

Distribution Date: January 15, 2015
CTEP Submission Date: December 19, 2014

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TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS
FROM: Jennifer I. Scott, Protocol Coordinator (E-mail: jscott@swog.org)
RE: **S9921**, "Adjuvant Androgen Deprivation Versus Mitoxantrone Plus Prednisone Plus Androgen Deprivation in Selected High Risk Prostate Cancer Patients Following Radical Prostatectomy, Phase III." Study Coordinators: Drs. L. M. Glode, M.H.A. Hussain, G. P. Swanson, D. P. Wood, Jr. and W. A. Sakr.

REVISION #18

Study Coordinator: L. Michael Glode, M.D.
Phone: 303/724-3853
E-mail: mike.glode@uchsc.edu

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206-667-4623
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IRB Review Requirements

- () Full board review required. Reason:
() Initial activation (should your institution choose to participate)
() Increased risk to patient
() Complete study redesign
() Addition of tissue banking requirements
() Study closure due to new risk information
- () Expedited review allowed
- (✓) No review required

REVISION #18

The above-referenced protocol has been revised as follows:

1. Pages 1 and 2a, Title Page: The version date has been updated. The participant list has been moved from Page 1 to Page 2a and revised to be consistent with the new NCTN/CTSU guidelines.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL AND INFORMATION OFFICE
Cathy M. Tangen, Dr. P.H.
Melissa Plets, M.S.
Jean Barce
Austin Hamm
Craig Silva

swog.org



Southwest Oncology Group

A National Clinical Research Group

Distribution Date: February 15, 2007
CTEP Submission Date: February 1, 2007

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP, AFFILIATE AND UCOP MEDICAL ONCOLOGISTS, RADIATION ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; EPP INSTITUTIONS; CALGB; AND CTSU

FROM: Jennifer I. Scott, Protocol Coordinator

RE: **S9921**, "Adjuvant Androgen Deprivation Versus Mitoxantrone Plus Prednisone Plus Androgen Deprivation in Selected High Risk Prostate Cancer Patients Following Radical Prostatectomy, Phase III." Study Coordinators: Drs. L. M. Glode, M.H.A. Hussain, G. P. Swanson, D. P. Wood, Jr. and W. A. Sakr.

REVISION #17

Study Coordinator: L. Michael Glode, M.D.
Phone: 303/724-3853
E-mail: mike.glode@uchsc.edu

IRB Review Requirements

- () Full board review required. Reason:
() Initial activation (should your institution choose to participate)
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() Complete study redesign
() Addition of tissue banking requirements
() Study closure due to new risk information
() Expedited review allowed
() No review required

REVISION #17

The above-noted protocol has been revised at the request of the Cancer Trials Support Unit (CTSU).

The Face Page (page 2), Section 13.5 (pages 26-27), Section 14.5 (page 28a), Section 15.2 (page 28e), Section 16.1f (page 28h), Section 19.0 (page 57), and Section 19.6 (page 65) have been revised to incorporate the CTSU forms tracking change to *basic service* for this protocol. Page 27a was added to prevent extensive repagination. The Face Page has been revised to reflect the current version date of the protocol and to update the Table of Contents page number for Section 14.0.

THIS STUDY REMAINS PERMANENTLY CLOSED.

Please append this notice to your copy of the protocol and insert the replacement pages noted above.

This memorandum serves to notify the NCI, CALGB, CTSU, EPP Institutions and the Southwest Oncology Group Statistical Center.

cc: PROTOCOL AND INFORMATION OFFICE Kendra Godfrey Barrow (CTSU)
Cathy M. Tangen, Dr. P.H. Kim Mosby (EMMES)
Bryan Goldman, M.S. Karen Bartels, R.N., O.C.N., M.B.A. (Astra Zeneca)
Michael A. Hussey, M.S. Robyn Philip-Norton (OSI Pharmaceuticals)
Jean Barce Robert B. Imani, M.D., Ph.D.
Janice Leaman (OSI Pharmaceuticals)
Monica Toth, M.S. Greg Friedman (Priority Healthcare)
Brian Zeller Charlie Drayton (Priority Healthcare)
John Taylor (CALGB) Michelle Dubois (UVI, Inc.)

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Southwest Oncology Group

A National Clinical Research Group

Distribution Date: February 1, 2007

Fax and E-mail Distribution Date: January 15, 2007

CTEP Submission Date: January 15, 2007

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP, AFFILIATE AND UCOP MEDICAL ONCOLOGISTS, RADIATION ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; EPP INSTITUTIONS; CALGB; AND CTSU

FROM: Laurence H. Baker, D.O., Group Chair

RE: **S9921**, "Adjuvant Androgen Deprivation Versus Mitoxantrone Plus Prednisone Plus Androgen Deprivation in Selected High Risk Prostate Cancer Patients Following Radical Prostatectomy, Phase III." Study Coordinators: Drs. L. M. Glode, M.H.A. Hussain, G. P. Swanson, D. P. Wood, Jr. and W. A. Sakr.

STATUS NOTICE

Study Coordinator: L. Michael Glode, M.D.

Phone: 303/724-3853

E-mail: mike.glode@uchsc.edu

IRB Review Requirements

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PERMANENT CLOSURE

We are distributing this memorandum to the Southwest Oncology Group, CALGB, CTSU and EPP investigators to notify them of the immediate closure of the above-referenced protocol.

Prompted by Southwest Oncology Group Investigators, the Southwest Oncology Group Data and Safety Monitoring Committee (DSMC) conducted an interim-analysis of this study on January 10, 2007 and recommended closing the study to accrual due to a patient safety issue related to an increased incident of acute myelogenous leukemia (AML). Three cases of AML have been reported among the 488 patients registered to the chemotherapy arm of this study, using mitoxantrone, with no cases reported on the hormone deprivation arm of the study.

As a result of the DSMC recommendations, we are closing the protocol to recruitment effective January 12, 2007 and mandating no further distribution of mitoxantrone. We are recommending that patients on both arms of this study continue to receive the protocol-mandated two years of hormonal treatment, and all patients should continue to be followed as specified in the protocol.

While clinical trials have contributed greatly to medical advancements, and the well-being of study participants is the integral focus in the design and implementation of clinical trials, this result is troubling and will be a grave source of concern for the 450+ study participants who were randomized to the chemotherapy arm of this study. It is with regret that I have to share this information.

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Additional details and instructions for contacting study participants on this trial will be provided to the involved institutions and investigators, and a press release will be issued to the general public on Thursday, January 18, 2007. You may contact any of the following for more details:

Headquarters Office, 734/998-7140

Dr. Laurence H. Baker, Group Chair, bakerl@umich.edu

Dr. Bruce Redman, Executive Officer, redmanb@umich.edu

Kati Laszlo, Administrator, Laszlo@umich.edu

Operations Office, 210-450-8808

Marjorie A. Godfrey, Administrator, mgodfrey@swog.org

Jennifer Scott, Protocol Coordinator, jscott@swog.org

Dr. E. David Crawford, Genitourinary Cancer Committee Chair, 720-848-0195, david.crawford@uchsc.edu

Dr. L. Michael Glode, Study Coordinator, 303-724-3853, mike.glode@uchsc.edu

This memorandum serves to notify the NCI, CALGB, CTSU, EPP Institutions and the Southwest Oncology Group Statistical Center.

cc: PROTOCOL AND INFORMATION OFFICE

Cathy M. Tangen, Dr. P.H.

Bryan Goldman, M.S.

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Brian Zeller

John Taylor (CALGB)

Kendra Godfrey Barrow (CTSU)

Kim Mosby (EMMES)

Karen Bartels, R.N., O.C.N., M.B.A. (Astra Zeneca)

Robyn Philip-Norton (OSI Pharmaceuticals)

Robert B. Imani, M.D., Ph.D.

(OSI Pharmaceuticals)

Greg Friedman (Priority Healthcare)

Charlie Drayton (Priority Healthcare)

Michelle Dubois (UVI, Inc.)



Southwest Oncology Group

A National Clinical Research Group

Protocol Distribution Date: April 15, 2006
CTEP Submission Date: April 3, 2006

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP, AFFILIATE AND UCOP MEDICAL ONCOLOGISTS, RADIATION ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; EPP INSTITUTIONS; CALGB; AND CTSU

FROM: Jennifer I. Scott, Protocol Coordinator

RE: **S9921**, "Adjuvant Androgen Deprivation Versus Mitoxantrone Plus Prednisone Plus Androgen Deprivation in Selected High Risk Prostate Cancer Patients Following Radical Prostatectomy, Phase III." Study Coordinators: Drs. L. M. Glode, M.H.A. Hussain, G. P. Swanson, D. P. Wood, Jr. and W. A. Sakr.

REVISION #16

Study Coordinator: L. Michael Glode, M.D.

Phone: 303/724-3853

E-mail: mike.glode@uchsc.edu

IRB Review Requirements

- () Full board review required. Reason:
() Initial activation (should your institution choose to participate)
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- (√) Expedited review allowed
- () No review required

REVISION #16

The above-noted protocol has been revised as follows:

Fast Fact Sheet: A Protocol Fast Fact Sheet has been added to this protocol.

Sections 5.5a, b, and c, page 14a: These three sections have been revised to delete the text "an undetectable." Patients must have a post-operative serum prostate specific antigen (PSA) less than or equal to 0.2 ng/ml as stated in these sections.

Section 7.5, page 17: The second paragraph of this section has been revised to clarify the timing of radiation therapy. The following sentence has been added to the sixth paragraph of this section, "The NCI's IMRT guidelines can be found on the Advanced Technologies Consortium web site (<http://atc.wustl.edu> under "News," then "NCI IMRT Letter").

Section 15.3, page 28e: This section has been revised to update the address for the CALGB Pathology Coordinating Office and to add information regarding submission of blood specimens which was inadvertently omitted in Amendment #3.

Section 19.3, page 61: The header has been revised to correctly reference "Amended 2/14/06" rather than "Amended 2/1/06." **Please note that the Returned Medication Packing Slip (Section 19.3) must be included when returning Casodex or Zoladex. Please note that Casodex and Zoladex must be returned to UVI, Inc. and the address to use for returns of Casodex or Zoladex is noted on this form along with a phone number for questions.**

Please append this notice to the front of your protocol and insert the replacement pages noted above. The face page reflects the current version date of the protocol.

Operations Office

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This memorandum serves to notify the NCI, CALGB, CTSU, EPP Institutions and the Southwest Oncology Group Statistical Center.

cc: PROTOCOL AND INFORMATION OFFICE
Cathy M. Tangen, Dr. P.H.
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Janice Leaman
Monica Toth, M.S.
Brian Zeller
John Taylor (CALGB)
Kendra Godfrey Barrow (CTSU)
Kim Mosby (EMMES)
Karen Bartels, R.N., O.C.N., M.B.A. (Astra Zeneca)
Robyn Philip-Norton (OSI Pharmaceuticals)
Robert B. Imani, M.D., Ph.D.
(OSI Pharmaceuticals)
Greg Friedman (Priority Healthcare)
Charlie Drayton (Priority Healthcare)
Michelle Dubois (UVI, Inc.)

CLOSED EFFECTIVE 01/12/2007



Southwest Oncology Group

A National Clinical Research Group

Protocol Distribution Date: March 15, 2006
CTEP Submission Date: February 14, 2006

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP, AFFILIATE AND UCOP MEDICAL ONCOLOGISTS, RADIATION ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; EPP INSTITUTIONS; CALGB; AND CTSU

FROM: Jennifer I. Scott, Protocol Coordinator

RE: **S9921**, "Adjuvant Androgen Deprivation Versus Mitoxantrone Plus Prednisone Plus Androgen Deprivation in Selected High Risk Prostate Cancer Patients Following Radical Prostatectomy, Phase III." Study Coordinators: Drs. L. M. Glode, M.H.A. Hussain, G. P. Swanson, D. P. Wood, Jr. and W. A. Sakr.

