SUMMARY OF CHANGES
Amendment 5, Version Date: January 31, 2007

RTOG 99-02, "A Phase III Protocol of Androgen Suppression ($AS$) and Radiation Therapy ($RT$) vs AS and RT Followed by Chemotherapy with Paclitaxel, Estramustine, and Etoposide ($TEE$) for Localized, High-Risk, Prostate Cancer"

Study Chair: Howard Sandler, MD; (734) 936-9338; hsandler@umich.edu

At the request of the Cancer Trials Support Unit (CTSU), RTOG 99-02 has been amended as follows:

Text regarding patient enrollments from institutions not aligned with RTOG was added to the page following the title page.

Prior CTSU logistics text in the following sections was replaced with new logistics text: Sections 5.3, 7.10, 10.8, 12.2, and 12.3.

New logistics concerning CTSU Regulatory and Monitoring were added as Section 7.11.
SUMMARY OF CHANGES
Update Date: September 29, 2004

RTOG 99-02, A Phase III Protocol of Androgen Suppression (AS) and Radiation Therapy (RT) vs AS and RT Followed by Chemotherapy with Paclitaxel, Estramustine, and Etoposide (TEE) for Localized, High-Risk, Prostate Cancer

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RTOG 99-02 has been updated as follows:

Section 5.3.1 — The contact information for CTSU has been updated.

Section 5.3.2 — CTSU Patient Registrar hours have been extended until 5:00 p.m. Eastern time.

Sections 7.9.2, 10.8.2, and 12.0 — The mailing address for RTOG Headquarters has been updated.

Section 7.10 — The requirements for CTSU toxicity reporting have been modified to reflect new CTSU procedures and related information.

Section 10.2 — The e-mail address for LDS Hospital has been updated.

Section 12.2 — The requirements for CTSU forms submission have been modified to reflect new CTSU procedures and related information.

Sections 10.8.1, and 12.3 — The name CTSU Data Center has been changed to reflect the Center’s current name, CTSU Data Operations Center.

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,” not as a revision.

An updated protocol is available (no password required) on the RTOG website: http://www.rtog.org/
In order to meet the needs and standards of prescribing long-term hormone therapy the following revisions were made to this protocol.

**RTOG 9902** has been revised as follows:

**SCHEMA**: Arms 1 and 2 both had the words “Zoladex, Lupron and Leuprolide “ replaced with “LHRH agonist.”

**Page 7, Section 6.0**: The following statement was added to comply with NCI guidelines: “NOTE: INTENSITY MODULATED RT (IMRT) IS NOT ALLOWED.”

**Page 9, Section 7.1.1**: “LHRH agonist” replaced the words “Zoladex or Lupron :Leuprolide.”

**Pages 10 & 11, Sections 7.2 Zoladex (goserelin) and 7.3 Lupron (leuprolide)** had specific drug information removed and a new section 7.2 LHRH agonists (such as leuprolide, goserelin , buserelin, triptorelin) was added to describe the general characteristics of this classification of drugs.

**Page 16, Section 7.9.2**: RTOG HQ fax number was changed to 717-0990.

**Page 18, Section 10.2**: The email address was changed to idhflinn@ihc.com to reflect change in staff.

**Page 29, Consent form, Treatment 1 paragraph**: REFERENCES to specific drugs (Zoladex and Lupron and leuprolide) were changed to generalized hormone treatment language. A final statement was added “Hormone treatment will be prescribed and given per package instruction and continue for about 20 more months.”

**Page 30, Consent form, Risks and Discomforts section**: “Leuprolide (Lupron) and
Zoladex (Goserelin) was changed to “Hormone treatments” with associated grammatical corrections added. The statement, “In animal studies, there is an increased incidence of non-cancerous tumors of the pituitary gland, pancreas, ovary, and adrenal gland with large doses of Zoladex. However there is no evidence to date that this has been associated with cancerous or non-cancerous tumors in humans.” since Zoladex is not specifically prescribed in the study. The statement “Your doctor will describe any other side effects described in the package instructions.” Was added.
SUMMARY OF CHANGES
Update Date: September 11, 2003

RTOG 99-02, A Phase III Protocol of Androgen Suppression (AS) and Radiation Therapy (RT) VS AS and RT Followed by Chemotherapy with Paclitaxel, Estramustine, and Etoposide (TEE) for Localized, High-Risk, Prostate Cancer

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RTOG 99-02 has been updated as follows:

Section 5.3.2 — Updated CTSU sites registration/randomization

Section 12.2 — Send Study Agent Shipment Form and other documents to the CTSU Regulatory Office in Philadelphia.

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”, not as a revision.

An updated protocol is available (no password required) on the RTOG website: http://www.rtog.org/
SUMMARY OF CHANGES
Update Date: August 22, 2003

RTOG 99-02, A Phase III Protocol of Androgen Suppression (AS) and Radiation Therapy (RT) VS AS and RT Followed by Chemotherapy with Paclitaxel, Estramustine, and Etoposide (TEE) for Localized, High-Risk, Prostate Cancer

Study Chair: Howard M. Sandler, M.D., (734) 936-9338; FAX # (734) 763-7371; hsandler@umich.edu

RTOG 99-02 has been updated as follows:

Section 5.1 — Sites in the U.S. will submit the Study Agent Shipment Form to the CTSU Regulatory Office versus RTOG Headquarters; this change also was made in Section 7.6.2, 7.7.2 and Appendix VI.

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”, not as a revision.

