and GM-CSF, 250µg/m <sup>2</sup> sc
<b>R</b>	<b>1. No</b>	<b>N</b>	
	<b>2. Yes</b>		or
<b>A</b>		<b>D</b>	
<b>T</b>		<b>O</b>	Radiation Therapy and Placebo, sc
<b>I</b>		<b>M</b>	
<b>F</b>		<b>I</b>	
<b>Y</b>		<b>Z</b>	
		<b>E</b>	

#### **Eligibility:** (See Section 3.0 for details)

- Confirmed histopathologic diagnosis of head and neck carcinoma excluding T1-T2 glottic tumors, as long as treatment includes  $\geq 50\%$  of oral pharynx, oral cavity, or both. Neck metastases from an unknown primary are eligible if the dose to  $\geq 50\%$  of the salivary gland is  $\geq 50$  Gy.
- Karnofsky Performance Score  $\geq 60$
- No prior radiotherapy to the head and neck
- Planned irradiation to total dose 60-70 Gy at 1.8-2.0 Gy/day, five days a week for 6-7 weeks.
- Pregnant or lactating females are not eligible
- No T1 or T2 glottic tumors
- No history of allergy or idiosyncratic response to GM-CSF
- No residual oral/oropharyngeal mucosal injury from chemotherapy
- Not using any of these oral care medications during RT: Amifostine (*Ethyol*), Chlorhexidine Gluconate (*Peridex*), Sucralfate tablets or slurry (*Carafate*), Benzydamine HCL rinses, or selective decontamination of the oral cavity (*i.e.*, *IB-367*)
- Cannot be enrolled on other RTOG head and neck studies
- Other than concurrent cisplatin, no other chemotherapy agent is allowed
- Not HIV positive
- Signed study-specific consent form prior to randomization

**Required Sample Size: 126**

Institution # \_\_\_\_\_  
RTOG 99-01 \_\_\_\_\_  
Case # \_\_\_\_\_

**ELIGIBILITY CHECK (10/9/00)**  
*(page 1 of 2)*

- \_\_\_\_\_(Y) 1. Is there histological confirmation of squamous cell carcinoma of the head and neck?
- \_\_\_\_\_(Y) 2. Does the treatment include  $\geq 50\%$  of the oral pharynx, oral cavity or both?
- \_\_\_\_\_(N) 3. Has the patient had any prior irradiation to the head or neck?
- \_\_\_\_\_(Y) 4. Does planned irradiation equal a total dose of 60-70 Gy at 1.8 – 2.0 Gy/day, 5 days a week for 6-7 weeks?
- \_\_\_\_\_(N) 5. Is the patient pregnant or lactating?
- \_\_\_\_\_(N) 6. Does the patient have a T1 or T2 glottic tumor?
- \_\_\_\_\_(N) 7. Does the patient have any residual oral/oropharyngeal mucosal injury from chemotherapy?
- \_\_\_\_\_(N) 8. Does the patient have a history of allergy or idiosyncratic response to GM-CSF?
- \_\_\_\_\_(N) 9. Will the patient be using any of the following during RT: Ethyol, Peridex, Carafate, Benzydamine HCL rinses, or selective decontamination of the oral cavity, i.e., IB-367?
- \_\_\_\_\_( $\geq 60$ )10. What is KPS score?
- \_\_\_\_\_(N) 11. Is the patient HIV positive?
- \_\_\_\_\_(Y) 12. Is the patient willing and able to comply with the protocol?
- \_\_\_\_\_(N) 13. Is the patient on any other RTOG head and neck study?

**The following questions will be asked at Study Registration:**

- \_\_\_\_\_ 1. Name of institutional person registering this case?
- \_\_\_\_\_(Y) 2. Has the Eligibility Checklist (*above*) been completed?
- \_\_\_\_\_(Y) 3. Is the patient eligible for this study?
- \_\_\_\_\_ 4. Date the study-specific Consent Form was signed? (*must be prior to study entry*)
- \_\_\_\_\_ 5. Patient's Name
- \_\_\_\_\_ 6. Verifying Physician
- \_\_\_\_\_ 7. Patient's ID Number
- \_\_\_\_\_ 8. Date of Birth
- \_\_\_\_\_ 9. Race
- \_\_\_\_\_ 10. Social Security Number

(continued on page 2)

Institution # \_\_\_\_\_  
RTOG 99-01  
Case # \_\_\_\_\_

**ELIGIBILITY CHECK (10/9/00)**  
(page 2 of 2)

- \_\_\_\_\_ 11. Gender
- \_\_\_\_\_ 12. Patient's Country of Residence
- \_\_\_\_\_ 13. Zip Code
- \_\_\_\_\_ 14. Patient's Insurance Status
- \_\_\_\_\_ 15. Will any component of the patient's care be given at a military or VA facility?
- \_\_\_\_\_ 16. Treatment Start Date (*allow for shipping time, see Section 7.3.5*)
- \_\_\_\_\_ 17. Concurrent Cisplatin (*no vs. yes*)
- BLINDED** Treatment Assignment

Completed by \_\_\_\_\_

Date \_\_\_\_\_

## **1.0 INTRODUCTION**

### **1.1 Background**

Mucositis is that condition wherein mucosae suffers toxic damage from direct or indirect action of antineoplastic therapies at the basal layer of mucosal epithelium, on the luminal surface of the mucosa and on the cells between lumen and basement membrane. Additionally, mucosal damage must include other objective or subjective elements to qualify as mucositis, e.g., pain (*as in the case of oral mucositis*). Although mucositis can affect several tissues and organs such as the vulvovaginal tract, the term generally applies to the gastrointestinal tract.<sup>1</sup> Although traditional wisdom has related mucosal damage to alterations at the proliferative area of mucosal epithelium, other pathways may be involved with this occurrence as suggested by indirect evidence that suggests that cellular proliferation is not essential to luminal restitution of mucosal denudation (*ulceration*).<sup>2</sup> The incidence of mucositis varies among various anti-cancer modalities. Certain conditioning regimens in allogeneic bone marrow transplantation (*BMT*) can induce up to 85% high grade mucositis<sup>3</sup>, and the incidence in curative radiation therapy targeting tumors of the oral cavity and/or the oropharynx will approach 100%, often expressing  $\geq$  grade III mucositis (*RTOG scale*). Oral/oropharyngeal mucositis, a transient toxic event, whether incited from standard chemotherapy, myeloablative chemotherapy with BMT rescue, or from irradiation to the head and neck, can have long term consequences. The obvious desire to moderate this painful condition for improved patient well being can be accentuated by the opportunity to maintain or increase planned dosing to optimize local control and even survival (*See Section 1.3*).

### **1.2 Mucositis Studies**

Mucositis, whether induced from curative radiation therapy, or by action of one or more chemotherapeutic agents, persists as a major dose-limiting toxicity that frequently hampers optimal delivery of these therapies. The recognition that no defined strategies for preventing mucosal injury or lessening its severity has led cancer patient caregivers to institute a variety of palliative measures designed to reduce the intense symptoms of this common and serious toxicity. Several approaches were tried over the years; some of which continue to be used.<sup>4,5,6,7,8</sup> Although limited success was observed in pain moderation and improvements in inflammation with some of these procedures, to date, no agent has been granted *a priori* approval as a prevention or therapy for cytotoxic mucositis. Within the past few years, however, the scientific community has observed an exponential growth in the development of newly sequenced and isolated cellular proteins (*cytokines, growth factors, etc.*) for possible medical exploitation. The emerging knowledge required to further the processes involved with DNA sequencing and recombinant technology has contributed to, as well as benefited from, the explosive gains made in understanding molecular and cellular biology and, specifically, the ability to better define the diverse pathways of chemo-radiotoxic mucosal injury. Up to the mid-to-late 1990s, the standard explanation of the pathophysiology of cytotoxic mucosal injury related to alterations in the cell cycle of the basal epithelium. In 1992 epidermal growth factor (*EGF*), a proliferation cytokine, was used to treat mucositis *in vivo* by accelerating basal layer mitosis and (*presumably*) maturation with the expectation that mucositis would likely lessen; yet mucositis actually worsened. But later, Dignass et al.<sup>9</sup> were able to show in an *in vitro* model that EGF is also able to act as an epithelial restitution-promoting cytokine that has defined efficacy in healing intestinal mucosal cells independent of proliferative activity; this is consistent with the pleiotropism that often characterizes cytokine activity. At about the same time it was noted that bone marrow transplantation (*BMT*) patients who received granulocyte-macrophage colony stimulating factor (*GM-CSF*), had measurably less *indirect* mucositis, i.e., mucositis complicated with opportunistic bacterial, viral or fungal infections, than previously seen. The stated purpose for treating BMT patients with GM-CSF is to reduce the severity and duration of the absolute neutrophil count (*ANC*) nadir by support of the clonal expansion of "reserve" hematopoietic progenitor cells of erythroid, megakaryocytic and myeloid lineages. The use of GM-CSF has allowed for an overall reduction in neutropenia in BMT patients as well as the serendipitous lessening of mucositis-associated infection and sepsis. This latter event promoted the logically sound question of whether GM-CSF could moderate direct, cytotoxic mucositis. Both radiation and chemotherapy models have been addressed in a series of prospective trials. Chi et al.,<sup>10</sup> used GM-CSF ( $4 \mu\text{g}/\text{kg}$ ) to treat 17 patients with Stage IV squamous cell carcinoma of the head and neck who were scheduled to receive two identical courses of cisplatin, 5-fluorouracil and Leucovorin, in a crossover design trial. Patients were either *de novo*, or had completed surgical resection alone or with adjuvant radiation therapy. The study showed statistically significant improvement in both severity and duration of mucositis as graded by RTOG scoring. Later, Throuvalas et al.,<sup>11</sup> completed a comparative pilot study wherein 10 head and neck cancer patients ( $>T2N1M0$ ) were enrolled in either a group receiving RT + GM-CSF ( $1\mu\text{g}/\text{kg}/\text{day}$ , 7 days/week, starting on week 3 and continuing until end of RT), or RT alone; standard fractionation was used. The group receiving GM-CSF showed significant improvement in all measures as compared to the RT group alone. In 1997, Dunphy et al.<sup>12</sup> treated 10 patients with advanced head and neck cancer with GM-CSF ( $250 \mu\text{g}/\text{m}^2$  sc daily