AMENDMENT #3

Study Coordinator: L. Michael Glode, M.D.
Phone: 303/724-3853
E-mail: mike.glode@uchsc.edu

IRB Review Requirements

- () Full board review required. Reason:
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- () Expedited review allowed
- () No review required

AMENDMENT #3

The above-noted study has been amended to mandate that all patients registered on or after June 15, 2006 be offered the opportunity to consent for specimen banking per Section 15.0. Institutions must submit a copy of the IRB approval of this amendment to the Coalition of National Cancer Cooperative Groups (and according to each Group's guidelines) by June 15, 2006 in order to accrue patients after that date. **If you have not submitted IRB approval of this amendment by June 15, 2006, you will not be able to enroll patients to this study.** Patients registered on or after June 15, 2006 must be consented using the version of the consent form included in this amendment. The previous version of the consent form will not be accepted for new patients after that time. If patients who have already been registered to this study desire to bank specimens, they will need to be reconsented.

Additionally, the protocol has been amended to update the contact information for the Study Coordinators; update drug ordering information, allow clinical Stage T3 patients; clarify the Zoladex retreatment interval, collect PSA every three months for five years and then every six months until 15 years or death; and to make the protocol more consistent with the Southwest Oncology Group and Cancer Trials Support Unit's current standards regarding registration, data forms, and data submission. Additionally, information has been added regarding the Southwest Oncology Group's On-Line Specimen Tracking system. Since the Group's On-Line Specimen Tracking System tracks all specimen submissions, registration to **SWOG-9205** is no longer necessary.

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Specific changes to the protocol are as follows:

Face Page: The Face Page has been revised to update the contact information for Drs. Glode, Hussain and Swanson. The Table of Contents has been revised to correct pagination which changed as a result of this amendment.

Page 2: Contact information has been updated for Dr. Wood. Bryan Goldman, M.S. has replaced James Faulkner, M.S., and his contact information has been added. The mail box number has been updated for the Southwest Oncology Group Statistical Center. Drs. Wael Sakr's and Cathy Tangen's e-mail addresses have been updated. The CTSU contact information has been updated to reflect their current standardized language. Page 2a was added to prevent extensive repagination and the sentences "Please refer all questions regarding chemotherapy treatment or dose modifications to Dr. L. Michael Glode. For radiation therapy related questions, contact Dr. Gregory P. Swanson." were added.

Schema, page 3: The second line of the schema has been amended to include clinical stages T1-T3 versus T1-T2. This is consistent with changes made to Section 5.1. Line four has been amended to correctly cross reference Section 5.1d rather than Section 5.1c.

Section 1.0, page 4: Sections 1.3-1.4 have been added in conjunction with the mandatory collection of PSA noted in Section 9.0. Section 1.5 has been added regarding biologic endpoints. Section 1.6 has been added regarding banking.

Section 3.1c, page 8 and 3.2c, page 10: The "Supplier" sections have been amended to reflect Oncology Therapeutics Network's name change to UVI, Inc. The contact names "Fadia Alaraj" and "Mike Proctor" have been replaced with the text "the clinical customer service staff at UVI, Inc." The fax number has been updated. Two sentences have been added to clarify method of drug shipment and expected time for delivery.

Section 3.2c, page 9: In the "Administration" section, the text "12 weeks" has been replaced with "3 months (13 weeks)."

Section 3.3c, page 10a: OSI Pharmaceuticals is now providing the drug mitoxantrone. This is reflected in the "Supplier" section.

Section 5.0, page 14: The header section of Section 5.0 has been amended to be consistent with current Southwest Oncology Group guidelines. Please note that submission of Section 5.0 to the Data Operations Center in Seattle is no longer required. Information regarding test results and dates should be recorded on the **S9921** Local Prostate Carcinoma Prestudy (Form #23968). Lines previously provided to indicate test results and dates have been removed throughout Section 5.0 [specifically from Sections 5.1 and 5.2 (page 14); Section 5.5 (page 14a); and Sections 5.7-5.9 (page 15)].

Section 5.1, page 14: This section has been amended to include clinical Stage T3 patients. All patients must also be considered operable for cure by their primary urologic surgeon. The "NOTE" paragraph has been deleted as specimen submissions will be tracked via the Southwest Oncology Group's On-Line Specimen Tracking System and registration to **SWOG-9205** is not necessary.

Section 5.5c, page 14a: This section has been added regarding PSA requirements for patients who started hormone therapy prior to prostatectomy. Section 5.7 has been added requiring that all patients registered on or after June 15, 2006 be offered the opportunity to consent for specimen banking per Section 15.0. The remainder of Section 5 has been renumbered accordingly.

Section 5.0, page 15: The header has been amended to capture "Patients Initials (L, F, M) rather than "Patient's Name".

Section 5.11, page 15: This section has been added to exclude patients known to be HIV positive. The remainder of the Section has been renumbered accordingly.

Section 5.15, page 15: This section has been amended to indicate that the treating institution's name and ID number must be provided to the Data Operations Center in Seattle rather than the Statistical Center.

Section 6.1a, page 16: This section has been amended to indicate that patients will be stratified by pathologic stage versus surgical extent of disease. Pathology staging has been added to Sections 6.1a.1-2 as clarification and "any T" to Section 6.1a.3, but the stratification levels remain unchanged.

Section 7.0, page 16: A paragraph has been added at the top of this section outlining where treatment-related questions should be directed.

Section 7.3a&b, page 16a: Sections 7.3a and 7.3b have been added to provide clarification regarding treatment. The table has been amended to clarify that the LHRH Agonist should be repeated "q 3 months (13 weeks) x 8". The note has been deleted from underneath the table and replaced with the comment that "All continuous hormonal treatment counts towards protocol treatment."

Section 7.4, page 17: The note section has been added to clarify that the Off Treatment Notice should not be submitted for patients on Arm 2 until patient is off all protocol treatment (including hormonal therapy).

Section 7.5, page 17: The text "can be planned with 3D conformal technique. IMRT is allowed as long as boundary parameters are met." Has been added just prior to the bolded text "AP/PA".

Section 7.7b, page 18: The text "protocol treatment" has been replaced with "2 years of hormonal therapy per protocol" as clarification.

Section 8.3a, page 19: The sentence "Patients who do not recover WBC or platelet counts to \leq CTC Grade 1 toxicity within 21 days should be reduced to dose level -1 for all subsequent cycles" has been added to this section.

Section 8.4, page 20: This section has been amended to update the phone numbers of the Study Coordinators.

Sections 9.1 and 9.2, pages 21-22: The " \dagger " symbol and its corresponding footnote have been deleted as digital rectal exam is no longer required. The " \ddagger " symbol has been added to the PSA and Testosterone lines of the calendar as well as a corresponding footnote. Testosterone must be collected every six months until it reaches the institutional lower limit of normal (ILLN). Follow-up requirements have been clarified in the " Ω " footnote. "Serum specimen" has been amended to reflect "Blood specimens" and an "X" has been added under the Month 7 column. The " π " footnote has been amended to reflect blood collection time points. An "X" has been added to the CT/MRI line of Section 9.2 as it was inadvertently omitted.

Section 10.1, page 23: Censoring language has been added to this section.

Section 10.2, page 23: This section has been amended to indicate that disease-free survival is measured from the date of randomization to the date of first observation of "recurrence" rather than "progressive disease." Censoring language has been added to this section.

Section 10.4, page 23: This section has been amended to change the title from "Progression" to "PSA Progression" and to also indicate "> 0.2 ng/mL" rather than "0.2 ng/mL or greater."

Section 10.5, page 23: This section has been added to provide a definition of PSA Progression-free Survival.

Sections 13.2-13.3, pages 24-25: These sections have been amended to reflect current Southwest Oncology Group Registration Guidelines.

Section 13.5, pages 26-27: This section has been amended to reflect current CTSU Registration Guidelines.

Section 13.6, page 27: This section has been amended to reflect current Southwest Oncology Group Guidelines regarding eligibility policies.

Section 14.2, page 27: This section has been amended to indicate that forms must be submitted to the Data Operations Center in Seattle rather than the Statistical Center. The sentence "Alternatively, data from approved SWOG institutions may be submitted on-line via the Web; see Section 14.3a for details" has been added.

Section 14.3, page 28: This section has been amended to reflect current Southwest Oncology Group Data Submission Guidelines.

Section 14.4, page 28a: This section has been amended to indicate that CALGB participants should submit date to the Southwest Oncology Group Data Operations Center rather than the Statistical Center. The address has been updated accordingly.

Section 14.5, page 28a: This section has been amended to reflect current CTSU Data Submission Guidelines.

Section 14.6, page 28a: The form number for the S9921 Local Prostate Carcinoma Prestudy has been amended to reflect the revised form. Reference to the completed copy of Section 5.0 and the Study Specific Solid Tumor Flow Sheet have been removed from this section.

Section 14.7, page 28a: This section has been added and the remainder of Section 14.0 renumbered accordingly.

Sections 14.8, 14.11 and 14.12, page 28b: The titles of these sections have been amended and the text within amended to reflect the revised forms to be submitted.

Section 14.9 and 14.11, page 28b: These sections have been added.

Section 14.13, page 28b: This section has been amended to reflect the revised forms to be submitted.

Section 15.1, page 28b-e: This section has been revised to include the Southwest Oncology Group Specimen Tracking System Guidelines. Instructions regarding submission of material for the Southwest Oncology Group Repository previously found in Section 15.2 have been incorporated into Section 15.1 and this section has been expanded to include more details regarding specimen processing and shipment.

Section 15.2, page 28e: This section was previously numbered Section 15.4.

Section 15.3, page 28e: Section 15.3b was deleted since the Southwest Oncology Group Specimen Submission Form has been removed from this study. The remainder of the section was renumbered accordingly.

Section 16.0, pages 28f-h: Version 5.0 of the NCI's AdEERS (Adverse Event Expedited Reporting System), released June 1, 2004, expands its capability for expedited reporting of serious adverse events (SAEs). SAEs on all types of treatment studies, i.e., those using commercial drugs, investigational drugs, a combination of commercial and investigational drugs, surgery, or radiation therapy, will now be reported in AdEERS. The MedWatch form will no longer be used for reporting SAEs on this study. Additionally, the format for the reporting guidelines has changed to conform with the suggested intergroup format. As a result the reporting guidelines in Section 16.0 have been revised to reflect these changes. The section titled "Adverse Experiences" was deleted, Section 16.1 added, and the reporting guidelines for CTSU investigators updated.

Section 18.0, Master Forms Set, page 32: The Southwest Oncology Group Registration Form and Guidelines have been updated (Form #26636 and Code Sheet dated 12/8/04). The **S9921** Specimen Submission Form (Form #34840) has been removed from the protocol as the Group's on-line Specimen Tracking system captures this information. The **S9921** Local Prostate Carcinoma Prestudy has been updated (Form #23968). The flow sheet has been removed from this protocol, and replaced with the **S9921** Treatment Form (Form #38859), the **S9921** Chemotherapy Treatment Form (Form # 61544) and the **S9921** Adverse Event Summary Form (Form # 27242). References to the flow sheet have been replaced with the appropriate form name. Specifically, changes regarding references to the flow sheet have been made to Sections 5.4 (page 14), 7.5 (page 17), 7.5a and b (page 18), and 7.8 (page 18). The **S9921** PSA Reporting Form (Form #59255) and the **S9921** Testosterone Reporting Form (Form #25939) have been added to the protocol. The standard Follow-Up Form, Off Treatment Notice, and Notice of Death have been replaced with the Group's current version (Forms # 64587, 8756, and 49467 respectively.)

