RADIATION THERAPY ONCOLOGY GROUP

RTOG

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RTOG 0615

A Phase II Study of Concurrent Chemoradiotherapy Using Three-Dimensional Conformal Radiotherapy (3D-CRT) or Intensity-Modulated Radiation Therapy (IMRT) + Bevacizumab (BV) [NSC 708865; IND 7921] for Locally or Regionally Advanced Nasopharyngeal Cancer

SCHEMA (4/21/08)

	Concurrent Phase	Adjuvant Phase
R	**3D-CRT or IMRT[a]**	**Chemotherapy[b]**
E	Gross disease PTV: 70 Gy/33	

RTOG Institution # _____

RTOG 0615 **ELIGIBILITY CHECKLIST (6/12/08)**

Case # _____ (page 1 of 3)

_____(Y) 1. Is the primary tumor site arising from the nasopharynx?

_____(Y) 2. Does the patient have Stage IIB-IVB disease?

_____(N) 3. Does the patient present with T1-2N1 disease in which node positivity is based on the

RTOG Institution # _____

RTOG 0615 **ELIGIBILITY CHECKLIST (12/13/06)**

[33] VEGF has been shown to play an important role in lymph node metastasis

in CRC (AVF2107), the incidence of arterial thromboembolic events was 1% in the IFL/placebo arm compared to 3% in the IFL/ bevacizumab arm. A pooled analysis of five randomized studies showed a two-fold increase in these events (4.4% vs. 1.9%). Certain baseline characteristics, such as age and prior arterial ischemic events, appear to confer additional risk.[60] In patients > 65

_____: h
b
d s
l proliferation, thereby having a
A

3.0 PATIENT SELECTION

NOTE: PER NCI GUIDELINES, EXCEPTIONS TO ELIGIBILITY ARE NOT PERMITTED.

3.1 Conditions for Patient Eligibility (11/7/07)

3.1.1 Biopsy proven (from primary lesion and/or lymph nodes) diagnosis of Stage IIB-IVB (AJCC, 6th ed.) non-metastatic cancer of the nasopharynx; Patients who present with T1-2N1 disease in which node positivity is based on the presenc

requirements or determining if they already have been met are available on the Radiological Physics Center (RPC) web site.

checklist, whether the patient was found to be eligible on the basis of the checklist, and the date the study-specific informed consent form was signed.

Once the system has verified that the patient is eligible and

Treatment will be delivered once daily, 5 fractions per week, over 6 weeks and 3 days. All targets will be treated simultaneously. Treatment breaks must be clearly indicated in the treatment record along with the reason(s) for the treatment break(s). Treatment breaks, if necessary, should ideally not exceed five treatment days at a time and ten treatment days total. Treatment breaks should be allowed only for resolution of severe acute toxicity and/or for intercurrent illness and not for social or logistical reasons. Any treat

radiation oncologist op16dne the radiologic extent of the primary tumor and neck nodes along with a neuro-radiologist. Whenever possible, it is recommended that the diagnostic images be

6.7 Compliance Criteria

6.7.1 *Quality Assurance of Target Volumes and Critical Structure Volumes*

The ITC will facilitate the review of all PTVs and designated critical structures on all cases submitted from each institution.

6.7.2 *Quality Assurance of Field Placement*

IMRT: The ITC will review one set of orthogonal (anterior posterior and lateral) prescription images for isocenter (or IMRT reference point) localization for each group of concurrently treated beams for the first five cases submitted by each institution. The digital reconstructed radiographs (DRRs) from the treatment planning program or, alternatively, a simulation verification radiograph shall be submitted for evaluation except where geomet

PTV_{54} (

To insure complete delivery of bevacizumab, the IV infusion line must be flushed with 0.9% sodium chloride. The following are two recommended methods for flushing the bevacizumab IV infusion line:

0.9% s

possible, allopurinol should be discontinued prior to starting on this regimen, and another agent substituted for it.

7.4.6 *Storage*

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

7.4.7 *Supply*

Commercially available.