for 7 days during week 1, then 3X/week for the remainder of RT, and 3X/week for one week post last dose of RT). The 10 treated patients were compared against 13 matched historical controls. Efficacy endpoints scored mucositis incidence, severity and incidence of radiation breaks. The GM-CSF group had 50% less severe mucositis and a 35% reduction in need for treatment breaks. No significant toxicity was reported in any of the three trials cited.

### **1.3 Quality of Life**

Over the past decade there has been a dramatic increase in the use of Quality of Life measurement in clinical trials. This has evolved from the growing interest and focus on supportive care and comprehensive health outcomes.<sup>13, 14</sup> Improving the quality of patients' lives has become as important as extending the quantity of life. The term, *quality of life*, refers to "a patient's appraisal of and satisfaction with their current level of functioning as compared to what they perceive to be possible or ideal".<sup>15</sup> Since the dimensions of quality of life are subjective, they are best measured from the patient's perspective.<sup>16, 17, 18</sup> Recent advances in cancer treatments for locally controlling cancers of the head and neck have prompted clinicians to turn their attention to supporting and preserving their patients' quality of life. Radiation therapy continues to be one of the primary modalities for treating head and neck cancers. Radiation-induced mucositis is a severe and ubiquitous acute complication of irradiation to the head and neck. It can produce pain, restrict nutritional intake, increase susceptibility to opportunistic infections, particularly fungal, and when severe, frequently initiates breaks in therapy that can occasion loss in local control of the disease. Put another way; if radiation therapy-induced mucositis could be prevented or, exhibit significantly less severity and shorter durations, local control of the tumor could be maintained or even improved were it possible to employ altered fractionation strategies with fewer breaks in therapy. It is assumed that the relief of a symptom is valued because of its benefit to a patient's functioning and well being. Equally important is evaluating the effectiveness of the intervention as it translates into improvement in the quality of life, (*e.g., less ambient pain, less functional pain, stable food intake & weight maintenance*). In this study the focus will be twofold: 1) to determine the impact of mucosal injury and pain on quality of life for patients receiving irradiation to the head and neck and, 2) the impact of symptom relief with GM-CSF as it relates to quality of life.

## **2.0 OBJECTIVES**

- 2.1 To reduce the severity of mucosal injury in the oral cavity and oropharynx as measured by an objective site-specific grading tool and standard National Cancer Institute Common Toxicity Criteria (*NCI-CTC*).
- 2.2 To reduce the expected duration of mucosal injury in the oral cavity and oropharynx.
- 2.3 To correlate quality of life improvement with reduced mucosal injury.

## **3.0 PATIENT SELECTION**

### **3.1 Eligibility Criteria**

- 3.1.1 Confirmed histologic diagnosis of head and neck carcinoma. excluding T1-T2 glottic tumors, as long as treatment includes 50% of oral pharynx, oral cavity, or both. Neck metastases from an unknown primary are eligible if the dose to  $\geq 50\%$  of the salivary gland is  $\geq 50$  Gy.
- 3.1.2 Planned external beam radiation delivered to the primary tumor, or standard ports for an unknown primary tumor; standard fractionation (*1.8-2.0 Gy/day/5 days/week*), 60-70 Gy total dose.
- 3.1.3 Karnofsky Performance Score  $\geq 60$  (*Appendix II*).
- 3.1.4 Patient must have undergone the objective site-specific mucosal assessment.
- 3.1.5 The patient must sign a study-specific informed consent prior to study entry (*Appendix I*).

### **3.2 Ineligibility Criteria**

- 3.2.1 Pregnant or lactating females are not eligible. Patients of childbearing potential should agree to use an effective method of contraception. The effects on the fetus of pleiotropic growth factor is unknown.
- 3.2.2 Patients with T1 or T2 glottic tumors.
- 3.2.3 Prior irradiation to the head and neck.
- 3.2.4 Allergy or idiosyncratic response to GM-CSF.
- 3.2.5 Residual oral/oropharyngeal mucosal injury from chemotherapy.
- 3.2.6 Use of the following oral care medications during course of RT:
  - Amifostine (*Ethyol*)
  - Chlorhexidine Gluconate (*Peridex*)
  - Sucralfate tablets or slurry (*Carafate*)
  - Benzydamine HCL rinses
  - Selective decontamination of the oral cavity, i.e. IB-367
- 3.2.7 HIV positive
- 3.2.8 Enrolled on other RTOG head and neck studies.

3.2.9 Any chemotherapy other than concurrent cisplatin.

#### **4.0 PRETREATMENT EVALUATION**

##### **4.1 Mandatory Evaluations** (*within 6 weeks prior to study entry*)

- 4.1.1 Complete history and physical examination.
- 4.1.2 Biopsy of primary tumor, or nodal diagnosis of an unknown primary tumor.
- 4.1.3 Diagram of lesion & nodes.
- 4.1.4 CT scan of oral cavity/oropharynx with standard slice increments.

##### **4.2 Mandatory Evaluations** (*within 1 week prior to study entry*)

- 4.2.1 Objective site-specific mucosal assessment.
- 4.2.2 Objective mucosal assessment (*NCI-CTC scale*).
- 4.2.3 Subjective assessment-ambient & functional pain, oral cavity/oropharynx/pharynx.
- 4.2.4 Pregnancy test for women of childbearing potential.

##### **4.3 Evaluations prior to any RT**

- 4.3.1 Dental examination (*may be performed by radiation oncologist*).
- 4.3.2 Complete QOL Head and Neck Symptom Questionnaire.
- 4.3.3 Baseline CBC and blood chemistry panel.

#### **5.0 REGISTRATION PROCEDURES**

- 5.1 Each institution must submit a typed Study Agent Shipment Form (*Appendix VI*) to RTOG headquarters prior to the randomization of its first case. Allow adequate processing time (*7-10 days*) before calling to register your first case.
- 5.2 Patients can be registered only after pretreatment evaluation is completed and eligibility criteria are met. Patients are registered prior to any protocol therapy by calling RTOG headquarters at (215) 574-3191, Monday through Friday 8:30 am to 5:00 p.m. ET. The patient will be registered to a treatment arm and a case number will be assigned and confirmed by mail. The Eligibility Checklist must be completed in its entirety prior to calling RTOG. The completed, signed and dated Checklist used at study entry must be retained in the patient's study file and will be evaluated during an institutional NCI/RTOG audit.