Model Informed Consent: The four paragraphs in the section titled "How Many People Will Take Part in the Study" regarding tissue banking have been removed from pages 33a and 34, and the Group's standard language regarding consent for use of specimens for research has been added as pages 41-41b. Since the standard consent for use of specimens for research contains standardized language regarding the level of consent, items a-c have been removed from underneath the "Signature" section of page 42. The risks and benefits of banking have also been removed from page 39 since they are duplicative of the information now provided in the Consent Form for Use of Specimens for Research. The Specimen Supplemental Sheets have been added to the protocol as pages 43-44. The text "12 weeks" has been replaced with "3 months" on page 35, Arm 1, Procedures, Goserelin Acetate and page 36, Arm 2, Procedures, Goserelin Acetate. "Loss of bone mineral density" was added as a "Very Likely" risk of Arm 1 on page 37. "Weakness, Anemia, Increased liver enzymes (blood tests), Weight gain, and Osteoarthritis" have been added as "Less Likely" risks for Arm 1. "Infection, Weight gain, Weight loss, Fever without infection, Shortness of breath, Nail bed changes, Mouth or lip sores, Sweats, Mood changes (anxiety, depression, irritability), Cough, and Heartburn" have been added as "Less Likely" risks for Arm 2 on page 38. A section "Rare, but serious" has been added for Arm 2 and the possible risk "leukemia" has been added on page 39. All risks have been put in bold text. OSI Pharmaceuticals is supplying the mitoxantrone rather than Immunex and this is now reflected in the Section titled "What Are the Costs" (last paragraph, page 40). Institutions must update their consent forms to include this information for future registrations. Patients currently being treated on this study must be informed of this information in the manner determined by their local Institutional Review Board (IRB).

Appendix, page 57: As a result of changes made throughout the protocol, the appendices have been repaginated. The Returned Medication Packing Slip has been amended to reference UVI, Inc. rather than Axion HealthCare Inc. Appendix 19.4, the Novantrone Drug Request Form has been amended to include Charlie Drayton and Greg Friedman as contact personnel at Priority Healthcare rather than Avis Moss. Their phone numbers have been added as well. Section 19.5, Determination of Expedited Adverse Event Reporting Requirements, has been added to the protocol.

Please append this notice to your copy of the protocol and replace the changed pages as noted above. Please insert the following new forms: **S9921** PSA Reporting Form (Form #59255), **S9921** Testosterone Reporting Form (Form #25939), **S9921** Treatment Form (Form #38859), **S9921** Chemotherapy Treatment Form (Form # 61544), and **S9921** Adverse Event Summary Form (Form #27242). Please replace the Southwest Oncology Group Registration Form (Form #26636 replaces Form #63220), **S9921** Local Prostate Carcinoma Prestudy (Form #23968 replaces Form #43343), Follow-Up Form (Form #64587 replaces Form #4120), Off Treatment Notice (Form #8756 replaces Form #25524), and Notice of Death (Form #49467 replaces Form #25076) with the form numbers referenced. Please remove the Study Specific Solid Tumor Flow Sheet and the **S9921** Specimen Submission Form (Form #34840). To prevent extensive repagination of the entire protocol pages 25 a-b, 27a-c, 40a, and 33a have been deleted and pages 2a, 28a-h, 38a, and 41a-b added.

This memorandum serves to notify the NCI, CALGB, CTSU, EPP Institutions and the Southwest Oncology Group Statistical Center.

cc: PROTOCOL AND INFORMATION OFFICE
Cathy M. Tangen, Dr. P.H.
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Charlie Drayton (Priority Healthcare)
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A National Clinical Research Group

June 15, 2005

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP, AFFILIATE AND UCOP MEDICAL ONCOLOGISTS, RADIATION ONCOLOGISTS, SURGEONS AND PATHOLOGISTS

FROM: Jennifer I. Scott, Protocol Coordinator

RE: S9921, "Adjuvant Androgen Deprivation Versus Mitoxantrone Plus Prednisone Plus Androgen Deprivation in Selected High Risk Prostate Cancer Patients Following Radical Prostatectomy, Phase III." Study Coordinators: Drs. L. M. Glode, M.H.A. Hussain, G. P. Swanson, D. P. Wood, Jr. and W. A. Sakr.

MEMORANDUM

Study Coordinator: L. Michael Glode, M.D. Phone: 303/315-4757
E-mail: mike.glode@uchsc.edu

IRB Review Requirements

- () Full board review required. Reason:
() Increased risk to patient
() Complete study redesign
() Addition of tissue banking requirements
() Study closure due to new risk information
- () Expedited review allowed
- (✓) No review required

MEMORANDUM

Understandably, Sanofi-Aventis is anxious to initiate an adjuvant therapy trial for high risk prostate cancer. We feel it is vital that we complete S9921 and sincerely ask that you do not open this trial at Southwest Oncology Group institutions. We have struggled successfully to keep our study open, and accrual has been improving in the past year. Indeed, at the present rate, it may be possible to complete accrual within 3 years.

However, there are very compelling scientific reasons for completing this trial as well. These include:

- a) Although statistically superior to mitoxantrone/prednisone in survival, the effect in Tax 327 and S9916 was small (3 months).
- b) Toxicities, long and short term may well be considerably different for the two approaches.
- c) There are examples in breast, colon, and lung cancer trials where the "best drug" did not necessarily translate to the best result in the adjuvant setting.
- d) It is possible that men could benefit from combining active regimens using single agents (e.g. Dr. Larry Norton's studies using sequential vs. combined therapies – all of which are active). For this to occur, one would need a second regimen with significant activity to build on.

Operations Office

14980 Omicron Drive•San Antonio, TX 78245-3217 • Telephone 210-677-8808 • FAX 210-677-0006 • <http://swog.org>



We recognize that compensation for the two studies may be different as well. Therefore, for both altruistic and scientific reasons, (and potentially at a financial disadvantage to you), we sincerely hope you will help us to complete the FIRST large scale prostate cancer adjuvant trial of the modern era, **S9921**, which already has a 5 year lead time advantage for the earliest patients entered, and could well be equally effective, less toxic, and potentially more cost effective than the taxotere-based adjuvant trial being launched by Sanofi-Aventis. We hope to collaborate with them in looking at biomarkers that could eventually sub-categorize patients who would benefit more from one approach than another.

This memorandum serves to notify the Southwest Oncology Group Statistical Center.

cc: Cathy M. Tangen, Dr. P.H.
Nadia Howlader, M.S.
Bryan Goldman, M.S.
Jean Barce
Janice Leaman
Jenni McNurlin
Bryan Zeller

CLOSED/EFFECTIVE 01/12/2007



Southwest Oncology Group

A National Clinical Research Group

Distribution Date: October 1, 2003
CTEP Submission Date: September 12, 2003

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP, AFFILIATE AND UCOP MEDICAL ONCOLOGISTS, RADIATION ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; EPP INSTITUTIONS; CALGB; CTSU
FROM: Jennifer I. Scott, Protocol Coordinator
RE: **S9921**, "Adjuvant Androgen Deprivation Versus Mitoxantrone Plus Prednisone Plus Androgen Deprivation in Selected High Risk Prostate Cancer Patients Following Radical Prostatectomy, Phase III." Study Coordinators: Drs. L. M. Glode, M.H.A. Hussain, G. P. Swanson, D. P. Wood, Jr. and W. A. Sakr.

AMENDMENT #2

Study Coordinator: L. Michael Glode, M.D. Phone: 303/315-4757
E-mail: mike.glode@uchsc.edu

IRB Review Requirements

- () Full board review required. Reason:
() Increased risk to patient
() Complete study redesign
() Addition of tissue banking requirements
() Study closure not built into study design
- () Expedited review allowed
() No review required

AMENDMENT #2

At the recommendation of the Data and Safety Monitoring Committee, the statistical section of the above-noted protocol has been revised to reflect the lower than anticipated accrual rate.

Section 11.2, page 23: This section has been amended to reflect that initially it was anticipated that 250 eligible patients would be accrued per year, but that accrual has been slower than expected. The accrual period estimate has been adjusted to 9.5 years.

Section 11.3, page 23: This section has been amended to also reflect an accrual period of 9.5 years, 4 years of follow up and a power of .92.

Section 11.6, page 24: This section has been amended to reflect that the first formal interim analysis will be done after 700 patients have been entered rather than 1,000 which will occur approximately six years after the study opens rather than four years. The last sentence has been amended to reflect that the final analysis will be performed approximately fours years after accrual has been completed rather than five.

Please append this notice to your copy of the protocol and insert the enclosed replacement pages. The face page reflects the current version date of the protocol.

This memorandum serves to notify the NCI, CALGB, CTSU, EPP Institutions and the Southwest Oncology Group Statistical Center.

cc: PROTOCOL AND INFORMATION OFFICE City Nasim (EMMES)
Cathy M. Tangen, Dr. P.H. Anita Nelson (CTSU)
James Faulkner, M.S. Denise Ferris (Astra Zeneca)
Jean Barce Robyn Philip-Norton (OSI)
Pharmaceuticals)
Kathy Bingham Avis Moss (Priority Healthcare)
Jenni McNurlin Mike Proctor (UintaVision)
John Taylor (CALGB)



Southwest Oncology Group

A National Clinical Research Group

September 1, 2003

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP, AFFILIATE AND UCOP MEDICAL ONCOLOGISTS, RADIATION ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; EPP INSTITUTIONS; CALGB; CTSU

FROM: Jennifer I. Scott, Protocol Coordinator

RE: **S9921**, "Adjuvant Androgen Deprivation Versus Mitoxantrone Plus Prednisone Plus Androgen Deprivation in Selected High Risk Prostate Cancer Patients Following Radical Prostatectomy, Phase III." Study Coordinators: Drs. L. M. Glode, M.H.A. Hussain, G. P. Swanson, D. P. Wood, Jr. and W. A. Sakr.

REVISION #15

Study Coordinator: L. Michael Glode, M.D. Phone: 303/315-4757
E-mail: mike.glode@uchsc.edu

IRB Review Requirements

- () Full board review required. Reason:
() Increased risk to patient
() Complete study redesign
() Addition of tissue banking requirements
() Study closure not built into study design
- () Expedited review allowed
- (✓) No review required

REVISION #15

The above-noted protocol has been revised as follows:

Appendix 19.4, the Novantrone Drug Request Form, has been revised to update the phone number for Priority Healthcare Corporation. Avis Moss has replaced Littleton Baty as the contact person at Priority Healthcare Corporation.

Please append this notice to your copy of the protocol and replace the face page, and the Novantrone Drug Request Form. The face page reflects the current version date of the protocol.

This memorandum serves to notify the NCI, CALGB, CTSU, EPP Institutions and the Southwest Oncology Group Statistical Center.

cc: PROTOCOL AND INFORMATION OFFICE
Cathy M. Tangen, Dr. P.H.
James Faulkner, M.S.
Jean Barce
Kathy Bingham
Jenni McNurlin
John Taylor (CALGB)
Gity Nasim (EMMES)
Anita Nelson (CTSU)
LeaAnn Longueira, R.N., C.R.S. (Astra Zeneca)
Robyn Philip-Norton (OSI Pharmaceuticals)
Avis Moss (Priority Healthcare)
Mike Proctor (UintaVision)



Southwest Oncology Group

A National Clinical Research Group

May 15, 2003

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP, AFFILIATE AND UCOP MEDICAL ONCOLOGISTS, RADIATION ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; EPP INSTITUTIONS; CALGB; CTSU

FROM: Jennifer I. Scott, Protocol Coordinator

RE: **S9921**, "Adjuvant Androgen Deprivation Versus Mitoxantrone Plus Prednisone Plus Androgen Deprivation in Selected High Risk Prostate Cancer Patients Following Radical Prostatectomy, Phase III." Study Coordinators: Drs. L. M. Glode, M.H.A. Hussain, G. P. Swanson, D. P. Wood, Jr. and W. A. Sakr.

REVISION #14

Study Coordinator: L. Michael Glode, M.D. Phone: 303/315-4757
E-mail: mike.glode@uchsc.edu

IRB Review Requirements

- () Full board review required. Reason:
() Increased risk to patient
() Complete study redesign
() Addition of tissue banking requirements
() Study closure not built into study design
- (✓) Expedited review allowed
- () No review required

REVISION #14

The above-noted protocol has been revised as follows:

The supplier portion of Section 3.3c and Appendix 19.4, the Novantrone Drug Request Form have been revised to update the fax and phone numbers for Priority Healthcare Corporation. Littleton Baty has replaced David Jones at Priority Healthcare Corporation.