7.5 Bevacizumab (rhuMAb VEGF, Avastin™) [NSC #7048865; IND 7921] **(4/21/08)**

7.5.8 *Preparation*
Vials contain no preservatives and are intended for single use only. Place the calculated dose in 100 mL of 0.9% sodium chloride for injection.

7.5.9

Category (Body System)	Adverse Events with Possible Relationship to Bevacizumab (CTCAE v3.0 Term)	'Agent Specific Adverse Event List' (ASAEL)

Category (Body	Adverse Events with Possible Relationship to Bevacizumab	'Agent Specific Adverse Event List' (ASAEL)

*If the patient is already at dose level 1, then decrease to dose level 2. If the patient is already at level 2, then discontinue concurrent cisplatin.

The third dose of cisplatin should be administered within 2 weeks of the end of radiation. If it cannot be administered in this timeframe, the dose should be held.

Treatment Modification for Bevacizumab-Related Adverse Events (11/7/07)

CTCAE, v. 3.0 Term	CTCAE Grade/Definition	Action to be Taken
	Grade 1: Transient flushing or rash; drug fever < 38 degrees C (< 100.4 degrees F) Grade 2: Rash; flushing;	If infusion-related or allergic reactions occur, premeds should be given with the next dose, and infusion time may be reduced for the subsequent infusion. Follow the guidelines in the Section 7.1.2.2 for bevacizumab administration.

CTCAE, v. 3.0 Term	CTCAE Grade/Definition	Action to be Taken
[illegible]	[illegible]	[illegible]

CTCAE, v. 3.0 Term	CTCAE Grade/Definition	Action to be Taken
	Grade 1: Asymptomatic, transient (< 24 hrs.) increase by >20 mmHg	

For other fistulas, see table below.

protocol; **not per protocol**

Definition of an SAE: Any adverse experience occurring during any part of protocol treatment and 30 days after 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;
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE drug experience, when, based upon medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition.

Pharmaceutically supported studies will require additional reporting over and above which is required by CTEP.

SAEs (more than 30 days after last treatment) attributed to the protocol treatment (possible, probable or definite) should be reported via AdEERS.

All supporting source documentation indicated as being provided in the Additional Information Section of the AdEERS Report must be properly labeled with the study/case numbers and the date of the adverse event and must be faxed to both the NCI at 301-230-0159 and the RTOG dedicated SAE FAX, 215-717-0990, before the five or ten-calendar-day deadline to allow RTOG to comply with the reporting requirements of the pharmaceutical company/companies supporting the RTOG trial. The RTOG Case Number without any leading zeros should be used as the Patient ID when reporting via AdEERS. Non-RTOG intergroup study and case numbers must also be included, when applicable. Submitted AdEERS Reports are forwarded to RTOG electronically via the AdEERS system.

SAE reporting is safety related and separate and in addition to the Data Management

10.1.4 A Specimen Transmittal Form clearly stating that tissue is being submitted for the RTOG Biospecimen Resource; if for translational research, this should be stated on the form. The form must include the RTOG protocol number and patient's case number.

10.2 Serum/Plasma Collection (5/7/07)

10.2.1 The RTOG Head and Neck Translational Program has an excellent tract record for conducting correlative biomarker studies. As discussed in Section 1.0, relevant to this protocol are primary tumor VEGF and VEGFR-2 expression and circulating EBV DNA.

10.2.2 *Plan and Hypotheses*

Serum and plasma will be banked to conduct preliminary analysis of the distribution of VEGF and VEGFR-2 expression and plasma EBV DNA titer by racial populations (Asian versus Caucasian and others).

10.2.3 In this study, 6 mL of blood (3 mL serum and 3 mL EDTA plasma) will be drawn at baseline,

top tube and centrifuged for serum	containing a minimum of 0.05 mL per aliquot in 1 mL

11.2.2 *Adjuvant Chemotherapy and Biologic Therapy, After Radiation Therapy* **(4/21/08)**

- History and physical, and CBC, differential, and platelets should be done within 24 hours prior to each treatment.
- Zubrod performance status, weight, adverse

If protocol treatment is discontinued, follow up and data collection will continue as specified in the protocol.