#### **6.0 RADIATION THERAPY**

- 6.1 *Field*: Treatment portals must include > 50% of the oral cavity/oropharynx, or both. This will insure inclusion of an adequate body of visible mucosa.
- 6.2 *Technique*: Oral cavity or oropharynx (*or both*) must be irradiated with opposed photon portals. Wedge-pair techniques that spare mucosa on one side will be excluded except when used to boost the primary tumor after delivery of a minimum dose of 60 Gy to mucosa. Patients may not be irradiated with homolateral electron beam or wedge-pair techniques.
- 6.3 *Dose*: Oral and oropharyngeal mucosa to receive a central axis midplane dose of 60 to 70 Gy over 6-7 weeks, 1.8 to 2 Gy once a day. Time of RT start must be documented in the treatment record.
- 6.4 *Equipment*: Cobalt 60, 4-6 MV x-rays or any combination of these megavoltage beams is acceptable.
- 6.5 *Blocks*: Portal margins may be collimated or shaped using cerrobend blocks or multileaves of a multileaf collimator.
- 6.6 *Compensating or wedge filters*: Compensating or wedge filters should be used to assure dose homogeneity throughout the irradiated volume that is  $\pm 5\%$  of the midplane central axis dose.
- 6.7 *Dose distribution*: A central axis distribution of radiation dose should be obtained.
- 6.8 All doses of GM-CSF must be given within two hours after RT.
- 6.9 *Dosimetry*: Copies of simulation films of each field and initial port films, the monitor unit calculation form, isodose distribution, treatment prescription, and treatment chart will be sent to RTOG Headquarters only if requested. Beam verification (*port*) films must be obtained for each field at least every 2 weeks during treatment and when any adjustments are made. Port films of each field will be submitted to the RTOG Headquarters only if specifically requested.

#### **7.0 DRUG THERAPY (DOUBLE BLINDED)**

##### **7.1 Granulocyte-Macrophage Colony Stimulating Factor (*rhu GM-CSF*)**

###### **7.1.1 Clinical Applications and Formulation (4/30/01)**

GM-CSF (*proprietary name: LEUKINE®*) is a glycoprotein that is FDA approved for use in promotion of hematopoietic reconstitution following autologous or allogeneic BMT for acute lymphocytic leukemia,

non-Hodgkin's lymphoma, and Hodgkin's disease, for myeloid reconstitution in patients undergoing allogeneic BMT, mobilization of peripheral blood stem cells (PBSC) and further myeloid reconstitution after PBSC transplantation, promotion of myeloid recovery in cases of failure or delay of engraftment following autologous and allogeneic BMT and accelerated time to neutrophil recovery, and severe and life-threatening infections in patients > 55 years of age with acute myelogenous leukemia. The specific activity of rhu GM-CSF is  $5.6 \times 10^6$  IU/mg. Each vial contains 40 mg mannitol, USP; 10 mg sucrose, NF; and 1.2 mg TRIS, USP, and 1.1% benzyl alcohol as a preservative. GM-CSF is produced by Immunex Corporation.

### 7.1.2 Pharmacokinetics and Metabolism

**7.1.2.1** Intravenous: Pharmacokinetic profiles of GM-CSF have been analyzed in controlled studies of 24 healthy male volunteers and 29 cancer patients receiving bone marrow or peripheral blood stem cell transplants. At the recommended dose of  $250 \mu\text{g}/\text{m}^2$ , liquid and lyophilized GM-CSF was compatible. When GM-CSF was administered IV over two hours, the mean beta half-life in healthy volunteers was approximately 60 minutes; in the transplant patients, the mean beta half-life of GM-CSF was 123 minutes. For all subjects, peak concentrations of GM-CSF were observed in blood samples obtained during or immediately after completion of GM-CSF infusion. The Cmax was 5.0-5.4 ng/mL in healthy volunteers and 17.2-26.4 ng/mL in transplant patients. The mean clearance rate was approximately 420-431 mL/min/ $\text{m}^2$  in healthy patients and 237-282 mL/min/ $\text{m}^2$  in transplant patients. GM-CSF was last detected in the 3hour or 6hour blood sample from healthy volunteers and was sometimes still detected at 8 hours, the last sampling interval, in transplant patients.

**7.1.2.2** Subcutaneous: When GM-CSF at a dose of  $250 \mu\text{g}/\text{m}^2$  was administered SC to healthy volunteers, it was detected in the serum at 15 minutes, the first sample point. The mean beta half-life was approximately 162 minutes. Peak levels occurred at 1 to 3 hours post injection, and GM-CSF remained detectable for up to 6 hours after injection. The mean Cmax was 1.5 ng/mL and mean clearance was 529-549 mL/min/ $\text{m}^2$ . The mean AUC (0-inf) was 501-549 ng/mL/min.

### 7.1.3 Reported Side Effects

Recombinant human GM-CSF is generally well tolerated after SC or IV administration at doses ranging between 50 and  $500 \mu\text{g}/\text{m}^2/\text{day}$ . Severe toxic manifestations are extremely rare in patients treated with yeast-derived GM-CSF in clinical studies. Diarrhea, asthenia, rash, and malaise were the only events observed more frequently in the GM-CSF group than in the placebo group in phase III controlled studies of patients undergoing bone marrow transplantation or peripheral blood stem cell transplantation for lymphoid malignancies. In a study of 399 subjects who were non-immunocompromised, subjects were randomized to receive either GM-CSF  $125 \mu\text{g}/\text{m}^2$ , and placebo for eight days via SC injection. GM-CSF was well tolerated and side effects, including fever were not significantly different from placebo. The only adverse events that occurred more frequently in the GM-CSF group than the placebo group were injection site reactions (3.5% vs. 0%,  $p=0.007$ ) and urticaria (2.5% vs. 0%,  $p=0.029$ ). These events were all mild (Grade 1-2), with the exception of a single case of severe (Grade 3) urticaria, which was treated with oral antihistamines. The concurrent use of GM-CSF with chemotherapy-radiotherapy was evaluated by Bunn et al.<sup>19</sup> in a cooperative group study investigating patients with small cell lung cancer. Significant increases in thrombocytopenia were noted as were other toxicities. However, as cited in references 10-12, GM-CSF did not produce any significant toxicities. Several other published studies using GM-CSF concurrently with radiation therapy alone, with chemotherapy alone, or in combination, have shown only mild toxicity.

### 7.1.4 Tumorigenicity of GM-CSF During Irradiation

In a murine model of lung metastasis (*Lewis Lung Carcinoma*), Guha et al.<sup>20</sup> looked at the effect of cytokines GM-CSF and Flt3L (*flat 3 ligand*) on the number of lung metastases when given concurrently with radiation therapy (RT). These two arms were compared to RT alone and to a control group of mice. The data show that RT + GM-CSF decreases metastases and improves short term (40 day) survival when compared to RT alone. Flt3L + RT decreases metastases and improves short and long term (70 day) survival. Of interest is that the GM-CSF group had fewer metastases than the longer surviving Flt3L group. This murine lung metastasis analysis has borne similar results in two other separate studies. Although the mechanism of action is not fully understood, the thought that angiostatin production may be induced is of significant interest.

NOTE: In these studies, metastases were measured by total lung weight in each group.

### **Survival Percent (8 mice / Treatment Group)**

	<b>Day 40</b>	<b>Day 70</b>	<b>Weight</b>
RT Alone	3/8 (38%)	0/8 (0%)	575 mg
RT + GM-CSF	8/8 (100%)	0/8 (0%)	337 mg
Ft3L + RT	8/8 (100%)	3/8 (38%)	431 mg
Normal Control	ND	ND	223 mg

## **7.2 Dosing**

**7.2.1** Patients randomized to GM-CSF 250 µg/m<sup>2</sup> or placebo SC will start one week prior to RT and stop two weeks after completion of RT. All doses are to be given within two hours after last daily RT fraction. Injections will be given on Mondays, Wednesdays and Fridays. The dose will be held, in all cases, on days patients are scheduled to receive concurrent chemotherapy.

**7.2.2** Patients must not miss more than 1 dose out of 6 consecutive doses during irradiation i.e., no more than one dose in a two week period if concurrent chemotherapy will not be given. If concurrent chemotherapy will be employed, the patient must not miss more than two doses out of 6 consecutive doses during irradiation. In the week prior to RT, patients must not miss more than 1 of 3 doses. In the two week period following RT (6 doses), patients must not miss more than 3 of 6 doses. All doses will be given by study personnel prior to patient's leaving the department. Dose, time, and site of injection must be recorded in the patient's record. A complete protocol treatment course is approximately 9 weeks.

## **7.3 Supplier, Distribution, and Study Agent Accountability**

### **7.3.1 Availability (4/30/01)**

GM-CSF and placebo will be supplied free of charge for this study by Immunex Corporation. Bacteriostatic water for reconstitution must be supplied by the participating site. Recombinant human GM-CSF is supplied as a lyophilized powder in vials containing 500 mcg of rhu GM-CSF protein.

### **7.3.2 Active ingredients are:**

- 40mg Mannitol, USP
- 10mg Sucrose, NF
- 1.2 mg Tromethamine, USP

The placebo control is a sterile lyophilized preparation containing only the inactive excipients. The storage, reconstitution and administration of placebo will be identical to that of rhu GM-CSF.