Please append this notice to your copy of the protocol and replace the face page, and pages 10a and 56, the Novantrone Drug Request Form. The face page reflects the current version date of the protocol.

This memorandum serves to notify the NCI, CALGB, CTSU, EPP Institutions and the Southwest Oncology Group Statistical Center.

cc: PROTOCOL AND INFORMATION OFFICE
Cathy M. Tangen, Dr. P.H.
James Faulkner, M.S.
Jean Barce
Kathy Bingham
Lori Clark
Jenni McNurlin
John Taylor (CALGB)
Gity Nasim (EMMES)
Anita Nelson (CTSU)
Megan Davis (Astra Zeneca)
Robyn Philip-Norton (OSI Pharmaceuticals)
Mike Proctor (UintaVision)

Operations Office

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Southwest Oncology Group

A National Clinical Research Group

November 1, 2002

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP, AFFILIATE AND UCOP MEDICAL ONCOLOGISTS, RADIATION ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; EPP INSTITUTIONS; CALGB; CTSU

FROM: Jennifer I. Scott, Protocol Coordinator

RE: **S9921**, "Adjuvant Androgen Deprivation Versus Mitoxantrone Plus Prednisone Plus Androgen Deprivation in Selected High Risk Prostate Cancer Patients Following Radical Prostatectomy, Phase III." Study Coordinators: Drs. L. M. Glode, M.H.A. Hussain, G. P. Swanson, D. P. Wood, Jr. and W. A. Sakr.

REVISION #13

Study Coordinator: L. Michael Glode, M.D. Phone: 303/315-4757
E-mail: mike.glode@uchsc.edu

IRB Review Requirements

- () Full board review required. Reason:
() Increased risk to patient
() Complete study redesign
() Addition of tissue banking requirements
() Study closure not built into study design
- (✓) Expedited review allowed
- () No review required

REVISION #13

The above-noted protocol has been revised as follows:

The supplier portion of Section 3.3c and Appendix 19.4, the Novantrone Drug Request Form have been revised to reflect that mitoxantrone must be ordered from Priority Healthcare Corporation.

Please append this notice to your copy of the protocol and replace the face page, and pages 10a and 56, the Novantrone Drug Request Form. The face page reflects the current version date of the protocol.

This memorandum serves to notify the NCI, CALGB, CTSU, EPP Institutions and the Southwest Oncology Group Statistical Center.

cc: PROTOCOL AND INFORMATION OFFICE
Cathy M. Tangen, Dr. P.H.
James Faulkner, M.S.
Jean Barce
Kathy Bingham
Lori Clark
Jenni McNurlin
John Taylor (CALGB)
Gity Nasim (EMMES)
Anita Nelson (CTSU)
Megan Davis (Astra Zeneca)
Rose Hesselbrock (Immunex)
Mike Proctor (UintaVision)



Southwest Oncology Group

A National Clinical Research Group

August 1, 2002

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP, AFFILIATE AND UCOP MEDICAL ONCOLOGISTS, RADIATION ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; EPP INSTITUTIONS; CALGB; CTSU

FROM: Jennifer I. Scott, Protocol Coordinator

RE: **S9921**, "Adjuvant Androgen Deprivation Versus Mitoxantrone Plus Prednisone Plus Androgen Deprivation in Selected High Risk Prostate Cancer Patients Following Radical Prostatectomy, Phase III." Study Coordinators: Drs. L. M. Glode, M.H.A. Hussain, G. P. Swanson, D. P. Wood, Jr. and W. A. Sakr.

REVISION #12

Study Coordinator: L. Michael Glode, M.D. Phone: 303/315-4757
E-mail: mike.glode@uchsc.edu

IRB Review Requirements

- () Full board review required. Reason:
() Increased risk to patient
() Complete study redesign
() Addition of tissue banking requirements
() Study closure not built into study design

() Expedited review allowed

(✓) No review required

REVISION #12

The above-noted protocol has been revised as follows:

- Face Page: In order to be consistent with the heading of Section 6.0, the Table of Contents has been revised to indicate that Section 6.0 is Stratification Factors/Randomization Scheme. The "Protocol Last Changed" date has been updated to 8/1/02.
 - Page 2 has been revised to update the e-mail addresses for the biostatisticians.
 - Page 26, Section 14.6 and page 32, Section 18.4: The form number for the **S9921** Local Prostate Carcinoma Prestudy Form has been revised to be consistent with the new form number for this form.
 - The **S9921** Local Prostate Carcinoma Prestudy Form has been revised to collect patient initials rather than name and to include a note clarifying reporting of the Gleason Score. The form number has been revised.

Please append this notice to your copy of the protocol and replace the face page, and pages 2, 26, 32 and the S9921 Local Prostate Carcinoma Prestudy (Form #43343).

This memorandum serves to notify the NCI, CALGB, CTSU, EPP Institutions and the Southwest Oncology Group Statistical Center.

cc: PROTOCOL AND INFORMATION OFFICE
Cathy M. Tangen, Dr. P.H.
James Faulkner, M.S.
Jean Barce
Kathy Bingham
Lori Clark

John Taylor (CALGB)
City Nasim (EMMES)
Anita Nelson (CTSU)
Megan Davis (Astra Zeneca)
Rose Hesselbrock (Immunex)
Mike Proctor (UintaVision)





**Southwest
Oncology Group**
A National Clinical Research Group

July 1, 2002

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP, AFFILIATE AND UCOP MEDICAL ONCOLOGISTS, RADIATION ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; EPP INSTITUTIONS; CALGB; CTSU

FROM: Jennifer I. Scott, Protocol Coordinator

RE: S9921, "Adjuvant Androgen Deprivation Versus Mitoxantrone Plus Prednisone Plus Androgen Deprivation in Selected High Risk Prostate Cancer Patients Following Radical Prostatectomy, Phase III." Study Coordinators: Drs. L. M. Glode, M.H.A. Hussain, G. P. Swanson, D. P. Wood, Jr. and W. A. Sakr.

REVISION #11

Study Coordinator: L. Michael Glode, M.D. Phone: 303/315-4757
E-mail: mike.glode@uchsc.edu

IRB Review Requirements

- () Full board review required. Reason:
() Increased risk to patient
() Complete study redesign
() Addition of tissue banking requirements
() Study closure not built into study design
- () Expedited review allowed
- (✓) No review required

REVISION #11

The above-noted protocol has been revised as follows:

- The old Registration Form (Form #15324) has been replaced with a new Registration Form (Form #63220) and the Coding Guidelines have been revised to be more consistent with current Group standards. The form number change is reflected in Section 18.2.

Please append this notice to your copy of the protocol and replace the face page, and page 32 and the Registration Form (Form #63220) and Guidelines. The face page reflects the date of the current revision.

This memorandum serves to notify the NCI, CALGB, CTSU, EPP Institutions and the Southwest Oncology Group Statistical Center.

cc: PROTOCOL AND INFORMATION OFFICE
Cathy M. Tangen, Dr. P.H.
James Faulkner, M.S.
Jean Barce
Kathy Bingham
Lori Clark
John Taylor (CALGB)
Gity Nasim (EMMES)
Anita Nelson (CTSU)
Megan Davis (Astra Zeneca)
Rose Hesselbrock (Immunex)
Mike Proctor (UintaVision)



Southwest Oncology Group

A National Clinical Research Group

April 1, 2002

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP, AFFILIATE AND UCOP MEDICAL ONCOLOGISTS, RADIATION ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; EPP INSTITUTIONS; CALGB; CTSU

FROM: Jennifer I. Scott, Protocol Coordinator

RE: **S9921**, "Adjuvant Androgen Deprivation Versus Mitoxantrone Plus Prednisone Plus Androgen Deprivation in Selected High Risk Prostate Cancer Patients Following Radical Prostatectomy, Phase III." Study Coordinators: Drs. L. M. Glode, M.H.A. Hussain, G. P. Swanson, D. P. Wood, Jr. and W. A. Saks.

REVISION #10

Study Coordinator: L. Michael Glode, M.D. Phone: 303/315-4757
E-mail: mike.glode@uchsc.edu

IRB Review Requirements

- () Full board review required
 - (√) Expedited review allowed
 - () No review required

REVISION #10

The above-noted protocol has been revised as follows:

- The Face Page has been revised to correct the phone numbers for Drs. Glode and Hussain. This change is also reflected in Section 8.4.
 - Page 2 has been revised to correct the e-mail addresses for Drs. Wood and Sakr and replace Tracy Glass with James Faulkner, M.S. as Secondary Statistician.
 - Section 5.0 has been revised to allow patients who have already started post-surgical hormone therapy to be eligible for **S9921**. These changes are reflected in Sections 5.4 and 5.5. A note has been added to Section 7.3 to indicate that if hormonal therapy has been started prior to randomization, every effort should be made to conform with the LHRH agonist administration schedule that is specified in the study calendar.
 - Sections 13.1 - 13.3 and 14.3 have been revised to reflect current Southwest Oncology Group registration and data submission guidelines.
 - Section 13.5 has been revised to change "CTSU Enrollment Coversheet" to "CTSU Patient Enrollment Transmittal Form."

Please append this notice to your copy of the protocol and replace the face page and pages 2, 14, 14a, 16, 16a, 20 and 24 - 25a - b. Pages 14a, 16a and 25b were added to prevent extensive repagination.

This memorandum serves to notify the NCI, CALGB, CTSU, EPP Institutions and the Southwest Oncology Group Statistical Center.

cc: PROTOCOL AND INFORMATION OFFICE
Cathy M. Tangen, Dr. P.H.
James Faulkner, M.S.
Jean Barce
Kathy Bingham
Lori Clark

John Taylor (CALGB)
Gity Nasim (EMMES)
Anita Nelson (CTSU)
Megan Davis (Astra Zeneca)
Rose Hesselbrock (Immunex)
Mike Proctor (UintaVision)





**Southwest
Oncology Group**
A National Clinical Research Group

February 15, 2002

TO: ALL SOUTHWEST ONCOLOGY GROUP, CCOP, AFFILIATE AND UCOP MEDICAL ONCOLOGISTS, RADIATION ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; EPP INSTITUTIONS; CALGB; CTSU

FROM: Jennifer I. Scott, Protocol Coordinator

RE: **S9921**, "Adjuvant Androgen Deprivation Versus Mitoxantrone Plus Prednisone Plus Androgen Deprivation in Selected High Risk Prostate Cancer Patients Following Radical Prostatectomy, Phase III." Study Coordinators: Drs. L. M. Glode, M.H.A. Hussain, G. P. Swanson, D. P. Wood, Jr. and W. A. Sakr.

REVISION #9

Study Coordinator: L. Michael Glode, M.D. Phone: 303/315-8801
E-mail: mike.glode@uchsc.edu

IRB Review Requirements

- () Full board review required
() Expedited review allowed
(√) No review required

REVISION #9

The Eastern Cooperative Oncology Group has elected to endorse **S9921**. Dr. Naomi Balzer-Haas has been added to the face page as ECOG Study Coordinator. **Please note that ECOG members will enroll patients to this trial and submit data via the Cancer Trials Support Unit (CTSU).**

Please append this notice to your copy of the protocol and replace the face page and page 2. The face page reflects the date of the current revision.

This memorandum serves to notify the NCI, CALGB, CTSU, EPP Institutions and the Southwest Oncology Group Statistical Center.

cc: PROTOCOL AND INFORMATION OFFICE
Cathy M. Tangen, Dr. P.H.
James Faulkner, M.S.
Jean Barce
Kathy Bingham
Lori Clark
Rodney Sutter
Tamra Oner
John Taylor (CALGB)
Gity Nasim (EMMES)
Anita Nelson (CTSU)
Megan Davis (Astra Zeneca)
Rose Hesselbrock (Immunex)
Mike Proctor (UintaVision)





**Southwest
Oncology Group**
A National Clinical Research Group

December 15, 2001

TO: ALL SOUTHWEST ONCOLOGY GROUP, CCOP, AFFILIATE AND UCOP MEDICAL ONCOLOGISTS, RADIATION ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; EPP INSTITUTIONS; CALGB; CTSU

FROM: Jennifer I. Scott, Protocol Coordinator

RE: **S9921**, "Adjuvant Androgen Deprivation Versus Mitoxantrone Plus Prednisone Plus Androgen Deprivation in Selected High Risk Prostate Cancer Patients Following Radical Prostatectomy, Phase III." Study Coordinators: Drs. L. M. Glode, M.H.A. Hussain, G. P. Swanson, D. P. Wood, Jr. and W. A. Sakr.