12.0 DATA COLLECTION

Data should be submitted to:

RTOG Headquarters*
1818 Market Street, Suite 1600
Philadelphia, PA 19103

***If a data form is available for web entry, it must be submitted electronically.**

Patients will be identified by initials only (first middle last); if there is no middle initial, a hyphen will be used (first-last). Last names with apostrophes will be identified by the first letter of the last name.

12.1 Summary of Data Submission

13.4 Analysis Plan

13.4.1 *Statistical Methods*

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Projected Distribution of Gender and Minorities

Gender

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APPENDIX I

Before you begin the study

>ou will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of theo001e8ftly, they may not need to be repeated. This will be up to your study doctor.

- A physical examination
- >ou will be weighed and asked about your ability to carry out your daily activities.
- >ou will be asked what medicines you are taking.
- An EKG, a test that measures the electrical activity of the heart on the surface of the chest
- A chest X-ray
- An MRI (Magnetic Resonance Imaging) of your tumor; an MRI is imaging using a strong magnetic field to look at one part of your body. Or a CT (Computed Tomography) scan of your tumor, if your study doctor001eommends this test

Less Likely

- Dizziness
- Decrease in blood counts, which can lead to a risk ods
- Anemia
- Low blood pressure
- Loss odsappetite
- Weight loss
- Itching, hives, welts odsthe skin
- Ulcers (open sores odsthe skin or mucus membranesthat sheds
- Nausea and/or vomiting
- Constipation
- I sult in stooTDnlampsa and/ordiarrhsea

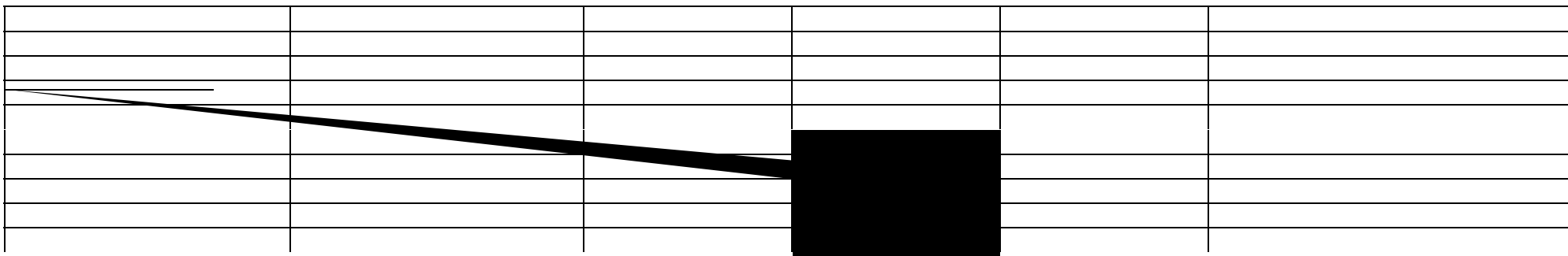
- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people
- Genentech, manufactucer of bevacizumab

What are the costs of taking part in this study?

You and/or your health plan/ insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

Genentech is supplying bevacizumab at no cost to you while you are participating in the study. However, if you should need to take bevacizumab much longer than is usual, it is possible that the supply of free bevacizumab could run out. If this happens, your study doctor will discuss with you how to obtain additional drug from the

Signature



APPENDIX III

ZUBROD PERFORMANCE SCALE

0	**Fully active, able to carry on all predisease activities without restriction (Karnofsky 90-100).**

APPENDIX IV

HEAD & NECK, 6th Edition

STAGINGtu191.6( )

APPENDIX V

MANAGEMENT OF DENTAL PROBLEMS IN IRRADIATED PATIENTS

Dental Care for Irradiated Patients

Goals for a dental care program include:

1. To reduce incidence of bone necrosis.
2. To reduce incidence of irradiation caries.

fluoride carriers, custom-made mouth guards, which provide local application of fluoride solution to the gingiva and tooth surfaces. Fluoride carriers are made individually with the use of casts. Material used for making a mouth guard is "Sta-Guard" plastic used in conjunction with vacutrole unit produced by