### **7.3.3 Stability and Storage**

Lyophilized product: vials of rhu GM-CSF should be stored refrigerated at 2-8°C (36-46°F). Do not freeze. Lyophilized drug is stable for at least 36 months at 2-8°C (36-46°F).

### **7.3.4 Reconstitution (4/30/01)**

Reconstitution of GM-CSF or placebo: aseptically inject 1.0 mL Bacteriostatic Water for injection, USP, containing 0.9% benzyl alcohol into the vial to dissolve the lyophilized powder. The diluent should be directed against the side of the vial and the contents gently swirled to avoid foaming during dissolution. Store at 2-8°C (36-46°F) in the original vials or in plastic syringes. The reconstituted solution is stable for at least 20 days at 2-8°C (36-46°F). Do not freeze after reconstitution. Do not filter during preparation or administration.

### **7.3.5 RTOG Institution Distribution**

Supplies of GM-CSF/placebo will be distributed to participating RTOG institutions. Each institution must submit a typed Study Agent Shipment Form (*Appendix VI*) to RTOG Headquarters prior to randomization of its first case. Allow adequate processing time (7-10 days) before calling to register your first case. Drug for randomizations assigned Monday-Wednesday between 8:30 a.m. and 2:30 p.m. ET will be shipped via overnight carrier to arrive the following business day. Drug for randomizations assigned Monday and Tuesday between 2:30 p.m. and 5:00 p.m. ET will be shipped the next day.

**Note: GM-CSF will only be shipped Monday through Wednesday. There will be no weekend or holiday delivery of drugs on or between December 22 and January 1. Please provide 2 days notice for request of drug prior to a holiday**

### **7.3.6 Drug Dispensers**

The drug dispenser containing 30 vials each of GM-CSF or placebo will be labeled with the treatment-specific double-blinded reference number, the RTOG patient/case number, the RTOG protocol number, the retest date and the lot number.

### **7.3.7 Vials**

Each vial will be labeled with the treatment-specific double-blinded reference number, the RTOG protocol number, the packaging lot number, the storage requirements, and all necessary information required by Federal Regulations. All vials shall be discarded in accordance with applicable federal and state laws and regulations. At the completion of the study, all unused vials shall be discarded in the same manner.

### **7.3.8 Study Agent Accountability**

The dosing records will be maintained by study personnel, as all doses will be given on-site after each radiation fraction. Drug accountability records should be kept according to NCI standards.

**7.4 Adverse Drug Reaction Reporting**

**7.4.1** The revised NCI Common Toxicity Criteria Version 2.0 (3/98) will be used to score chemotherapy and acute radiation (≤ 90 days) toxicities. The following guidelines for reporting adverse drug reactions (ADRs) apply to any research protocol that uses commercial anticancer agents. The following ADRs experienced by patients accrued to these protocols and attributed to the commercial agent(s) should be reported to the Investigational Drug Branch, Cancer Therapy Evaluation Program, within 10 working days. This study will be monitored by the Clinical Data Update System (CDUS) version 1.X. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31.

**7.4.1.1** Any ADR which is both serious (*life threatening, fatal*) and unexpected.

**7.4.1.2** Any increased incidence of a known ADR which has been reported on the package insert or the literature.

**7.4.1.3** Any death on study if clearly related to the commercial agent(s)

**7.4.2** The ADR report should be documented on Form FDA 3500 and mailed to the address on the form, to RTOG Headquarters and to:

**Investigational Drug Branch  
P.O. Box 30012  
Bethesda, MD 20824  
(301) 230-2330  
Available 24 hours  
Fax (301) 230-0159**

**8.0 SURGERY**

Not applicable to this study.

**9.0 OTHER THERAPY**

The use of concurrent cisplatin chemotherapy will be a stratification component. Details of dose/regimen will be recorded on the data forms.

**10.0 PATHOLOGY**

Not applicable to this study

**11.0 PATIENT ASSESSMENTS**

**11.1 Patient Evaluations**

Assessment	Pre Rx	During Rx	At Follow-up See Section 12.0
Complete history, P & E	X		X
KPS and weight	X	X <sup>c</sup>	X
Biopsy	X		X <sup>a</sup>
CT oral cavity/oropharynx	X		
Dental evaluation	X		
Tumor diagram	X <sup>b</sup>		
QOL Assessment	X	X <sup>d</sup>	X <sup>e</sup>
Mucosal Assessment	X	X <sup>f</sup>	X <sup>g</sup>
CBC	X	X <sup>c</sup>	X <sup>h</sup>
Chemistry Panel	X	X <sup>d</sup>	X <sup>h</sup>
Use of Narcotics		X <sup>i</sup>	
Pregnancy test	X <sup>b</sup>		
Toxicity Evaluation		X <sup>c</sup>	X

a. For confirmation of recurrent tumor in head and neck as applicable.

b. As applicable.

- c. Weekly.
- d. Week 4 of RT.
- e. At 3, 6 and 12 months from start of RT.
- f. Mondays, Wednesdays and Fridays during RT.
- g. At 2 weeks post RT.
- h. At conclusion of RT (*within 5 days*).
- i. By prescriptive records.

**11.2 Evaluations (during the course of RT)**

- 11.2.1 Oral care (*not using any of these oral care medications during RT: Pilocarpine tablets [Salagen], Chlorhexidine Gluconate [Peridex], and Sucralfate tablets or slurry [Carafate]*).
- 11.2.2 Narcotic use.
- 11.2.3 Weekly CBC and within 5 days after the end of RT.
- 11.2.4 Blood chemistry panel at midpoint of RT therapy.
- 11.2.5 Blood chemistry panel at the conclusion of RT.

**11.3 Mucosal Reaction**

- 11.3.1 *Objective Scoring:* Visual signs of radiation-induced mucosal damage will be independently assessed three times a week during the course of radiation therapy by the radiation oncologist or other trained study personnel. Both the NCI-CTC and the protocol-specific scoring systems will be used (*Appendix IV*). Separate assessments will be made of sites within the radiation volume as applicable; labial mucosa, buccal mucosal, dorsum & lateral borders of the tongue, ventral tongue & floor of mouth, hard palate & gingivae, soft palate & fauces and alveolar ridge.

**12.0 DATA COLLECTION**

*(RTOG, 1101 MARKET STREET, PHILADELPHIA, PA 19107, FAX# 215.928.0153)*

<u>Item</u>	<u>Due</u>
Demographic Forms (A5) Initial Evaluation form (I1) Diagnostic Pathology Report (P1) Primary Site Staging Worksheet (I6) Nodal Site Staging Worksheet (I7) Pretreatment Symptom Scale Questionnaire (QL)	Within 2 weeks of study entry
Radiotherapy Form (T1)	Within 1 week after end of RT
Tissue Reaction Form (F2) <i>(Must include pretreatment baseline assessments)</i>	Within 2 weeks after completion or termination of RT, and at 13 and 26 weeks
Study Specific Flowsheet (SF)	At 4 weeks and within 3 weeks after completion of RT
Follow-up Symptom Scale Questionnaire (SS)	At 4,13, 26 and 48 weeks from start of RT
Initial Follow-up Form (FS)	At 13 weeks
Follow-up Form (F1)	At 26 and 48 weeks from start of RT

**13.0 STATISTICAL CONSIDERATIONS**

**13.1 Study Endpoints**

- 13.1.1 The primary endpoint of this trial is the severity and duration of acute mucositis.
- 13.1.2 The secondary endpoint is the quality of life as measured using the University of Washington Head and Neck Symptom Questionnaire.

**13.2 Sample Size**

**13.2.1 Mucositis Endpoint**

The primary endpoint of this trial is the severity of acute radiation mucositis. This endpoint will be measured using the mucositis scoring system, which concentrates on erythema and ulceration. This instrument has been validated<sup>21</sup> and shown to be reliable when investigators have been trained in its usage. The mucositis scoring system separately evaluates erythema and ulceration in multiple anatomical

sites within the oral cavity and oropharynx. Sample size will be estimated based upon mean mucositis score (*sum of average erythema and average ulceration*). The mean score will be taken over the acute toxicity period (*i.e. 90 days from the start of radiation therapy*). It is expected that an average difference in mucositis score of 0.6 between the placebo and GM-CSF arms will be clinically meaningful. If the standard deviation is 1.0 then the study will have at least 90% statistical power to detect an average mucositis decrease of 0.6 between the two patient groups at the 0.05 (*two-sided*) significance level. It is estimated that 60 evaluable patients per arm will be required. Assuming that 5% of patients enrolled will be ineligible or inevaluable, then **the required sample size is 126 patients**.

