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_____(N) 18. Did the patient have previous irradiation to the head and neck that would result in overlap in radiation fields?

_____(N) 19. Has the patient had any major surgery within 3 weeks prior to registration?

_____

RTOG Institution # ___

1.0 INTRODUCTION

1.1 Treatment of Head and Neck Squamous Cell Carcinoma

Of the approximately 43,000 cases of head and neck squamous cell carcinoma (HNSCC) diagnosed annually in the United States, two thirds

dsecasa

HNSC

episodes were reported (Van Cruijsen 2005). Building on this strategy is a recently initiated Phase I trial at Duke University that combines either erlotinib or bevacizumab with chemo-

combined with RT (Brazelle 2006). Irrespective of sequencing, combination therapy resulted in a significantly greater growth delay than either RT or vandetanib treatment alone.

In contrast to vandetanib, data seem to suggest that the activity of some other anti-angiogenic agents is more schedule-dependent and certain timing could even result in tumor protection.

In the NCI-P441 human lung adenocarcinoma model, vandetanib was found to be more effective than paclitaxel when combined with radiation in inducing apoptosis of tumors and surrounding endothelium, reducing endothelial prolifer

3.2.6.12 Patients with ≥ grade 1 CTCAE, v. 3.0 diarrhea (Increase of < 4 stools per day over baseline; mild increase in ostomy output compared to baseline);

3.2.6.13 Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration

3.2.6.14 Chronic Obstructive Pulmonary Disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy within 30 days prior to registration;

3.2.6.15 Hepatic insufficiency resulting in clinical jaundice and/or coagulation defects; note, however, that laboratory tests coagulation parameters are not required for entry into this protocol.

3.2.6.16 Acquired Immune Deficiency Syndrome (AIDS) based upon current CDC definition; note, however, that HIV testing is not required for entry into this protocol. The need to exclude patients with AIDS from this protocol is necessary because the treatments involved in this protocol may be significantly immunosuppressive. Protocol-specific requirements may also exclude immuno-compromised patients.

3.2.7 Pregnancy, breast feeding, or women of childbearing potential and men who are sexually active and not willing/able to use medically acceptable forms of contraception; this exclusion is necessary because the treatment involved in this study may be significantly teratogenic.

3.2.8 Prior allergic reaction to cisplatin or vandetanib allergic reac

5.3.4.2 Non-Canadian International Institutions:
Please refer to your LOI Approval Notification. Your institution will be responsible for

Other techniques, e.g. physical compensators, are acceptable as long as dose specifications and constraints are satisfied.

6.3 Localization, Simulation, and Immobilization for 3D-CRT or IMRT

no more than 5% of the unspecified dose should exceed the level of the boost dose, and no more than 1% or 1 cc should exceed the boost dose value plus 10%.

6.6 Documentation Requirements

6.6.1

and on days on when radiation therapy is being held. Vandetanib will be taken on days on which make-up radiation therapy is administered.

7.1.3.2 Weekly Cisplatin

Patients will receive cisplatin at 30 mg/m^2 intravenously weekly for 6 weeks beginning on day 1 of RT. Cisplatin will start within 24 hours from the start of radiotherapy and be administered on Monday, Tuesday, or Wednesday (and on the same day each week). For patients starting radiotherapy on a Thursday or Friday, cisplatin should start on the following week.

Patients must be adequately hydrated prior to receiving cisplatin. The cisplatin should be infused over 1 hour. It is highly recommended that all patients receive 1 liter of sodium chloride 0.9% over 2 hours prior to treatment. Attention should be given to K+ and Mg++ levels with replacement as needed.

Institutional guidelines for emetogenic regimens should be followed for cisplatin administration. See Section 7.1.1.1 for suggested regimens.

7.1.4 *Dose Modifications for Vandetanib, Weekly Cisplatin K+anET1354.72 28.02 refBT/TT3 1 Tf0Tc 0Tw 10 0 0 10 346.4 49*

7.2.4 *Administration*: Intravenous.

7.2.5 *Adverse Events*

The following adverse events are anticipated:

- Á Hematologic: Myelosuppression, often with delayed erythrosuppression; rarely, acute leukemia;
- Á Gastrointestinal: Nausea, vomiting, anorexia, loss of taste;
- Á Dermatologic: Alopecia;
- Á Renal: Elevation of BUN, creatinine and impairment of endogenous creatinine clearance, as well as renal tubular damage which appears to be transient); hyperuricemia; much more severe and prolonged adverse events have been observed in patients with abnormal or obstructed urinary excretory tracts;
- Á Hepatic: Hypomagnesemia, hypokalemia, hypocalcemia,
- Á Neurologic: Restlessness; involuntary movements; loss of coordination; seizures; peripheral neuropathy;
- Á Allergic: Flushing, bronchoconstriction, tachycardia, hypotension;
- Á Other: Ototoxicity (with hearing loss which initially is in the high-frequency range, as well as tinnitusausemuscle cramps; weakness.

7.2.6 *Storage:* Intact vials of the dry powder and the aqueous injection should be stored at room temperature (15-25°C) and protected from

7.3.6 *Pharmacokinetics: Dose and Time-Dependencies*

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

Grade 1	Grade 2	Grade 2	Grade 3	Grade 3

(excluding lip, nasopharynx, or sinuses) within 6 weeks of randomization. Patients with cancers of
involved margin is NOT permitted.
le.

