SUMMARY OF CHANGES
Revision 6, Version Date: August 3, 2004

RTOG 99-03, A Randomized Phase III Trial To Assess The Effect Of Erythropoietin On Local-Regional Control In Anemic Patients Treated With Radiotherapy For Carcinoma Of The Head And Neck

Study Chair: Mitchell Machtay, M.D., (215) 955-6702; FAX (215) 955-0412; Mitchell.Machtay@mail.tju.edu

RTOG 99-03 has been revised as follows:

Section 10.1.5: The email for LDS Hospital was updated.

Section 12.0: The address for data submission was updated.

Section 13.1.1: This section has been revised from “Local-regional failure in the first two years is the primary endpoint. (Failure: disease recurrence in the primary tumor or regional nodes)” to

“Local-regional failure is the primary endpoint. (Failure: persistent or recurrent disease in the primary tumor or regional nodes”).

The original protocol analysis called for testing of local-regional failure rates to be done with Gray’s test. However, that test utilizes the times when the failures occurred. Local-regional failures, although uncommon in head and neck after two years, do occur. In order to make this endpoint consistent with the test to be used, the restriction to the first two years has been deleted. The definition of failure for this endpoint has been modified by adding “persistent” so that it is consistent with the definition of failure for local-regional progression-free survival.

Section 13.1.1.1: The definition of failure was revised to “local-regional failure or death in the absence of local-regional failure”.

Two-sided tests versus a one-sided test will be utilized to evaluate erythropoietin treatment. A paragraph concerning this change was added at the end of Sections 13.2 and 13.6.3.1.

A revised protocol is available (no password required) on the RTOG Web site, http://www.rtog.org
SUMMARY OF CHANGES
Revision 5, Version Date: March 5, 2004

RTOG 99-03, A Randomized Phase III Trial To Assess The Effect Of Erythropoietin On Local-Regional Control In Anemic Patients Treated With Radiotherapy For Carcinoma Of The Head And Neck

Study Chair: Mitchell Machtay, M.D., (215) 955-6702; FAX (215) 955-0412; Mitchell.Machtay@mail.tju.edu

IRB Review Requirements:
( ) Full board review required
(X) Expedited review allowed; however, site IRB requirements take precedence.
( ) No review required

RTOG 99-03 has been revised as follows:

Dr. Machtay’s affiliation and contact information was updated.

The analyses plans for the study have been revised. Section 13.2, an overview of the reasons for the study closure and change in analyses plans, was added, and subsequent sections were appropriately renumbered. Sections 13.1.1.1 and 13.6.3.1 also were added.

Collection of QOL data is discontinued. There will be no statistical analysis of any collected QOL data. The QOL Co-Chair was deleted from the title page and the following sections have been revised for this change: Sections 1.3, 2.3, 4.4, 11.7, 13.1, 13.3.3, 13.6.3, and Appendix I, the sample consent. In Section 11.1, the quality of life assessments were deleted from the table, and in Section 12.1, the quality of life forms were deleted.

A revised protocol is available (no password required) on the RTOG Web site, http://www.rtog.org
SUMMARY OF CHANGES
Update Date: September 2, 2003

RTOG 99-03, A RANDOMIZED PHASE III TRIAL TO ASSESS THE EFFECT OF ERYTHROPOIETIN ON LOCAL-REGIONAL CONTROL IN ANEMIC PATIENTS TREATED WITH RADIOTHERAPY FOR CARCINOMA OF THE HEAD AND NECK

Study Chair: Mitchell Machtay, M.D., 215-662-2428; FAX # 215-349-5949; machtay@xrt.upenn.edu

RTOG 99-03 has been updated as follows:

Section 5.1 — Sites in the U.S. will submit the Study Drug Shipment Form to the CTSU Regulatory Office versus RTOG Headquarters; this change also was made in Section 7.1.6.1 and Appendix VI.

Section 7.1.6.5 — Updated Ortho Biotech contact information

NOTE: This is an editorial/administrative change to the protocol. NCI now requires that these changes be documented on the protocol title page with the date of the update noted as “Update Date”.

An updated protocol is available (no password required) on the RTOG website: http://www.rtog.org/
RTOG 99-03, A RANDOMIZED PHASE III TRIAL TO ASSESS THE EFFECT OF ERYTHROPOIETIN ON LOCAL-REGIONAL CONTROL IN ANEMIC PATIENTS TREATED WITH RADIOTHERAPY FOR CARCINOMA OF THE HEAD AND NECK

Study Chair: Mitchell Machtay, M.D., 215-662-2428; FAX # 215-349-5949; machtay@xrt.upenn.edu

IRB Review Requirements:
( X ) Full board review required
(   ) Expedited review allowed
(   ) No review required

RTOG 99-03 has been revised as follows:

Patients with stage III/IV cancers can now receive accelerated fractionation RT +/- single-agent cisplatin OR standard fractionation RT plus low dose platinum-based chemotherapy. The following sections have been revised for this change: Schema; eligibility list on the Schema page; Eligibility Checklist, page 1, question 5; Sections 1.2 (12th paragraph); 3.1.4, 3.1.7, 4.2.1, 4.2.4, 6.1.2, 7.2.4, 9.1 (was added); 11.1 (“and/or Transferrin levels” was added to 6th row); REFERENCES (citations 23-27 were added and subsequent citations renumbered); Appendix I, under “Description of Procedures”, Treatment 1 and 2 and under “Risks Associated With Chemotherapy (Cisplatin).