13.2.2 In RTOG 85-27 the incidence of acute radiation mucositis was:

**Grade of Mucositis**

0	1	2	3	4
14%	22%	45%	18%	1%

This is the worst severity observed in either the pharynx, palate, tongue, or buccal tissues within 90 days from the start of radiotherapy. These toxicities were graded using the RTOG Acute Radiation Morbidity Scale which is equivalent to the new NCI Common Toxicity Criteria for radiation-induced mucositis. Assuming that the application of GM-CSF during and post radiotherapy reduces the incidence of grade 2-4 mucositis by 50%, then the estimate incidence is 32% on the GM-CSF arm. Setting the significance level at 0.05 and statistical power at 90% the estimated sample size is 56 patients per arm.

13.2.3 Quality of Life Endpoint

The possible benefit of GM-CSF is the reduction of mucositis toxicity; however, what value is this to the patient? Another endpoint of this trial is assessing the difference in quality of life among patients randomized to the two treatments. The University of Washington Head and Neck Symptom Questionnaire summary score (*HNSS*) will be the primary variables of interest in assessing quality of life.<sup>25</sup> With 120 evaluable patients there will be greater than 90% power to detect an average difference of 5 points in HNSS at 90 days from the start of radiotherapy between the two treatments adjusted for their baseline value.

13.2.4 Patient Accrual

The following table displays the length of time necessary to accrue 126 patients given different average monthly accruals.

**Average Monthly Accrual Time to Accrue 126 Patients**

12.0	11 months
11.0	1 year
10.0	1.1 years
9.0	1.2 years
8.0	1.4 years

The average monthly accrual is expected to be 9 patients per month, thus it will take 1.2 years to complete the accrual phase of the study. However, if the monthly accrual is less than five patients per month, the feasibility will be re-evaluated.

13.2.5 Randomization Scheme

The treatment allocation will be done using a randomized permuted block within strata to balance patient factors other than institution. There will be a check on the balance of treatment assignments within each institution. Patients will be assigned with equal probability to each treatment by the RTOG.

13.2.6 Inclusion of Women and Minorities

In conformance with the National Institutes of Health (*NIH*) Revitalization Act of 1993 with regard to inclusion of women and minorities in clinical research, we make the following observations. The recursive partitioning analysis of the RTOG database for patients entered into operable head and neck trials failed to show any treatment interaction with gender.<sup>22</sup> Analysis of the operable Intergroup Study 0034 and RTOG 88-24 also failed to show a treatment interaction with gender.<sup>23</sup> No information about race was collected in the RTOG Registry study and treatment studies prior to 1990. The SEER data suggest a difference in outcome by race. In a retrospective analysis, no difference in outcome for patients treated for laryngeal cancer at a single institution was reported.<sup>24</sup> The RTOG Special Population Committee is unaware of any other published data on patients with clinically localized head and neck cancer. Since there are no publications found to support a possible interaction between different radiation therapy

schedules and either gender or race, the sample size will remain the same. The sample size will be represented as follows:

**Planned Gender and Minority Inclusion**

	American Indian or Alaskan Native	Asian or Pacific Islander	Black, not of Hispanic Origin	Hispanic	White, not of Hispanic Origin	Other or Unknown	Total
Female	0	1	6	1	22	0	30
Male	0	2	34	10	49	1	96
Unknown	0	0	0	0	0	0	0
Total	0	3	40	11	71	1	126

**13.3 Analysis Plans**

**13.3.1 Interim Analyses of Accrual and Toxicity Data**

Interim reports with statistical analyses will be prepared every six months until the initial paper reporting the treatment results has been submitted. In general the interim reports will contain information about:

- a) The patient accrual rate with projected completion date for the accrual phase.
- b) The distribution of patients with respect to pretreatment characteristics.
- c) Compliance rate of treatment delivery with respect to the protocol prescription.
- d) The frequency and severity of the toxicities not separated by treatment arm.

**13.3.2 Interim Analyses of Primary Study Endpoints**

There will be three interim analyses of acute radiation mucositis toxicity and quality of life. The interim analyses will proceed according to the table below after all patients have been followed for three months. All endpoints will be tested independently at these significance levels.

<u>Total Accrual</u>	<u>Significance Level</u>
25%	0.003
50%	0.004
75%	0.0049
100%	0.046 ( <i>final analysis</i> )

If any of the interim analyses exceed the listed significance level, which were calculated to ensure an overall significance level of 0.05, then accrual will be terminated. The results of these interim analyses will be reported in a blinded fashion, only to RTOG data monitoring committee as privileged communications. A report with recommendations will be given to the study chairman. Any problems or recommendations identified by the data monitoring committee, not results, will be reported to the cancer control committee which is responsible for this study, and, if necessary, the CCOP and RTOG Executive Committees, so that corrective action can be taken.

**13.3.3 Analyses and Reporting of Initial Treatment Results**

The major analysis will be undertaken when each patient has been potentially followed for a minimum of three months. The usual components of this analysis are:

- a) tabulation of all cases entered and any excluded from the analysis with the reasons for such exclusions
- b) reporting institutional accrual
- c) distribution of the important prognostic factors by assigned treatment
- d) observed results with respect to the study endpoints
  - i) acute mucositis will be evaluated using the modified T-score as suggested by Sonis et al.<sup>21</sup>
  - ii) the worst mucositis score is commonly reported in the literature and will be reported in this study. Comparisons of the distribution of worst mucositis score will be performed by the Wilcoxon statistic.
  - iii) The primary quality of life endpoint will occur at the end of the acute toxicity period. Difference at three months and pretreatment values will be computed and comparisons between treatment arms will be performed using either the two-sample t-test or Wilcoxon test depending upon distributional assumptions.
  - iv) Other secondary endpoints may be investigated in an exploratory fashion. The two-sided p-value of 0.046 will be used for comparing treatment arms, thus correcting for previous interim tests.

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## **APPENDIX I**

### **RTOG 99-01**

#### **SAMPLE CONSENT FOR RESEARCH STUDY**

##### **STUDY TITLE**

##### **A PHASE III STUDY TO TEST THE EFFICACY AND SAFETY OF GM-CSF TO REDUCE THE SEVERITY AND DURATION OF MUCOSAL INJURY AND PAIN (*MUCOSITIS*) ASSOCIATED WITH CURATIVE RADIATION THERAPY IN HEAD AND NECK CANCER PATIENTS**

This is a clinical trial (*a type of research study*). Clinical trials include only patients who choose to take part. Please take your time to make your decision. Discuss it with your friends and family. The National Cancer Institute (*NCI*) booklet “Taking Part in Clinical Trials: What Cancer Patients Need to Know” is available from your doctor.

You are being asked to take part in this study because you have head and neck cancer.

##### **WHY IS THIS STUDY BEING DONE?**

Radiation therapy has been recommended to treat your cancer. One of the possible side effects of radiation therapy to the head and neck is the development of mouth sores. This condition (*radiation mucositis*) can produce redness and painful ulcers. It can interfere with eating and even talking for a period of several weeks during the radiation.

The purpose of this study is to see whether GM-CSF given during radiation will be able to reduce the severity of the mucositis and its duration. Previous, but as yet unproved, studies have shown that radiation mucositis (*mouth soreness*) may be lessened by taking GM-CSF (*a growth factor*) during the radiation therapy. GM-CSF is an approved drug for treating low white counts in blood in patients who have been given chemotherapy. The study will compare the effects (*good and bad*) of the GM-CSF with placebo (*inactive agent*) on you when used with radiation. In addition, this study will attempt to see how you view the quality of your life before treatment, during treatment, at the end of treatment and at intervals afterwards.

##### **HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?**

About 126 people will take part in this study.

##### **WHAT IS INVOLVED IN THE STUDY?**

You will be “randomized” into one of the study groups described below. Randomization means that you are put into a group by chance. It is like flipping a coin. Which group you are put in is done by a computer. Neither you nor the researcher will choose what group you will be in. You will have an equal chance of being placed in either group. You will be assigned to one of the following:

- Group 1: If you are assigned to this group, you will receive GM-CSF subcutaneously (*just under the skin in your arm or thigh*) beginning one week before starting radiation therapy. The injections will stop two

weeks after the end of radiation therapy. The injections will be given on Mondays, Wednesdays and Fridays. If you are scheduled to receive chemotherapy along with the radiation therapy, the dose of GM-CSF will not be given on days you receive chemotherapy.

- **Group 2:** If you are assigned to this group, you will receive a placebo (*an inactive subcutaneous injection in your arm or thigh*) beginning one week before starting radiation therapy. The injection will stop two weeks after completion of the radiation therapy. The injections will be given on Mondays, Wednesdays and Fridays. If you are scheduled to receive chemotherapy along with the radiation therapy, the doses of placebo will not be given on days you receive chemotherapy.

Both GM-CSF and placebo will be supplied free of charge for study use.