10.3 Tissue Collection for HPV Analysis: Required (6/8/09)

Patients with oropharyngeal carcinoma must consent to participate in use of submitted tissue for HPV analysis.

Institutions must ship tissue blocks from patients with oropharyngeal carcinoma to the RTOG

- VEGF (preliminary data suggest it predictive value for response to vandetanib);
- Lysyl oxidase, a marker for tumor hypoxia, which we recently found to be a marker for

10.6 Reimbursement (2/25/10)

For specimens submitted via RTOG 0514: Sites should consult the RTOG 0514 protocol for details of reimbursement. Sites can access RTOG 0514 at http://www.rtog.org/members/protocols/0514/0514.pdf

For institutions unable to open RTOG 0514 at the time of patient registration: RTOG will reimburse institutions per case for the protocol specified materials submitted 0 TtoaccNiopecimens

years 1-2, then every 6 months for years 3-6, then annually

12.2 Summary of Dosimetry Digital Data Submission for 3D-CRT or IMRT (Submit to ITC; see Section 12.2.1) [10/13/09]

Item

13.0 STATISTICAL CONSIDERATIONS

13.1.1 *Primary Endpoint* **(6/8/09)**

Disease-free survival

13.1.2 *Secondary Endpoints*

13.1.2.1 CTCAE, v. 3.0 grade 3-5 adverse events: cardiac arrhythmia, cardiac general, pulmonary/upper respiratory, gastrointestinal, and hemorrhage/bleeding (see Section 13.5.3 for more details);

13.1.2.2 Other grade 3-5 adverse events;

13.1.2.3 Death during or within 30 days of discontinuation of protocol treatment;

13.1.2.4 Local-regional control;

13.1.2.5 Time to distant metastases;

13.1.2.6 Overall survival.

13.2 Background and Sample Size Determination (6/8/09)

recommendation of increasing the sample size will

- Tabulation of all cases entered, and any

References (6/8/09)

Akimoto T, Hunter ER, Buchmiller L, et al. Inverse

References (Continued)ntinu A35d.473.15 1.222 Td( )Tc -024019 Tw15 1.22D

Vokes EE, Weichselbaum RR, Lippman SM, et al. Head and neck cancer. *NEJM*. 328:184-194, 1993.

Vokes EE, Kies MS, Haraf DJ, et al. Concomitant chemoradiotherapy as primary therapy for

APPENDIX I

Before you begin the study: (6/8/09)
You will need to have the following exams, tests or procedur

Study Plan

Another way to find out what will happen to you during the study is to read the chart below. Start reading at the top and read down the list, following the lines and arrows.

Risks and side effects include:

Risks Associated with Radiation to the Head and Neck

Combining cisplatin with radiation to the head and neck can increase the effectiveness of radiation therapy on your cancer, but also can increase the side effects of radiation on normal tissue in treatment area. In addition, receiving a combination of cisplatin with radiation can result in the side effects described below being more likely or more severe.

Very Likely
Á

- Restlessness
- Loss of hair, which is temporary
- Blood clots
- Low blood pressure

Less Likely, But Serious

- Seizures
- A severe allergic reaction, which could be life threatening
-

For more information on clinical trials and insurance coverage, you can visit the National Cancer

APPENDIX III

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 Jelrus Technical Products,

Appendix VII (6/8/09)

Medications Generally Accepted by Authorities to Have a Risk of Causing Torsades De Pointes (Tdp)

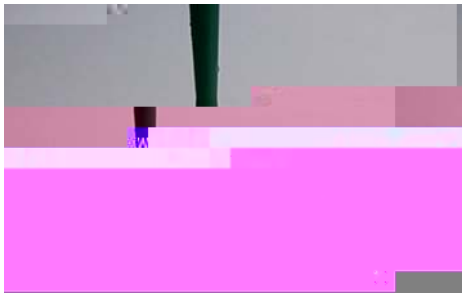
It has been recognized for a number of years that certain prescription medications can prolong the QT/QTc interval and cause a form of acquired Long QT syndrome, known as drug induced LQTS. Many drugs prolong the QT/QTc interval but do not have

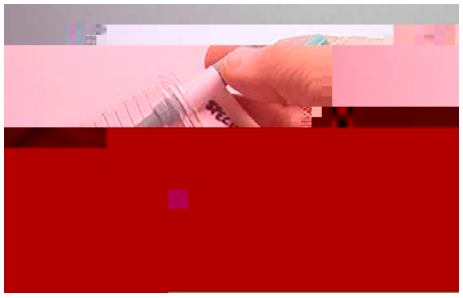
Table 1

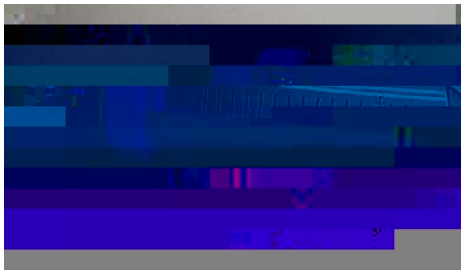
APPENDIX VIII (2/25/10)

RTOG FFPE SPECIMEN PLUG KIT INSTRUCTIONS

The specimen plug kit contains a shipping tube and a punch tool.







Step 1 Use the punch tool on the paraffin block over the selected tumor area. (Ask a pathologist to select area with tumor.) Push the punch into the paraffin block. Twist the punch tool once around to separate the plug from the block. Then pull the punch tool out of the block. The punch should be filled with tissue sample.

- Include all RTOG paperwork in pocket of biohazard bag.