Further information concerning toxicities associated with erythropoietin has been added. The following sections have been revised for this change: Section 7.1.4 and Appendix I, sample consent, under risks associated with erythropoietin.

Other Changes

Title page — Matthew B. Parliament, M.D., Cross Cancer Institute, University of Alberta, Canada, has been added as co-Principal Investigator; Jin S. Lee, M.D. is no longer a study chair.

Section 7.0 — The parenthetical phrase, “Also see Section 9.0, ‘Other Therapy’”, was added to the header of this section.

Section 7.1.6.5 — Contact information for Ortho Biotech was updated.
Section 7.1.6.7 — Required documentation for Canadian sites was revised; contact information for Ortho Biotech Canada was updated.

Section 9.2 — This section was renumbered and was revised for clarity.

References — Citation number 40 was updated with publication information; citation number 56 was added, and the subsequent citation was appropriately renumbered.

A revised protocol is available (no password required) on the RTOG website: http://www.rtog.org/
SUMMARY OF CHANGES

RTOG 99-03, Head and Neck

January 15, 2002

The following changes have been made:

**Title Page** — There is no longer a Biological Modifier study chair.

**Schema Page** — The stratification variable, “Chemotherapy for Stage III/IV” was deleted, and whether or not Stage III/IV patients receive chemotherapy was made part of the stratification variable, “Stage”; details were added to the first bullet of Eligibility, to correspond to Section 3.1.1.

**Eligibility Checklist** — Section 3.1.1 was referenced on page 1 of the Eligibility Checklist (number 1); the revision in the stratification variable, “Stage”, was made on page 2 of the Eligibility Checklist (number 20) to correspond to the Schema.

**Section 12.1** — The Chemotherapy Summary Form (M4) was deleted, as Section 12.2 was added in Revision #2 on 9/28/01.

A revised protocol is available (no password required) on the RTOG website: [http://www.rtog.org](http://www.rtog.org)
SUMMARY OF CHANGES

RTOG 99-03 Head and Neck

The following changes have been made:

**Title Page** — Dr. Lee’s contact information was updated; Dr. Herschock was added as a study chair.

**Schema Page** — A stratification variable, whether or not Stage III/IV patients receive chemotherapy, was added; the following item was added to Eligibility: “If the patient is to receive concurrent chemotherapy (cisplatin), serum creatinine, creatinine clearance, absolute neutrophil count (ANC), and platelet count must be as specified in Sections 3.1.7 and 3.1.8.”; this eligibility criteria also was added to page 1 of the Eligibility Checklist (number 6) and added as Sections 3.1.7 and 3.1.8.

**Eligibility Checklist** — Number 20 was added to page 2.

**Section 1.2** — In the 7th paragraph, “alfa” was added following each mention of “Epoetin”; this change also was made throughout the protocol for consistency; the last four paragraphs of this section were added with references; subsequent references were appropriately renumbered.

**Section 2.1** — The phrase “radiation or chemoradiation” has replaced “radiotherapy” in this objective.

**Section 3.1.9** was added, requiring laboratory studies as specified in Section 4.0, and the subsequent section was renumbered.

**Section 3.2.11** — The phrase “prior or concurrent chemotherapy” was revised to “prior chemotherapy”.

**Section 4.2.5** — “Creatinine” in the first sentence was revised to “Serum Creatinine [24 hr. or calculated creatinine clearance are acceptable] ”.

**Section 4.2.7** was added.

**Section 7.4**, Cisplatin, was added, and the subsequent section, Toxicity Reporting, was renumbered as Section 7.5.

**Section 11.0** — In Section 11.1, serum creatinine, creatinine clearance, and ANC were
added to the “Pre-Rx” and “During XRT” assessments, and items “g” and “h” were added; The last sentence in Section 11.3.3 was revised; Sections 11.3.6 and 11.6.3 were added.

Section 12.0 was updated for data collection for patients receiving concurrent chemotherapy.

Sections 13.2.1.1, 13.2.2.1, 13.4.1, involving the revision to include the option of chemoradiation, were added.

Appendix I, Sample Consent Form — In the section “Description of Procedures,” Treatment 1 and Treatment 2 have been revised to include the option of chemoradiation; risks associated with chemotherapy were added to “Risks and Discomforts”.

A revised protocol is attached.
SUMMARY OF CHANGES

RTOG 99-03 Head and Neck July 13, 2001

The following changes are in effect for participation by Canadian institutions:

**Section 1.1** – Eprex® was added to the third sentence.

**Section 5.1** – was changed to include the Canadian regulatory documents requirements.

**Section 7.1** - Eprex® was added to the title.

**Section 7.1.4** - Eprex® was added to the last sentence.

**Section 7.1.6.5** – An address was provided for Canadian institutions to return study drug.

**Section 7.1.6.7** – This Section was updated for Canadian institutions.

**Section 7.4.3.3** - Eprex® was added.

**Section 7.4.6** – Additional reporting was added *(also to Appendix V #D [new]).*

**Appendix I** – The Sample Consent Form was updated for Canadian institutions.

**Other Changes** – *Cover Page* - Dr. Yoo’s telephone number and e-mail address were updated; Dr. Machtay’s fax number was updated.

**Section 13.5.1** – Added “Toxicity report will usually consist of . . . reporting the results in abstract or manuscript.”

**Section 13.5.2** – Added “In addition . . . for testing binomial proportions.”

* A replacement protocol is attached. 

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**EACH PATIENT RANDOMIZATION SINCE JANUARY 1, 2001 WILL RECEIVE TWO CASE CREDITS**