The lining of your mouth, lips, cheeks, tongue, palate, gums and denture-bearing areas will be examined by your physician or one of the research staff. They will check you before the first radiation treatment and then three times a week throughout the radiation therapy. After completion of the radiation therapy, you will be examined again by the research staff with a bright penlight. Changes noted will be marked on a scoring sheet. Other evaluations include:

Before Study Entry: physical exam, tumor biopsy, CT scan of the head, blood work, pregnancy test (*as appropriate*), and baseline quality of life forms.

During and After Treatment: physical exams (*weekly for 6 weeks*), recording of other medications, quality of life forms will be completed at 3, 6, and 12 months from start of radiation therapy. If your doctor thinks the tumor has come back, you may need to have the suspicious area biopsied.

### **HOW LONG WILL I BE IN THE STUDY?**

We think you will be in the study between 8 and 10 weeks depending on the length of your radiation treatment. After your treatment is finished, your doctor will examine you at 3 months, then 3 months later, and finally 5 months after that.

Your doctor may decide to take you off this study if your mucositis becomes worse, if the side effects become very severe, if new scientific developments occur that indicate this research study is not in your best interest, if your physician feels that this study is no longer in your best interest or the sponsor may withdraw support for the study.

You can stop participating at any time. However, if you decide to stop participating in the study, we encourage you to talk to the researcher and your regular doctor first. There are no known serious consequences of sudden withdrawal from the study. Your radiation therapy may be continued to completion if medically appropriate.

### **WHAT ARE THE RISKS OF THE STUDY?**

Cancer treatments, whether given in a research study or in the ordinary practice of medicine, may often hurt or harm you (*side effects*). While on the study, you are at risk for these side effects. You should discuss these with the researcher and/or your regular doctor. This study may cause all, some, or none of the side effects listed. In addition, there is always the risk of very uncommon or previously unknown side effects occurring.

*GM-CSF Risks:* Drugs often have side effects. The drug used in this study, GM-CSF, is a Food and Drug Administration (FDA) approved agent for treating low white blood cell counts following bone marrow transplantation for treatment of acute leukemia, Hodgkin's disease and other related diseases. All side effects of this drug may not be known. Severe side effects are rare in patients treated with GM-CSF. Patients receiving GM-CSF have experienced fever; chills; nausea; vomiting; diarrhea; fatigue; weakness; headache; decreased appetite; blood clots; rapid or irregular heartbeat or other heart problems; feeling of faintness; facial flushing; pain in the bones, muscles, chest, abdomen, or joints; local reaction at the site of injection; rashes; and kidney and liver abnormalities. Changes in the number of white blood cells may occur.

There have been infrequent reports of fluid accumulation or worsening of pre-existing fluid accumulation in the extremities, in the lungs, and around the heart that may result in breathing problems or heart failure. Rarely, patients have developed acute allergic reactions. There have also been reports of low blood pressure, hypoxia, transient loss of consciousness, and difficulty in breathing after the first injection of GM-CSF. These signs may or may not recur with additional injections of GM-CSF. Patients with prior heart, lung, kidney, or liver problems may have worsening of their symptoms following administration of GM-CSF.

Your physician will be checking you closely to see if any of these side effects are occurring. Patients who have taken GM-CSF for several months have tolerated it well. Side effects usually disappear after the study treatment is stopped. In the meantime, your doctor may prescribe other drugs to make side effects less serious and uncomfortable.

*Placebo Risks:* In a small percentage of patients, injection of placebo may result in reactions at the site of the injections under the skin. Injection site reactions with placebo include redness, pain swelling, or itching.

*Reproductive Risks:* This study may be harmful to an unborn child. Little medical information is available to determine whether the study treatment administered to a pregnant woman causes significant risks to the fetus. If you are a woman of childbearing age and have not been surgically sterilized (*tubal ligation or hysterectomy*), you should have a pregnancy test before enrolling in this study. You must use adequate birth control measures to prevent pregnancy while participating in this study. If you are unwilling to use adequate birth control measures to prevent pregnancy, you should not participate in this study. If you should become pregnant while on this study, you must tell your doctor immediately.

## **ARE THERE BENEFITS TO TAKING PART IN THE STUDY?**

If you agree to take part in this study, there may or may not be direct medical benefit to you. You may benefit by having less severe and a shorter duration of mucositis and the pain associated with mucositis of the tissues that line your cheeks, lips, tongue and palate during radiation therapy. This may reduce your need for pain medication during radiation and allow you to continue the radiation therapy without delays. We hope the information learned from this study will benefit other patients with head and neck cancer in the future.

## **WHAT OTHER OPTIONS ARE THERE?**

Instead of being in this study you have these options:

Symptom management therapies are permissible while on study such as management of pain with pain medications, oral medication and elixirs for mouth care. The alternatives to participation in this trial include use

of pain medicine and oral care as needed, avoiding hot and spicy foods, or participation in trials involving other experimental therapies.

Your doctor can tell you more about your condition and the possible benefits of the different available interventions. You should discuss your condition and the expected outcome with your doctor. Your doctor will be available to answer any questions. You are encouraged to ask your doctor any questions you have about this research study and the choices of treatment available to you. If you have any questions at all, please ask your doctor.

### **WHAT ABOUT CONFIDENTIALITY?**

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality, however, the central computer record is carefully guarded. Your personal information may be disclosed if required by law.

Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as the Food and Drug Administration (*FDA*), the National Cancer Institute (*NCI*), qualified representatives of applicable drug manufacturers, and other groups or organizations that have a role in this study. Records of your progress while on the study will be kept in a confidential form at this institution and in a computer file at the headquarters of the Radiation Therapy Oncology Group (*RTOG*).

### **WHAT ARE THE COSTS?**

Taking part in this study may lead to added costs to you or your insurance company. Please ask about any expected added costs or insurance problems.

In the case of injury or illness resulting from this study, emergency medical treatment is available but will be provided at the usual charge. No funds have been set aside to compensate you in the event of injury.

You or your insurance company will be charged for continuing medical care and/or hospitalization.

You will receive no payment for taking part in this study.

### **WHAT ARE MY RIGHTS AS A PARTICIPANT?**

Taking part in this study is voluntary. You may choose to not take part or may leave the study at any time. Leaving the study will not result in any penalty or loss of benefits to which you are entitled.

We will tell you about new information that may affect your health, welfare, or willingness to stay in this study.

A Data Safety and Monitoring Board, an independent group of experts, will be reviewing the data from this research. We will tell you about the new information from this or other studies that may effect your health, welfare, or willingness to stay in this study.

**WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?**

*(This section must be completed)*

For information about your disease and research-related injury, you may contact:

\_\_\_\_\_  
Name

\_\_\_\_\_  
Telephone Number

For information about this study, you may contact:

\_\_\_\_\_  
Name

\_\_\_\_\_  
Telephone Number

For information about your rights as a research subject, you may contact:

*(OPRR suggests that this person not be the investigator or anyone else directly involved with the research)*

\_\_\_\_\_  
Name

\_\_\_\_\_  
Telephone Number

**WHERE CAN I GET MORE INFORMATION?**

You may call the NCI's **Cancer Information Service at 1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615** or visit the NCI's Web sites for comprehensive clinical trials information <http://cancertrials.nci.nih.gov> or <http://cancernet.nci.nih.gov>.

**SIGNATURE**

**I have read all the above, asked questions, and received answers concerning areas I did not understand. I have had the opportunity to take this consent form home for review or discussion.**

**I willingly give my consent to participate in this program. Upon signing this form I will receive a copy. I may also request a copy of the protocol (*full study plan*).**

\_\_\_\_\_  
Participant

\_\_\_\_\_  
Date

## APPENDIX II

### **KARNOFSKY PERFORMANCE SCALE**

100	Normal; no complaints; no evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of disease
80	Normal activity with effort; some sign or symptoms of disease
70	Cares for self; unable to carry on normal activity or do active work
60	Requires occasional assistance, but is able to care for most personal needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospitalization is indicated, although death not imminent
20	Very sick; hospitalization necessary; active support treatment is necessary
10	Moribund; fatal processes progressing rapidly
0	Dead

### **ZUBROD PERFORMANCE SCALE**

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

## APPENDIX III

### AJCC STAGING HEAD & NECK, 5<sup>th</sup> Edition

#### STAGING-PRIMARY TUMOR (T)

- TX Primary tumor cannot be assessed
- T0 No evidence of primary tumor
- T<sub>is</sub> Carcinoma *in situ*

#### ORAL CAVITY

- Buccal mucosa
- Lower alveolar ridge
- Upper alveolar ridge
- Retromolar gingiva (*Retromolar trigone*)
- Floor of mouth
- Hard palate
- Anterior two-thirds of the oral tongue

- T1 Tumor 2 cm or less in greatest dimension
- T2 Tumor more than 2 cm but not more than 4 cm in greatest dimension
- T3 Tumor more than 4 cm in greatest dimension
- T4 Tumor invades adjacent structures (*e.g. through cortical bone, into deep [extrinsic] muscle of tongue, maxillary sinus, skin. Superficial erosion of bone/tooth socket by gingival primary is not sufficient to classify as T4*).