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

RTOG 99-02 High Risk Prostate

June 3, 2002

The following changes have been made:

For patients randomized to Arm 2 (chemotherapy), Coumadin® (warfarin) will be given continuously to keep the INR > 1.5 and < 2.5 beginning with the start of chemotherapy until 4 weeks after the end of the fourth cycle of chemotherapy. This change is reflected on the Schema page, Sections 7.1.1 and 7.1.2. The continued use of Coumadin® for four weeks following the last cycle of chemotherapy is to address any residual estrogenic effects. Coumadin® risks and the procedures involved in taking Coumadin® have been added to the Sample Consent, Risks and Discomforts, under the heading: “For patients that are randomized to Treatment 2”; Coumadin® usage has also been added to Description of Procedures, under Treatment 2.

“No prior history of thromboembolic events or contraindications to Coumadin® therapy” have been added as ineligibility criteria on the Schema page, Question #16 on the Eligibility Checklist, and Sections 3.2.9 and 3.2.10.

Section 1.0 — The last paragraph has been added as the rationale for this revision.

Section 7.1.2 — Timing of PT/INR testing has been added to this section as well as to Section 11.1 and footnote a.

Section 7.1.3.2 — Platelet count for administration of VP-16 and paclitaxel must be ≥ 100,000 instead of > 100,000.

Section 7.1.3.3 — This section has been added. Chemotherapy will be discontinued if the patient suffers from a thromboembolic event or a bleeding event that requires discontinuation of Coumadin® therapy.

Section 7.6.5 — Deep venous thrombosis and other cardiovascular events have been added as toxicities associated with estramustine. These toxicities have also been added to the Sample Consent under Emcyt.

Section 7.6.6 — This section on Coumadin® has been added.

Section 7.7.2 — Contact information for Etoposide has been changed; an additional sentence has been added concerning study drug destruction on site.

Section 7.9.3 — This section has been added; all grades (1-5) of any thromboembolic
event that occurs in a patient on this protocol must be reported.

**Section 11.1** — In footnote b, the monthly testosterone requirement during oral androgen therapy has been removed.

**Section 13.3.1** — For Arm 2, an additional monitoring schedule for thromboembolic events has been added.

*This amendment requires IRB approval. Documentation of IRB approval must be received at RTOG (from RTOG members) prior to study entry.*

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

RTOG 99-02 High Risk Prostate November 16, 2001

The following changes have been made:

Section 3.1.1 - Upper limit of PSA eligibility has been decreased to \( \leq 100 \) (also affects Schema, Eligibility Checklist, and Section 3.2.1).

Section 3.1.4 now states: “Pre-treatment serum PSA is mandatory prior to randomization and must be obtained prior to any hormone therapy”.

Section 3.1.12 was changed to “onset of androgen ablation is \( \leq 30 \) days prior to the date of randomization” (also affects Schema and Eligibility Checklist).

Section 4.3 - Timing for PSA testing allowing up to 8 weeks prior to hormone start for patients already on hormones has been deleted.

Section 7.9 - RTOG Headquarters information has been added.

Section 10.8 – Pathology report(s) should be sent to the CTSU Data Center (also affects Section 12.2).

Section 11.1 – Follow-up schedule has been clarified in footnote d (also affects Sections 11.2.1 and 11.2.2).

Section 12.1 – Long Term Follow-up Form has been added.

Section 12.2 – The Radiotherapy Form (T1) and Dosimetry Transmittal Form should be sent to CTSU (also affects Section 12.3).

A replacement protocol is attached.
SUMMARY OF CHANGES

RTOG 99-02 High Risk Prostate

The following changes are in effect:

Cancer Trials Support Unit (CTSU)

The CTSU was added. Changes were made to the Cover page, the Eligibility Checklist, Sections 5.3 (new), 7.10 (new), 10.8 (new), 12.2 (new), 12.3 (new), the Sample Consent Form in Appendix I (see Research Study and Confidentiality), and Appendix VI.

Cover Page – Dr. Rosenthal’s information was updated.

Section 3.1.1 - Upper limit of PSA has been increased to ≤ 200 (also affects Schema, Eligibility Checklist, and Section 3.2.1).

Section 3.1.4 was changed to “. . . must be obtained within 8 weeks prior to study entry. If hormones have been started prior to randomization, the PSA must have been obtained within 8 weeks prior to hormone start.”

Section 3.1.7.4 – Creatinine clearance must be at least 15 mL/min. Patients with a creatinine clearance of 15-50 ml/min will have their etoposide dose decreased by 25% (also affects the Schema, and Sections 7.1.3.1, 7.1.3.2, and 11.1g).

Section 3.1.12 was changed to “onset of androgen ablation is ≤ 50 days prior to the date of randomization” (also affects Schema and Eligibility Checklist).

Section 4.3 - Timing for PSA allows up to 8 weeks prior to hormone start for patients already on hormones.

Section 5.1 was clarified for drug shipments. One form will be used for both drugs.

Section 5.2 was updated for randomization procedures.

Section 7.6.2 – Deleted “Emcyt” from line 2. One form will be used for both drugs.

Section 7.7.2 – Etoposide will be supplied free of charge by BMS. Details were added (also affects Appendix VI and the Consent Form in Appendix I). IND #61, 009 was added to Sections 7.7 and 7.8.
Section 13.2.3 was corrected to “A two-sided, log rank test . . .”

Section 13.4.1 was changed to “Overall survival and disease free survival will be calculated by Kaplan-Meier method. The treatment effect by chemotherapy with respect to all the endpoints will be done using log rank test statistics without any stratification. All randomized patients will be included in the intent-to-treat analysis. All eligible patients will be included in a secondary analysis.

A replacement protocol is attached.