MEMORANDUM

Study Coordinator: L. Michael Glode, M.D. Phone: 303/315-8801
E-mail: mike.glode@uchsc.edu

IRB Review Requirements

- () Full board review required
() Expedited review allowed
(√) No review required

MEMORANDUM

Immunex has notified the Southwest Oncology Group that they will be closed at the end of the business day on Friday, December 21, 2001 through Tuesday, January 1, 2002 and will reopen on Wednesday, January 2, 2002. During this period, Immunex will not ship study drug (mitoxantrone).

ORDERING DRUG

To prepare for the holiday close, Immunex asks that you check with your investigational pharmacist to assure that there will be an adequate supply of mitoxantrone during this time. If you need additional drug, please have the pharmacist order drug no later than 10:00 AM Pacific time on Monday, December 17, 2001. This will allow Immunex to ship the drug and confirm its arrival before the holiday break.

Please append this notice to your copy of the protocol.

This memorandum serves to notify the NCI, CALGB, CTSU, EPP Institutions and the Southwest Oncology Group Statistical Center.

cc: PROTOCOL AND INFORMATION OFFICE John Taylor (CALGB)
Cathy M. Tangen, Dr. P.H. Gity Nasim (EMMES)
James Faulkner, M.S. Anita Nelson (CTSU)
Jean Barce Megan Davis (Astra Zeneca)
Kathy Bingham Rose Hesselbrock (Immunex)
Lori Clark Mike Proctor (UintaVision)
Rodney Sutter
Tamra Oner

Operations Office

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**Southwest
Oncology Group**
A National Clinical Research Group

July 15, 2001

TO: ALL SOUTHWEST ONCOLOGY GROUP, CCOP, AFFILIATE AND UCOP MEDICAL ONCOLOGISTS, RADIATION ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; EPP INSTITUTIONS; CALGB; CTSU

FROM: Jennifer I. Scott, Protocol Coordinator

RE: **S9921**, "Adjuvant Androgen Deprivation Versus Mitoxantrone Plus Prednisone Plus Androgen Deprivation in Selected High Risk Prostate Cancer Patients Following Radical Prostatectomy, Phase III." Study Coordinators: Drs. L. M. Glode, M.H.A. Hussain, G. P. Swanson, D. P. Wood, Jr. and W. A. Sakr.

REVISION #8

Study Coordinator: L. Michael Glode, M.D. Phone: 303/315-8801
E-mail: mike.glode@uchsc.edu

IRB Review Requirements

- () Full board review required
(√) Expedited review allowed
() No review required

REVISION #8

The Immunex Drug Distribution fax number has changed. The revised number is reflected under "supplier" on page 10a and on the Novantrone Drug Request Form (Appendix 19.4).

Please append this notice to your copy of the protocol and replace the face page and pages 10a and 56. The face page reflects the date of the current revision.

This memorandum serves to notify the NCI, CALGB, CTSU, EPP Institutions and the Southwest Oncology Group Statistical Center.

cc: PROTOCOL AND INFORMATION OFFICE
Cathy M. Tangen, Dr. P.H.
Tracy R. Glass, M.S.
Kathy Bingham
Rodney Sutter
Jean Barce
Lori Clark
Nickey McCasland, R.N.
John Taylor (CALGB)
Gity Nasim (EMMES)
Anita Nelson (CTSU)
Megan Davis (Astra Zeneca)
Rose Hesselbrock (Immunex)
Mike Proctor (Uinta Vision)





July 1, 2001

TO: ALL SOUTHWEST ONCOLOGY GROUP, CCOP, AFFILIATE AND UCOP MEDICAL ONCOLOGISTS, RADIATION ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; EPP INSTITUTIONS; CALGB; CTSU

FROM: Jennifer I. Scott, Protocol Coordinator

RE: **S9921**, "Adjuvant Androgen Deprivation Versus Mitoxantrone Plus Prednisone Plus Androgen Deprivation in Selected High Risk Prostate Cancer Patients Following Radical Prostatectomy, Phase III." Study Coordinators: Drs. L. M. Glode, M.H.A. Hussain, G. P. Swanson, D. P. Wood, Jr. and W. A. Sakr.

REVISION #7

Study Coordinator: L. Michael Glode, M.D. Phone: 303/315-8801
E-mail: mike.glode@uchsc.edu

IRB Review Requirements

- () Full board review required
(√) Expedited review allowed
() No review required

REVISION #7

The above noted protocol has been revised as follows:

- The heading of Section 5.0 has been revised to indicate that this section must be photocopied, completed and submitted as part of the initial forms set. Section 14.6 has been revised to include a completed copy of Section 5.0 as part of the initial forms set.
- Section 5.1c has been revised to remove the verbiage "and pT3a (extra-prostatic extension)" since it is felt that all patients with a pathologic Gleason's sum of 7 and positive margins are at high risk. Section 5.1d has been revised to remove "have received preoperative hormone therapy" to expand the criteria to allow patients with similar features regardless of preoperative hormone therapy status. The following statement has been added to Section 5.4: "The use of low dose megace (< 40 mg/day) for the treatment of hot flashes is allowed." Section 5.5 has been revised to clarify that PSA must be less than or equal to 0.2 ng/ml.
- In keeping with standard medical practice, Section 7.4b and the Study Calendar have been revised to indicate that prednisone treatment should be tapered at the discretion of the treating physician.
- The Study Calendar has been revised to clarify that follow up MUGAs or 2-d echos are only needed for those patients who required one at baseline.

Operations Office

14980 Omicron Drive • San Antonio, TX 78245-3217 • Telephone 210-677-8808 • FAX 210-677-0006 • <http://swog.org>



- CALGB institutions participating on Southwest Oncology Group-coordinated studies will now submit data directly to the Southwest Oncology Group Statistical Center rather than routing it through the CALGB Data Management Center. Data submission instructions for CALGB institutions have been revised in Section 14.4.
- The heading "FOR CTSU INVESTIGATORS ONLY" which appears on the first page of the model informed consent has been replaced with the following text, "It is suggested that CTSU institutions incorporate the following paragraph in their consent form." The section of the model informed consent that addresses the level of patient's consent regarding additional use of specimens has been put in bolded text. This was inadvertently not done at the time the protocol was distributed.

As a reminder, for those patients randomized to the mitoxantrone arm, mitoxantrone will be supplied and distributed by Immunex for this study. Mitoxantrone should be requested by faxing an **S9921** Novantrone® Drug Request Form (see Section 19.4) to the Immunex Drug Distribution Center (see Section 3.3.c). Drug will be shipped Monday through Wednesday and a minimum of two days notice is required.

Please append this notice to your copy of the protocol and replace the face page and pages 14, 17, 22, 25a, 26, 33 and 42. The face page reflects the date of the current revision.

This memorandum serves to notify the NCI, CALGB, CTSU, EPP Institutions and the Southwest Oncology Group Statistical Center.

cc: PROTOCOL AND INFORMATION OFFICE
Cathy M. Tangen, Dr. P.H.
Tracy R. Glass, M.S.
Kathy Bingham
Rodney Sutter
Jean Barce
Lori Clark
Nickey McCasland, R.N.
John Taylor (CALGB)
Gity Nasim (EMMES)
Anita Nelson (CTSU)
Megan Davis (Astra Zeneca)
Rose Hesselbrock (Immunex)
Mike Proctor (Uinta Vision)



Southwest Oncology Group

A National Clinical Research Group

February 1, 2001

TO: ALL SOUTHWEST ONCOLOGY GROUP, CCOP, AFFILIATE AND UCOP MEDICAL ONCOLOGISTS, RADIATION ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; EPP INSTITUTIONS; CALGB; CTSU

FROM: Jennifer I. Scott, Protocol Coordinator

RE: **S9921**, "Adjuvant Androgen Deprivation Versus Mitoxantrone Plus Prednisone Plus Androgen Deprivation in Selected High Risk Prostate Cancer Patients Following Radical Prostatectomy, Phase III." Study Coordinators: Drs. L. M. Glode, M.H.A. Hussain, G. P. Swanson, D. P. Wood, Jr. and W. A. Saks.

REVISION #6

Study Coordinator: L. Michael Glode, M.D. Phone: 303/315-8801
E-mail: mike.glode@uchsc.edu

IRB Review Requirements

- () Full board review required
(√) Expedited review allowed
() No review required

REVISION #6

Attached please find a copy of a brochure prepared by the Study Coordinator for your use as a recruitment tool for the above noted study.

Also please note that section 3.3 c of the above noted protocol has been revised under "Formulation" to indicate that only the 12.5 ml vial will be supplied for this study.

Please append this notice to your copy of the protocol and replace the face page and page 10a. The face page reflects the date of the current revision.

This memorandum serves to notify the NCI, CALGB, CTSU, EPP Institutions and the Southwest Oncology Group Statistical Center.

cc: PROTOCOL AND INFORMATION OFFICE

Cathy M. Tangen, Dr. P.H.

Tracy R. Glass, M.S.

Kathy Bingham

Rodney Sutter

Jean Barce

Lori Clark

Nickey McCasland, R.N.

John Taylor (CALGB)

Gity Nasim (EMMES)

Anita Nelson (CTSU)

Megan Davis (Astra Zeneca)

Rose Hesselbrock (Immunex)

Mike Proctor (OTN)

Operations Office

14980 Omicron Drive•San Antonio, TX 78245-3217 • Telephone 210-677-8808 • FAX 210-677-0006 • <http://swog.org>



Improving the OUTCOME for High Risk Prostate Cancer Patients

THE PROBLEM

1. Prostate cancer patients do well after surgery IF their pathology is favorable.
2. High Risk patients are usually not cured by surgery alone.
3. For breast cancer, hormonal and chemotherapy adds significantly to survival.

THE SOLUTION

Both Urologists and Patients should discuss the final pathology results, considering the risk factors for relapse.

High Risk means having one or more of the following:

- ◆ Gleason Sum ≥ 8
- ◆ Positive lymph nodes
- ◆ Positive surgical margin
- ◆ Positive seminal vesicles

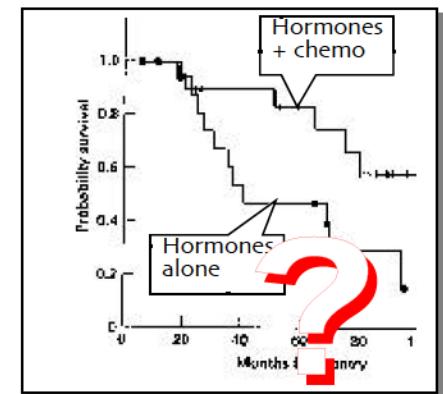
If one or more of these conditions exist, consider participating in the **S9921** Clinical Trial



SOUTHWEST ONCOLOGY GROUP
14980 Omicron Drive
San Antonio, TX 78245-3217
(210) 677-8808
(210) 677-0006

Prostate Cancer: Treating High Risk Patients After Surgery

NOW WE ALL CAN
DO MORE!



This figure shows the disease specific survival among 19 patients in each arm of a clinical trial comparing hormone treatment to hormone treatment plus chemotherapy. None of these patients had surgery on the prostate. Also, none of them had positive bone or CT scans. The question is whether such treatment would work after surgery in high risk patients. Reference: BJU International (2000), 86:675-689

ABOUT CLINICAL TRIALS

A clinical trial is a research study to answer specific questions about vaccines, new therapies, or new ways of using standard treatments. Clinical trials (also called medical research and research studies) are used to determine whether new drugs or treatments are both safe and effective. Carefully conducted clinical trials are the safest and most efficient way to find treatments that work. Unlike other fields, placebo-controlled trials in cancer research are rare and are used only if there is no known treatment available.