#### PHARYNX

##### **Nasopharynx**

- Postero-superior walls
- Lateral walls
- Inferior (*anterior*) wall, consists of the superior surface of the soft palate

- T1 Tumor confined to the nasopharynx
- T2 Tumor extends to soft tissues of oropharynx and or nasal fossa
  - T2a without parapharyngeal extension
  - T2b with parapharyngeal extension
- T3 Tumor invades bony structures and/or paranasal sinuses
- T4 Tumor with intracranial extension and/or involvement of cranial nerves, infratemporal fossa, hypopharynx, or orbit.

##### **Oropharynx**

- Faucial arch including soft palate, uvula and anterior tonsillar pillar
- Glossotonsillar sulci and pharyngeal tonsils
- Base of tongue
- Pharyngeal wall including lateral and posterior walls and posterior tonsillar pillar

- T1 Tumor 2 cm or less in greatest dimension
- T2 Tumor more than 2 cm but not more than 4 cm in greatest dimension
- T3 Tumor more than 4 cm in greatest dimension
- T4 Tumor invades adjacent structures (*e.g. pterygoid muscle[s], mandible, hard palate, deep muscle of tongue, larynx*)

## **Hypopharynx**

Pyramidal fossae  
Postcricoid region  
Lateral and posterior hypopharyngeal walls

- T1 Tumor limited to one subsite of hypopharynx and 2 cm or less in greatest dimension.
- T2 Tumor invades more than one subsite of hypopharynx or an adjacent site, or measures more than 2 cm but not more than 4 cm in greatest diameter without fixation of hemilarynx.
- T3 Tumor measures more than 4 cm in greatest dimension or with fixation of hemilarynx.
- T4 Tumor invades adjacent structures (*e.g. thyroid/cricoid cartilage, carotid artery, soft tissues of neck, prevertebral fascia/muscles, thyroid and/or esophagus*).

## **LARYNX**

### **Supraglottis**

Suprahyoid epiglottis  
Infrahyoid epiglottis  
Aryepiglottic folds (*laryngeal aspect*)  
Ventricular bands (*false cords*)  
Arytenoids

- T1 Tumor limited to one subsite of supraglottis with normal vocal cord mobility
- T2 Tumor invades mucosa of more than one adjacent subsite of supraglottis or glottis or region outside the supraglottis (*e.g., mucosa of base of tongue, vallecula, medial wall of pyriform sinus*) without fixation of the larynx.
- T3 Tumor limited to larynx with vocal cord fixation and/or invades any of the following: postcricoid area, pre-epiglottic tissues.
- T4 Tumor extends through the thyroid cartilage, and/or extends into soft tissues of the neck, thyroid and/or esophagus.

### **Glottis**

True vocal cords including anterior and posterior commissures

- T1 Tumor limited to the vocal cord(s) (*may involve anterior or posterior commissures*) with normal mobility
  - T1a Tumor limited to one vocal cord
  - T1b Tumor involves both vocal cords
- T2 Tumor extends to supraglottis and/or subglottis and/or with impaired vocal cord mobility
- T3 Tumor limited to the larynx with vocal cord fixation
- T4 Tumor invades through thyroid cartilage and/or extends to other tissues beyond the larynx (*e.g., trachea, soft tissues of neck including thyroid, pharynx*)

### **Subglottis**

- T1 Tumor limited to the subglottis
- T2 Tumor extends to vocal cord(s) with normal or impaired mobility
- T3 Tumor limited to larynx with vocal cord fixation
- T4 Tumor invades through cricoid or thyroid cartilage and/or extends to other tissues beyond the larynx (*e.g. trachea, or soft tissues of the neck including thyroid, esophagus*)

## **REGIONAL LYMPH NODES (N) Excluding Nasopharynx**

- NX Regional lymph nodes cannot be assessed
- N0 No regional lymph node metastasis
- N1 Metastasis in a single ipsilateral node, 3 cm or less in greatest dimension.

- N2 Metastasis in a single ipsilateral node, more than 3 cm, but not more than 6 cm in greatest dimension or multiple ipsilateral lymph nodes, none greater than 6 cm in greatest dimension, or bilateral or contralateral nodes, none more than 6 cm in greatest dimension.
  - N2a Metastasis in a single ipsilateral node more than 3 cm, but not more than 6 cm in greatest dimension.
  - N2b Metastasis in multiple ipsilateral nodes, none more than 6 cm in greatest dimension.
  - N2c Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension.
- N3 Metastases in a lymph node more than 6 cm in greatest dimension.

**REGIONAL LYMPH NODES (N) Nasopharynx Only**

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

**DISTANT METASTASIS (M)**

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

**STAGE GROUPING Excluding Nasopharynx**

**STAGE GROUPING Nasopharynx**

Stage 0	Tis, N0, M0	Stage 0	Tis, N0, M0
Stage I	T1, N0, M0	Stage I	T1, N0, M0
Stage II	T2, N0, M0	Stage IIA	T2a, N0, M0
Stage III	T3, N0, M0 T1-3, N1, M0	Stage IIB	T1-T2a, N1, M0 T2b, N0-1, M0
Stage IVA	T4, N0-1, M0 Any T, N2, M0	Stage III	T1-T2b, N2, M0 T3, N0-2, M0
Stage IVB	Any T, N3, M0	Stage IVA	T4, N0-2, M0
Stage IVC	Any T, Any N, M1	Stage IVB	Any T, N3, M0
		Stage IVC	Any T, Any N, M1

RTOG/EORTC Late Radiation Morbidity Scoring Scheme					APPENDIX IV
ORGAN TISSUE	0	GRADE 1	GRADE 2	GRADE 3	GRADE 4
SKIN	None	Slight atrophy; Pigmentation change; Some hair loss	Patch atrophy; Moderate telangiectasia; Total hair loss	Marked atrophy; Gross telangiectasia	Ulceration
SUBCUTANEOUS TISSUE	None	Slight induration (fibrosis) and loss of subcutaneous fat	Moderate fibrosis but asymptomatic; Slight field contracture; <10% linear reduction	Severe induration and loss of subcutaneous tissue; Field contracture > 10% linear measurement	Necrosis
MUCOUS MEMBRANE	None	Slight atrophy and dryness	Moderate atrophy and telangiectasia; Little mucous	Marked atrophy with complete dryness; Severe telangiectasia	Ulceration
SALIVARY GLANDS	None	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
SPINAL CORD	None	Mild L'Hermitte's syndrome	Severe L'Hermitte's syndrome	Objective neurological findings at or below cord level treated	Mono, para quadriplegia
BRAIN	None	Mild headache; Slight lethargy	Moderate headache; Great lethargy	Severe headaches; Severe CNS dysfunction (partial loss of power or dyskinesia)	Seizures or paralysis; Coma
EYE	None	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
LARYNX	None	Hoarseness; Slight arytenoid edema	Moderate arytenoid edema; Chondritis	Severe edema; Severe chondritis	Necrosis
LUNG	None	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 O2/Assisted ventilation
HEART	None	Asymptomatic or mild symptoms; Transient T wave inversion & ST Changes; Sinus tachycardia >110 (at rest)	Moderate angina on effort; Mild pericarditis; Normal heart size; Persistent abnormal T wave and ST changes ; Low ORS	Severe angina; Pericardial effusion; Constrictive pericarditis; Moderate heart failure; Cardiac enlargement; EKG abnormalities	Tamponade/Severe heart failure/Severe constrictive pericarditis
ESOPHAGUS	None	Mild fibrosis; Slight difficulty in swallowing solids; No pain on swallowing	Unable to take solid food normally; Swallowing semi-solid food; Dilation may be indicated	Severe fibrosis; Able to swallow only liquids; May have pain on swallowing Dilation required	Necrosis/Perforation Fistula
SMALL/LARGE INTESTINE	None	Mild diarrhea; Mild cramping; Bowel movement 5 times daily Slight rectal discharge or bleeding	Moderate diarrhea and colic; Bowel movement >5 times daily; Excessive rectal mucus or intermittent bleeding	Obstruction or bleeding, requiring surgery	Necrosis/Perforation Fistula
LIVER	None	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
KIDNEY	None	Transient albuminuria; No hypertension; Mild impairment of renal function; Urea 25-35 mg%;Creatinine 1.5-2.0 mg%; Creatinine clearance > 75%	Persistent moderate albuminuria (2+); Mild hypertension; No related anemia; Moderate impairment of renal function; Urea > 36-60mg% Creatinine clearance (50-74%)	Severe albuminuria; Severe hypertension Persistent anemia (< 10%); Severe renal failure; Urea >60 mg% Creatinine >4.0 mg% Creatinine clearance < 50%	Malignant hypotension; Uremic coma/Urea > 100%
BLADDER	None	Slight epithelial atrophy; Minor telangiectasia (microscopic hematuria)	Moderate frequency; Generalized telangiectasia; Intermittent macroscopic hematuria	Severe frequency & dysuria Severe generalized Telangiectasia (often with petechiae); Frequent hematuria; Reduction in bladder capacity (< 150 cc)	Necrosis/Contracted bladder (capacity < 100 cc); Severe hemorrhagic cystitis