All patients on the S9921 Clinical Trial receive additional hormone therapy. This will consist of Zoladex and Casodex, two drugs that reduce the effect of testosterone on any cancer cells remaining in the body. In addition, half of the patients receive Prednisone and Mitoxantrone, two drugs known to be effective in killing additional prostate cancer cells. Prednisone is a hormone, and Mitoxantrone is a chemotherapy drug.

WHY DOESN'T EVERYONE GET ALL OF THE DRUGS?

■ It is unknown whether additional chemotherapy plus prednisone will be helpful *after surgery*, and there are side effects of chemotherapy. The figure on the front of this brochure compared hormone treatment alone to hormones plus chemotherapy in a very limited number of patients (19 per group). *None of these patients had surgery* on the prostate, and none had any evidence of metastases. **S9921** compares the two treatment methods in patients after surgery.

HOW WILL MY TREATMENT BE DETERMINED?

■ If you and your doctor find that you are eligible for the study, you will be asked to sign a detailed consent form that explains all the risks and benefits of participating in the trial. You would then start either the hormone only (Zoladex/Casodex) treatment OR the same treatment plus the Prednisone/Mitoxantrone. A computer will randomize patients onto the two arms of the study.

WHO WILL BE IN CHARGE?

Your urologist will work closely with other cancer specialists in caring for you. Some patients may receive additional treatment with radiation therapy to the prostate bed if the doctors feel this would be best for controlling local disease. A medical oncologist will most likely be the person directing the chemotherapy. Many times, this type of "team approach" can result in the best of care.

Call 210-677-8808 for more information on S9921

HOW CAN I LEARN MORE ABOUT THIS TRIAL?

A consent form is available for you to read which explains the risks and benefits of participating in this trial. Simply ask your doctor for a copy.

WHAT OTHER TREATMENTS ARE AVAILABLE?

For patients with high risk prostate cancer, no further therapy has been the standard of care until very recently. Many physician experts in the field now feel that hormone treatment such as is given to **ALL** patients in this trial will improve survival. Radiation therapy to the prostate bed is another consideration, since it can kill cells which might have been left behind. Its overall impact on survival is less clear, and like chemotherapy, it produces some side effects. Ongoing research on vaccines, gene therapy, anti-angiogenesis, and novel hormonal treatments are sometimes considered in cases of high risk prostate cancer, but none of these are considered standard and none have been proven to improve outcomes.

WHERE CAN I LEARN MORE?

There are many useful books written for prostate cancer patients and brochures are available from the National Cancer Institute. For general questions, call 1-800-4-Cancer or visit the National Cancer Institute Website (www.nci.nih.gov). Additional information is available from the American Cancer Society (www.cancer.org), the American Society of Clinical Oncology (www.asco.org) and the American Urologic Association (www.auanet.org).



January 1, 2001

TO: ALL SOUTHWEST ONCOLOGY GROUP, CCOP, AFFILIATE AND UCOP MEDICAL ONCOLOGISTS, RADIATION ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; EPP INSTITUTIONS; CALGB; CTSU

FROM: Jennifer I. Scott, Protocol Coordinator

RE: **S9921**, "Adjuvant Androgen Deprivation Versus Mitoxantrone Plus Prednisone Plus Androgen Deprivation in Selected High Risk Prostate Cancer Patients Following Radical Prostatectomy, Phase III." Study Coordinators: Drs. L. M. Glode, M.H.A. Hussain, G. P. Swanson, D. P. Wood, Jr. and W. A. Sakr.

REVISION #5

Study Coordinator: L. Michael Glode, M.D. Phone: 303/315-8801
E-mail: mike.glode@uchsc.edu

IRB Review Requirements

- () Full board review required
() Expedited review allowed
() No review required

REVISION #5

The above-noted protocol has been revised as follows:

The Table of Contents has been revised to correct the page numbers indicated for the Data Submission Schedule, Special Instructions and Ethical and Regulatory Considerations.

Section 5.4 has been revised to clarify that patients must not have received prior radiation therapy. If the treating physician wishes to have RT administered, then the patient should be registered to the study FIRST and then optional RT can be given on protocol. All RT should be documented on the flow sheet.

Section 7.5 has been revised to correctly indicate that radiation therapy for patients on either arm of the study will be allowed at the physician's discretion following the guidelines outlined in this section. This applies to all patients, not just those with positive surgical margins.

Section 9.2, the study calendar for arm 2, has been corrected as follows: the "x"s have been deleted under Month 4 for mitoxantrone and prednisone; "x"s have been added for bicalutamide since it is taken daily; and "x"s have been moved from Month 4 to Day 106 (Cycle 6) for history and physical exam and weight and performance status.

Operations Office

14980 Omicron Drive • San Antonio, TX 78245-3217 • Telephone 210-677-8808 • FAX 210-677-0006 • <http://swog.org>



Attached please find a report of an adverse event submitted to the Food and Drug Administration (FDA) by AstraZeneca. The decision to amend the local consent form should be made by the local institutional review board.

Please append this notice to your copy of the protocol and replace the face page and pages 14, 17 and 22. The face page reflects the date of the current revision.

This memorandum serves to notify the NCI, CALGB, CTSU, EPP Institutions and the Southwest Oncology Group Statistical Center.

cc: PROTOCOL AND INFORMATION OFFICE

Cathy M. Tangen, Dr. P.H.
Tracy R. Glass, M.S.
Kathy Bingham
Rodney Sutter
Jean Barce
Lori Clark
Nickey McCasland, R.N.
John Taylor (CALGB)
Gity Nasim (EMMES)
Anita Nelson (CTSU)
Megan Davis (Astra Zeneca)
Rose Hesselbrock (Immunex)
Mike Proctor (OTN)





ATTENTION: THIS INFORMATION MUST BE REPORTED TO YOUR INSTITUTIONAL REVIEW BOARD AND FILED IN YOUR INVESTIGATOR BROCHURE.

15 August, 2000

Majorie A. Godfrey
Director of Operations
14980 Omicron Drive
San Antonio TX 78245-3217

RE: 7054IL/0023; 7054IL/0018; 7054IL/0021; 7054US/0003; 7054US/0004; 7054US/0005; 7054US/0006;
7054US/0007; 7054US/0008; 7054US/0009; 7054US/0011; **7054US/0012 (SWOG Study 9921);**
7054US/0013; 7054US/0016

Dear Ms. Godfrey:

This is a follow-up report to initial information sent on 08 March 2000.

The adverse event described in this letter has been recently reported to AstraZeneca Pharmaceuticals, and is being forward to the Food and Drug Administration (FDA) and to you in accordance with the requirements for IND safety reporting under the FDA's Investigational New Drug regulations. The adverse experience occurred in clinical trial 0023 entitled "A RANDOMIZED DOUBLE-BLIND COMPARATIVE TRIAL OF BICALUTAMIDE (CASODEX™) VERSUS PLACEBO IN PATIENTS WITH EARLY PROSTATE CANCER."

Subject: JRK (7054IL/0023/0094/0044): This 73-year-old Caucasian man with stage T2A prostate cancer began blinded trial therapy on 13 May 1997 and completed on 9 March 1999. On 8 February 2000, 11-months post trial treatment, the patient was found to have a 1.5 cm nodule in his left breast. The patient also has a concurrent history of gynecomastia that was diagnosed on 15 November 1997. A left subcutaneous mastectomy was performed on 1 March 2000 and the subsequent pathology report demonstrated a grade III tumor with lymphovascular infiltration.

^On 16 March 2000, the patient underwent a left radical modified mastectomy. Additional treatment included, TAMOXIFEN™, and chemotherapy, followed by a course of local radiation to reduce the risk of local recurrence. There were no complications following the procedure, and the patient was discharged in stable condition. ^ The investigator considered the carcinoma of the left breast to be possibly related to trial therapy.

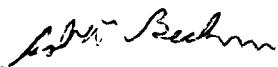
^Worldwide exposure to CASODEX™ since launch in 1995 is estimated at greater than 330,000 patient years. The age adjusted incidence of breast cancer in males is 1 per 100,000 patient years (SEER Cancer Statistics Review, 1973-1997, National Cancer Institute, Table IV-2). Therefore, while the causal role of CASODEX™ cannot be completely ruled out, the observation of this one case of male breast cancer is consistent with the spontaneous rate in the general population. ^ AstraZeneca has reviewed the safety database for CASODEX™ and has not found any other prior cases of confirmed breast cancer.

Page Two
Majorie A. Godfrey
15 August, 2000

We wish to remind you that it is your responsibility to report the occurrence of all serious and unexpected adverse experiences, regardless of the causality, to AstraZeneca Pharmaceuticals immediately following the occurrence of the event. Life-threatening or fatal events should be reported immediately via a telephone call.

As in the past, we will continue to monitor all patients receiving 7054IL (CASODEX™) therapy and will report any significant adverse experiences to you promptly. It is your responsibility to provide this information to your institution's Review Board or Ethics Committee. Please feel free to call me at 1-800-456-3669, extension 68388 if you have any questions or concerns.

Yours sincerely,



Robert A Beckman, MD
Project Physician
AstraZeneca Pharmaceuticals



Southwest Oncology Group

A National Clinical Research Group

Faxed: December 15, 2000
Mailed: January 1, 2001

TO: ALL SOUTHWEST ONCOLOGY GROUP, CCOP, AFFILIATE AND UCOP MEDICAL ONCOLOGISTS, RADIATION ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; EPP INSTITUTIONS; CALGB; CTSU

FROM: Jennifer I. Scott, Protocol Coordinator

RE: **S9921**, "Adjuvant Androgen Deprivation Versus Mitoxantrone Plus Prednisone Plus Androgen Deprivation in Selected High Risk Prostate Cancer Patients Following Radical Prostatectomy, Phase III." Study Coordinators: Drs. L. M. Glode, M.H.A. Hussain, G. P. Swanson, D. P. Wood, Jr. and W. A. Sakr.

MEMORANDUM

Study Coordinator: L. Michael Glode, M.D. Phone: 303/315-8801
E-mail: mike.glode@uchsc.edu

IRB Review Requirements

- () Full board review required
() Expedited review allowed
(✓) No review required

MEMORANDUM

Immunex has notified the Southwest Oncology Group that they will be closed at the end of the business day on Thursday, December 21, 2000 through Monday, January 1, 2001 and will reopen on Tuesday, January 2, 2001. During this period, Immunex will not ship study drug (mitoxantrone).

ORDERING DRUG

To prepare for the holiday close, Immunex asks that you check with your investigational pharmacist to assure that there will be an adequate supply of mitoxantrone during this time. If you need additional drug, please have the pharmacist order drug no later than 10:00 AM Pacific time on Tuesday, December 19, 2000. This will allow Immunex to ship the drug and confirm its arrival before the holiday break.

Please append this notice to your copy of the protocol.

This memorandum serves to notify the NCI and the Southwest Oncology Group Statistical Center.

cc: PROTOCOL AND INFORMATION OFFICE
Cathy M. Tangen, Dr. P.H.
Tracy R. Glass, M.S.
Kathy Bingham
Rodney Sutter
Jean Barce
Lori Clark

John Taylor (CALGB)
Gity Nasim (EMMES)
Anita Nelson (CTSU)
Megan Davis (Astra Zeneca)
Rose Hesselbrock (Immunex)
Mike Proctor (OTN)





July 15, 2000

TO: ALL SOUTHWEST ONCOLOGY GROUP, CCOP, AFFILIATE AND UCOP MEDICAL ONCOLOGISTS, RADIATION ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; EPP INSTITUTIONS; CALGB; CTSU

FROM: Jennifer Scott Gazvoda, Protocol Coordinator

RE: **S9921**, "Adjuvant Androgen Deprivation Versus Mitoxantrone Plus Prednisone Plus Androgen Deprivation in Selected High Risk Prostate Cancer Patients Following Radical Prostatectomy, Phase III." Study Coordinators: Drs. L. M. Glode, M.H.A. Hussain, G. P. Swanson, D. P. Wood, Jr. and W. A. Sakr.