<b>BONE</b>	None	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
<b>JOINT</b>	None	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

## APPENDIX V

### ADVERSE EVENT REPORTING GUIDELINES

#### A. GENERAL GUIDELINES

In order to assure prompt and complete reporting of toxicities, the following general guidelines are to be observed. These apply to all RTOG studies and Intergroup Studies in which RTOG participates. **When a protocol toxicity requires more intense, special handling, study-specific reporting procedures supersede the General Guidelines.**

1. The Principal Investigator will report the details of any unusual, significant, fatal or life-threatening protocol treatment reaction to the RTOG Group Chairman and to the Headquarters Data Management Staff (215/574-3214) within 24 hours of discovery. When telephone reporting is required, the Principal Investigator should have all relevant material available. See the protocol-specific criteria to grade the severity of the reaction.
  - a. All deaths during protocol treatment or within 30 days of completion or termination of protocol treatment regardless of cause requires telephone notification within 24 hours of discovery.
2. The Principal Investigator will also report the details of the significant reaction to the Study Chairman by telephone.
3. A written report, including all relevant study forms, containing all relevant clinical information concerning the reported event will be sent to RTOG Headquarters by the Principal Investigator. This must be sent within 10 working days of the discovery of the toxicity unless specified sooner by the protocol (FAX #215/928-0153).
4. The Group Chairman in consultation with the Study Chairman will take appropriate and prompt action to inform the membership and statistical personnel of any protocol modifications and/or precautionary measures if this is warranted.
5. For those incidents requiring telephone reporting to the National Cancer Institute (NCI), Investigational Drug Branch (IDB) or Food and Drug Administration (FDA), the Principal Investigator should first call RTOG (as outlined above) unless this will unduly delay the notification process required by the federal agencies.

A copy of all correspondence submitted to NCI, or to another Cooperative Group (in the case of RTOG-coordinated intergroup studies) must also be submitted to RTOG Headquarters when applicable.

6. The Principal Investigator, when participating in RTOG-coordinated Intergroup studies, is obligated to comply with all additional reporting specifications required by an individual study.
7. Institutions must also comply with their individual Institutional Review Board policy with regard to toxicity reporting procedure.
8. Failure to comply with reporting requirements in a timely manner may result in suspension of patient registration.

#### B. RADIATION TOXICITY GUIDELINES

1. All fatal toxicities (grade 5) resulting from protocol treatment must be reported by telephone to the Group Chairman, to RTOG Headquarters Data Management and to the primary Study Chairman within 24 hours of discovery.

2. All life-threatening (*grade 4*) toxicities resulting from protocol treatment using non-standard fractionated treatment, brachytherapy, radiopharmaceuticals and radiosurgery must be reported by telephone to the Group Chairman, to RTOG Headquarters Data Management and to the primary Study Chairman within 24 hours of discovery.
3. Appropriate data forms, and if requested a written report, must be submitted to Headquarters within 10 working days of the telephone report.

### **C. ADVERSE DRUG REACTIONS DRUG AND BIOLOGICS**

An adverse reaction is a toxicity or an undesirable effect usually of severe nature. Specifically, this may include major organ toxicities of the liver, kidneys, cardiovascular system, central nervous system, skin, bone marrow, or anaphylaxis. These undesirable effects may be further classified as "known" or "unknown" toxicities.

Known toxicities are those which have been previously identified as having resulted from administration of the agent. They may be identified in the literature, the protocol, the consent form or noted in the drug insert.

Unknown toxicities are those thought to have resulted from the agent but have not previously been identified as a known side effect.

#### **Commercial and Non-Investigational Agents**

- i. Any fatal (*grade 5*) or life threatening (*grade 4*) adverse reaction which is due to or suspected to be the result of a protocol drug must be reported to the Group Chairman or to RTOG Headquarters' Data Management Staff and to the Study Chairman by telephone within 24 hours of discovery. Known grade 4 hematologic toxicities need not be reported by telephone.
- ii. Unknown adverse reactions ( $\geq$  *grade 2*) resulting from commercial drugs prescribed in an RTOG protocol are to be reported to the Group Chairman or RTOG Headquarters' Data Management, to the Study Chairman and to the IDB within 10 working days of discovery. FDA Form 3500 is to be used in reporting details. All relevant data forms must accompany the RTOG copy of Form 3500.
- iii. All neurotoxicities ( $\geq$  *grade 3*) from radiosensitizer or protector drugs are to be reported within 24 hours by phone to RTOG Headquarters and to the Study Chairman.
- iv. All relevant data forms must be submitted to RTOG Headquarters within 10 working days on all reactions requiring telephone reporting. A special written report may be required.

Reactions definitely thought not to be treatment related should not be reported, however, a report should be made of applicable effects if there is a reasonable suspicion that the effect is due to protocol treatment.

#### **Investigational Agents**

Prompt reporting of adverse reactions in patients treated with investigational agents is mandatory. Adverse reactions from NCI sponsored drugs are reported to:

**Investigational Drug Branch (IDB)**  
**P. O. Box 30012**  
**Bethesda, MD 20824**  
**Telephone number available 24 hours**  
**(301) 230-2330 FAX # 301-230-0159**

i. Phase I Studies Utilizing Investigational Agents

- All deaths during therapy with the agent. Report **by phone** within 24 hours to IDB and RTOG Headquarters.  
\*\*A written report to follow within 10 working days.
- All deaths within 30 days of termination of the agent. As above
- All life threatening (*grade 4*) events which may be due to agent. As above
- First occurrence of any toxicity (*regardless of grade*). Report by **phone within 24 hours** to IDB drug monitor and RTOG Headquarters.  
\*\*A written report may be required.

ii. Phase II, III Studies Utilizing Investigational Agents

- All fatal (*grade 5*) and life threatening (*grade 4*) known adverse reactions due to investigational agent. Report **by phone** to RTOG Headquarters and the Study Chairman within 24 hours  
\*\*A written report must be sent to RTOG within 10 working days with a copy to IDB.  
(*Grade 4 myelosuppression not reported to IDB*)
- All fatal (*grade 5*) and life threatening (*grade 4*) unknown adverse reactions resulting from or suspected to be related to investigational agent. Report **by phone** to RTOG Headquarters, the Study Chairman and IDB within **24 hours**.  
\*\*A written report to follow within 10 working days.
- All grade 2, 3 unknown adverse reactions resulting from or suspected to be related to investigational agent. \*\*Report **in writing** to RTOG Headquarters and IDB within 10 working days.

\*\* See attached (*if applicable to this study*) NCI Adverse Drug Reaction Reporting Form

**APPENDIX VI**

**RTOG 99-01  
GM-CSF/PLACEBO SHIPMENT FORM  
(must be typed)**

Double-blinded GM-CSF/placebo will be shipped only to institutions who have identified a single individual associated with the investigational drug unit of the institution. This form must be completed and returned to RTOG Headquarters prior to registering any patients on study. Allow adequate processing time (7-10 days) before calling to randomize your first patient.

**SHIP TO:**

Name: \_\_\_\_\_

Address: (no P.O. Boxes) \_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

Telephone: \_\_\_\_\_

Fax#: \_\_\_\_\_

RTOG Institution#: \_\_\_\_\_

Institution Name: \_\_\_\_\_

IRB Approval Date: \_\_\_\_\_

Investigator (PI) Signature \_\_\_\_\_ Date: \_\_\_\_\_

Investigator Name (Print) \_\_\_\_\_

Investigator NCI # \_\_\_\_\_

*Send Completed Form to:*

*RTOG Headquarters  
1101 Market Street  
Philadelphia, PA 19107*

**ATTN: ELAINE PAKURIS  
FAX 215-574-0300**

RTOG Headquarters Approval \_\_\_\_\_ Date: \_\_\_\_\_