REVISION #4

Study Coordinator: L. Michael Glode, M.D. Phone: 303/315-8801
E-mail: mike.glode@uchsc.edu

IRB Review Requirements

- () Full board review required
() Expedited review allowed
() No review required

REVISION #4

The above-noted protocol has been revised as follows:

Section 13.1 has been revised to indicate that patients must be registered prior to initiation of treatment (no more than ten working days prior to planned start of treatment). The additional time is to allow for the ordering and shipment of mitoxantrone for patients randomized to Arm 2.

Please append this notice to your copy of the protocol and replace page 24.

This memorandum serves to notify the NCI and the Southwest Oncology Group Statistical Center.

cc: PROTOCOL AND INFORMATION OFFICE
Cathy M. Tangen, Dr. P.H.
Tracy R. Glass, M.S.
Kathy Bingham
Rodney Sutter
Jean Barce
John Taylor (CALGB)
Gity Nasim (EMMES)
Anita Nelson (CTSU)
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Mike Proctor (OTN)

Operations Office

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Southwest Oncology Group

A National Clinical Research Group

July 1, 2000

TO: ALL SOUTHWEST ONCOLOGY GROUP, CCOP, AFFILIATE AND UCOP MEDICAL ONCOLOGISTS, RADIATION ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; EPP INSTITUTIONS; CALGB; CTSU

FROM: Jennifer Scott Gazvoda, Protocol Coordinator

RE: **S9921**, "Adjuvant Androgen Deprivation Versus Mitoxantrone Plus Prednisone Plus Androgen Deprivation in Selected High Risk Prostate Cancer Patients Following Radical Prostatectomy, Phase III." Study Coordinators: Drs. L. M. Glode, M.H.A. Hussain, G. P. Swanson, D. P. Wood, Jr. and W. A. Saks.

AMENDMENT #1

Study Coordinator: L. Michael Glode, M.D. Phone: 303/315-8801
E-mail: mike.glode@uchsc.edu

IRB Review Requirements

- (✓) Full board review required
 - () Expedited review allowed
 - () No review required

AMENDMENT #1

The above-noted protocol has been amended as follows:

Section 1.1b has been amended to read "mitoxantrone + prednisone administered with Casodex® + Zoladex®" to be consistent with the treatment section of the protocol.

The area code for the Immunex Drug Distribution Center has been changed to 425. This change is reflected in Section 3.3c and Appendix 19.4.

Currently, patients with a history of neoadjuvant hormones are eligible for this study. The following has been added as Section 5.1d to allow for patients who have cT1-2 and are considered high risk: "Patients who have received preoperative hormone therapy and have either a preoperative serum PSA value of > 15 ng/ml, or a biopsy Gleason score > 7, or a serum PSA level of > 10 ng/ml and a biopsy Gleason score > 6 are eligible."

Please append this notice to your copy of the protocol and replace pages 4, 10a, 14 - 15 and 56.

This memorandum serves to notify the NCI and the Southwest Oncology Group Statistical Center.

cc: PROTOCOL AND INFORMATION OFFICE John Taylor (CALGB)
Cathy M. Tangen, Dr. P.H. Gity Nasim (EMMES)
Tracy R. Glass, M.S. Anita Nelson (CTSU)
Kathy Bingham Megan Davis (Astra Zeneca)
Rodney Sutter Rose Hesselbrock (Immunex)
Jean Barce Mike Proctor (OTN)





June 1, 2000

TO: ALL SOUTHWEST ONCOLOGY GROUP, CCOP, AFFILIATE AND UCOP MEDICAL ONCOLOGISTS, RADIATION ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; EPP INSTITUTIONS; CALGB; CTSU

FROM: Jennifer Scott Gazvoda, Protocol Coordinator

RE: **S9921**, "Adjuvant Androgen Deprivation Versus Mitoxantrone Plus Prednisone Plus Androgen Deprivation in Selected High Risk Prostate Cancer Patients Following Radical Prostatectomy, Phase III." Study Coordinators: Drs. L. M. Glode, M.H.A. Hussain, G. P. Swanson, D. P. Wood, Jr. and W. A. Sakr.

REVISION #3

Study Coordinator: L. Michael Glode, M.D. Phone: 303/315-8801
E-mail: mike.glode@uchsc.edu

REVISION #3

The above-noted protocol has been revised as follows:

1. The Cancer Trials Support Unit (CTSU) has been added as a participant in this study. The logistics for CTSU are reflected in the Title Page (Pages 1 and 2), Section 13.5 (Registration Guidelines), Section 14.5 (Data Submission Schedule), Section 16.0 (Adverse Event Reporting) and the Informed Consent Document. Sections 13.0 and 14.0 were re-numbered accordingly. References to Section 14.0 were corrected in Section 5.0.
2. The notes regarding Regional Lymph Nodes have been revised on the Local Prostate Carcinoma Prestudy Form.

Replacement pages are enclosed for the face page, pages 2, 14, 25 - 27c, 33, 33a, 40, 40a and the Local Prostate Carcinoma Prestudy and should be inserted into your protocol. Pages 27b, 27c, 33a and 40a were added to prevent extensive repagination.

This memorandum serves to notify the NCI and the Southwest Oncology Group Statistical Center.

cc: PROTOCOL AND INFORMATION OFFICE
Cathy M. Tangen, Dr. P.H.
Tracy R. Glass, M.S.
Kathy Bingham
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Mike Proctor (OTN)

Operations Office

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May 15, 2000

TO: ALL SOUTHWEST ONCOLOGY GROUP, CCOP, AFFILIATE AND UCOP MEDICAL ONCOLOGISTS, RADIATION ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; EPP INSTITUTIONS; CALGB

FROM: Jennifer Scott Gazvoda, Protocol Coordinator

RE: **S9921**, "Adjuvant Androgen Deprivation Versus Mitoxantrone Plus Prednisone Plus Androgen Deprivation in Selected High Risk Prostate Cancer Patients Following Radical Prostatectomy, Phase III." Study Coordinators: Drs. L. M. Glode, M.H.A. Hussain, G. P. Swanson, D. P. Wood, Jr. and W. A. Sakr.

REVISION #2

Study Coordinator: L. Michael Glode, M.D. Phone: 303/315-8801
E-mail: mike.glode@uchsc.edu

REVISION #2

The above noted study has been revised to indicate that the prestudy lymph node dissection should be obtained within 120 days prior to registration as a part of Good Medical Practice rather than eligibility. This change is reflected in Sections 5.1 and 7.1 of the protocol.

CALGB has been added as a participant to this study. The addition of CALGB is reflected on the face page and in Sections 13.4, 14.4, 15.3, 16.0 and the model informed consent. References to Section 14.4 throughout the protocol have been revised to 14.5 accordingly.

Section 13.1 has been revised to be consistent with current Southwest Oncology Group standard requirements.

Section 3.3c and Appendix 19.4 have been revised to indicate that mitoxantrone will be shipped Monday through Wednesday. The Immunex protocol number has been added to Appendix 19.4.

Replacement pages are enclosed for the face page, pages 2, 10a, 14, 16, 24 - 27, 40 and Appendix 19.4 and should be inserted into your protocol. Pages 25a and 27a were added to prevent extensive repagination.

This memorandum serves to notify the NCI and the Southwest Oncology Group Statistical Center.

cc: PROTOCOL AND INFORMATION OFFICE
Cathy M. Tangen, Dr. P.H.
Tracy R. Glass, M.S.
Kathy Bingham
Rodney Sutter
Jean Barce
John Taylor (CALGB)
Gity Nasim (EMMES)
Andrew Farnsworth (AstraZeneca)
Rose Hesselbrock (Immunex)





April 15, 2000

TO: ALL SOUTHWEST ONCOLOGY GROUP, CCOP, AFFILIATE AND UCOP MEDICAL ONCOLOGISTS, RADIATION ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; EPP INSTITUTIONS

FROM: Jennifer Scott Gazvoda, Protocol Coordinator

RE: **S9921**, "Adjuvant Androgen Deprivation Versus Mitoxantrone Plus Prednisone Plus Androgen Deprivation in Selected High Risk Prostate Cancer Patients Following Radical Prostatectomy, Phase III." Study Coordinators: Drs. L. M. Glode, M.H.A. Hussain, G. P. Swanson, D. P. Wood, Jr. and W. A. Sakr.

REVISION #1

Study Coordinator: L. Michael Glode, M.D. Phone: 303/315-8801
E-mail: mike.glode@uchsc.edu

REVISION #1

The above-noted study has been revised to indicate that Astra Zeneca Pharmaceuticals will provide Casodex® and Zoladex® free of charge to patients registered to this protocol. Additionally, Immunex has agreed to provide mitoxantrone free of charge to patients registered to Arm 2 of this protocol. These changes are reflected in Sections 3.1c, 3.2c and 3.3c (supplier), the Model Informed Consent Form, and the addition of two appendices. The new appendices are: Section 19.3 - the Returned Medication Packing Slip (for Casodex® and Zoladex®) and 19.4 the **S9921** Novantrone® Drug Request Form.

Additionally, Dr. Swanson's contact information has been updated on the face page and in Section 8.4. The time frame for prestudy prostatectomy has been lengthened from a maximum of 90 days to a maximum of 120 days prior to registration (the time frames in Sections 5.1 and 5.11 guidelines, as well as both Study Calendars have been revised accordingly). Radiation timing guidelines have been added in Section 7.5 and two typographical errors were corrected in the same section. Standard statements regarding IRB approval were updated in Sections 5.13 and 13.3. The term "Affiliates" replaced the term "CGOPs/Member Affiliates" on the face page, Section 13.1 and Section 14.3. The "Ω" footnote on both Study Calendars was corrected to clarify the intent and timing for off treatment follow-up. Study Calendar 9.2 was corrected to show the intended timing of history and physical examinations during chemotherapy (every cycle). Additionally, Section 11.5 was revised to clarify that three interim analyses are planned for this study.

Replacement pages are enclosed for the face page, pages 8 - 10, 14, 15, 17, 18, 20 - 22, 24, 25, 40 and 51. The new appendices, Sections 19.3 and 19.4 are also enclosed and should be inserted at the end of your protocol. Page 10a was added to prevent extensive repagination.

This memorandum serves to notify the NCI and the Southwest Oncology Group Statistical Center.

cc: Cathy M. Tangen, Dr. P.H.
Tracy R. Glass, M.S.
Kathy Sears

Gity Nasim (EMMES)
Andrew Farnsworth (AstraZeneca)
Rose Hesselbrock (Immunex)





October 15, 1999

TO: ALL SOUTHWEST ONCOLOGY GROUP, CCOP, CGOP/MEMBER AFFILIATES, AND UCOP MEDICAL ONCOLOGISTS, RADIATION ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; EPP INSTITUTIONS

FROM: Steven K. McGee, Protocol Coordinator

RE: **S9921**, "Adjuvant Androgen Deprivation Versus Mitoxantrone Plus Prednisone Plus Androgen Deprivation in Selected High Risk Prostate Cancer Patients Following Radical Prostatectomy, Phase III." Study Coordinator: Dr. M.L. Glode.

STATUS NOTICE

Study Coordinator: Michael L. Glode, M.D. Phone: 303/315-8801
E-mail: mike.glode@uchsc.edu

ACTIVATION

The study referenced above is now open for registration. Entire copies of the protocol are enclosed for your use.

This memorandum serves to notify the NCI and the Southwest Oncology Group Statistical Center.

cc: Cathy M. Tangen, Dr. P.H.
Tracy R. Glass, M.S.
Kathy Sears
Gity Nasim (EMMES)



SOUTHWEST ONCOLOGY GROUP
PROTOCOL FAST FACT SHEET

*THIS FORM HAS BEEN DESIGNED AS A RESOURCE ONLY AND IS NOT INTENDED FOR USE IN THE
FULFILLMENT OF PATIENT REGISTRATION AND TREATMENT REQUIREMENTS*

S9921

**Adjuvant Androgen Deprivation versus Mitoxantrone Plus Prednisone Plus Androgen Deprivation
in Selected High Risk Prostate Cancer Patients Following Radical Prostatectomy**

Treatment Initiation: Within 10 working day of randomization.

Drugs Provided: Casodex and Zoladex will be provided by UVI, Inc.

Mitoxantrone will be provided by OSI Pharmaceuticals.

Prednisone must be purchased commercially.

ARM 1	ARM 2
Casodex 50mg po daily X 2 years Zoladex 10.8mg SC Q 3 months X 8	OR Casodex 50mg po daily X 2 years Zoladex 10.8mg SC Q 3 months X 8 Mitoxantrone 12mg/m ² IV day 1 Q 21 days X 6 Prednisone 5mg po bid Q 21 days X 6

Eligibility	Ineligibility
Clinically localized adenocarcinoma of the prostate (Stage T1– T3, N0, M0) prior to surgery	No other therapy aimed at treatment for this diagnosis may be given while receiving protocol treatment
Must have had radical prostatectomy within 120 days of registration and fulfill one or more of the following: <ul style="list-style-type: none">• Pathology Gleason's ≥ 8• pT3b (seminal vesicle) or pT4 or N1• Pathology Gleason's of 7 + positive margin• Pre-op PSA > 15 ng/ml or biopsy Gleason's > 7 or PSA > 10 ng/ml and biopsy Gleason's > 6	No prior malignancy except for adequately treated basal cell or squamous cell skin cancer, adequately treated Stage I or II cancer from which pt is currently in remission, or other cancer for which pt has been disease-free for 5 years.
Testosterone level within 28 days prior to registration. Post-op PSA must be < 0.2ng/ml.	No distant mets (must be confirmed through appropriate pre-registration testing).
Prior neoadjuvant hormonal therapy (≤ 4mos) prior to surgery allowed.	No prior RT. RT may be administered after registration.
Pts with pre-op PSA > 20ng/ml must have pre-study bone scan negative for metastatic disease.	No CHF unless well controlled and LVEF > 50%.
Pre-op EKG required within 42 days prior to registration. LVEF ≥ 50% by MUGA or 2-d echo (if history of cardiac disease) required within 42 days of registration. Must be offered specimen banking.	
PS 0 – 1.	

PRE-REGISTRATION REQUIREMENTS

H & P, wt, PS

Labs: CBC/plt/diff, PSA, bili, AST, testosterone

Scans: EKG (required), LVEF via MUGA or 2-d echo, CT abdomen/pelvis, bone scan (if indicated)

Tissue/serum specimen (per consent, see Section 15.0)/

PATIENT FOLLOW-UP

Labs: CBC/plt/diff weekly while on chemo, PSA monthly, testosterone at 4 & 7 mo, end of treatment

Scans: q 3 months while on chemo

Follow-up post chemo: q 3 mo PSA, bone scan, CT until progression

Follow-up post progression: q 6 months X 2 yrs, then annually for 3 yrs.

*This form has been developed with the support of the SWOG Nurse Oncologists' Committee.



**PRIVILEGED COMMUNICATION
FOR INVESTIGATIONAL USE ONLY**

Revised 6/1/00
Revised 1/1/01
Revised 4/1/02
Revised 8/1/02

S9921
Activated 10/15/99
Amended 2/14/06
Revised 2/1/07
Revised 12/19/14

SOUTHWEST ONCOLOGY GROUP

ADJUVANT ANDROGEN DEPRIVATION VERSUS MITOXANTRONE PLUS PREDNISONE PLUS
ANDROGEN DEPRIVATION IN SELECTED HIGH RISK PROSTATE CANCER PATIENTS FOLLOWING
RADICAL PROSTATECTOMY

PHASE III

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This study is supported by the NCI Cancer Trials Support Unit (CTSU).

Institutions not aligned with the Southwest Oncology Group will participate through the CTSU mechanism as outlined below and detailed in the CTSU logistical appendix.

- The **study protocol and all related forms and documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at <https://members.ctsu.org>.
- Send completed **site registration documents** to the CTSU Regulatory Office. Refer to the CTSU logistical appendix for specific instructions and documents to be submitted.
- **Patient enrollments** will be conducted by the CTSU.
- Data management will be performed by the Southwest Oncology Group. **Case report forms** (with the exception of patient enrollment forms), **clinical reports, and transmittals** must be sent to the Southwest Oncology Group Data Operations Office unless otherwise directed by the protocol. Do not send study data or case report forms to the CTSU Data Operations.
- **Data query and delinquency reports** will be sent directly to the enrolling site by the Southwest Oncology Group. Please send query responses and delinquent data to the Southwest Oncology Group Data Operations Office and do not copy the CTSU Data Operations.
- Each site should have a designated CTSU Administrator and Data Administrator and must keep their CTEP AMS account contact information current. This will ensure timely communication between the clinical site and the Southwest Oncology Group Data Operations Office.



ECOG STUDY COORDINATOR:

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CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION:

To submit site registration documents:	For patient enrollments:	Submit study data directly to the Lead Cooperative Group unless otherwise specified in the protocol:
CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA 19103 Phone - 1-888-823-5923 Fax - 215-569-0206	CTSU Patient Registration Voice Mail – 1-888-462-3009 Fax – 1-888-691-8039 Hours: 8:00 AM – 8:00 PM Eastern Time, Monday – Friday (excluding holidays) [For CTSU patient enrollments that must be completed within approximately one hour, or other extenuating circumstances, call 301-704-2376. Please use the 1-888-462-3009 number for ALL other CTSU patient enrollments.]	Southwest Oncology Group Data Operations Office Fax: 800/892-4007 Do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions.
<u>For patient eligibility or treatment-related questions</u> contact the Study PI of the Coordinating Group.		
<u>For questions unrelated to patient eligibility, treatment, or data submission</u> contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com . All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU Public Web site is located at: www.ctsu.org The CTSU Registered Member Web site is located at https://members.ctsu.org		

PARTICIPANTS

ALLIANCE/Alliance for Clinical Trials in Oncology

ECOG-ACRIN/ECOG-ACRIN Cancer Research Group
SWOG/SWOG

Please refer to all questions regarding chemotherapy treatment or dose modifications to Dr. L. Michael Glode. For radiation therapy related questions, contact Dr. Gregory P. Swanson.



SCHEMA

Prostate Cancer
Clinical Stage T1-T3



Radical Prostatectomy
(high risk as defined in Sections 5.1a - d)



Any pT, N0, N1



RANDOMIZE



Casodex
and Zoladex
X 24 months

Mitoxantrone and
Prednisone X 6 cycles
plus Casodex and
Zoladex X 24 months

Follow for Survival or
for a maximum of 15

1.0 OBJECTIVES

- 1.1 The primary objective is to evaluate overall survival using adjuvant systemic therapy in high risk localized prostate cancer patients following radical prostatectomy. Disease-free survival will also be evaluated. Patients will be randomized to one of the following arms:
 - a. bicalutamide (Casodex[®]) + goserelin acetate (Zoladex[®])
 - b. mitoxantrone + prednisone administered with Casodex[®] + Zoladex[®].
- 1.2 To compare qualitative and quantitative toxicity between the two study arms.
- 1.3 To compare the two treatment arms with respect to PSA progression-free survival.
- 1.4 To test whether PSA progression is a surrogate endpoint for survival or disease-free survival in this clinical trial.
- 1.5 To evaluate promising biomarkers with respect to predicting PSA progression, disease-free survival, and overall survival.
- 1.6 To collect specimens (blood and prostatectomy blocks) for future biomarker (immunohistochemistry, proteomics, genomics) studies and correlations with outcomes.

2.0 BACKGROUND**Introduction**

Historically the management of localized adenocarcinoma of the prostate has followed a monotherapy strategy. (1, 2) For several decades, patients thought to have organ-confined prostate cancer or minimal risk of extracapsular disease were offered either radical prostatectomy or radical irradiation. Although these therapies are considered curative, it is well recognized that the potential for cure is highly dependent on stage and grade. Approximately 30% of patients with organ-confined prostate cancer and up to 60% of patients with T3 tumors are at risk for a systemic relapse despite curative intent radical prostatectomy. (3) The figure is higher if the nodes are positive.

In patients with clinically organ confined prostate cancer, freedom from biochemical relapse at 5 years is related to Gleason score, PSA, pathologic T and N stage and status of the surgical margin. (4 - 8) Freedom from relapse at 5 years ranging from 83% - 95% is especially associated with Gleason score of ≤ 6, pT1-T2 with a pre-therapy PSA of < 10 ng/ml. (5) A preoperative PSA of > 20 ng/ml, poorly differentiated histology (Gleason ≥ 8), seminal vesicle or extensive surgical margin involvement or nodal metastases define a high risk group of patients with a 50% or greater biochemical relapse rate at 5 years. (5 - 8) These data suggest the presence of occult systemic disease at time of initial diagnosis underscoring the potential importance of early systemic therapy. The case for the latter may be strengthened by the knowledge that recurrent/metastatic prostate cancer is currently incurable in the majority of cases.

A greater recognition of the importance of eliminating subclinical residual disease or occult systemic metastases in a variety of solid tumors has led to the investigation and development of multimodality treatment approaches. Survival improvements had become more achievable particularly with the addition of systemic therapy such as the case in breast, colorectal, and lung cancers and melanoma. (9 - 12) By comparison the evolution of multimodality therapy for prostate cancer has been relatively slow. This lag may in part be attributed to the perceived lack of precise prognostic criteria capable of predicting relapse risk for a particular individual, the long natural history which impacts on the timely evaluation of therapeutic efficacy, the lack of "effective" systemic nonhormonal therapy and the concern regarding the morbidity and negative quality of life effects of long-term hormonal therapy. However, a number of recent innovations have made it more feasible to investigate multimodality strategies including the introduction of PSA, the improvement in patient selection for local therapy and in surgical and radiation techniques, the development of long-acting reversible androgen-suppressing agents with minimal side effects and the development of systemic chemotherapy with modest but definite activity in the setting of refractory prostate cancer.

Neoadjuvant Therapy

In prostate cancer the use of systemic therapy (adjuvant or neoadjuvant), is not a new concept. Since the early 1970s, androgen deprivation has been investigated primarily in patients with locally advanced prostate cancer undergoing radiation therapy. Several trials have been reported including a randomized RTOG trial comparing 4 months of neoadjuvant hormonal therapy plus



local irradiation to an irradiation-only arm in patients with locally advanced disease (RTOG 86-10). (13, 14) A statistically significant improvement in local control and in 5 years incidence of distant metastases in favor of the combined therapy arm was demonstrated. (13)

A similar approach was adopted for patients undergoing radical prostatectomy, as 30%-60% of patients clinically thought to have organ-confined prostate cancer will have extraprostatic disease, thus are at a higher risk for relapse. (15, 16) Neoadjuvant androgen deprivation was used to decrease the number of patients with positive surgical margins with the assumption that this would translate to fewer relapses. The data from these studies to date are mixed in that neoadjuvant hormonal therapy can decrease the incidence of positive surgical margins but does not improve the disease-free or overall survival. (17 - 22) Initial reports with short follow up have suggested no difference in biochemical recurrence rates between patients treated with neoadjuvant androgen deprivation plus radical prostatectomy and those treated with radical prostatectomy alone. (22) While the reasons for the lack of objective benefits are unclear it may be that brief exposure to androgen deprivation is ineffective in controlling occult systemic disease. The latter is not entirely surprising since in breast cancer, another hormone sensitive tumor, it has been demonstrated that longer duration of therapy is superior to shorter duration of hormonal manipulation. (23) Furthermore, the neoadjuvant studies that have been conducted were designed with short follow-up to detect pathologic but not survival differences, and it could be suggested that hormonal therapy can induce changes in the prostate cancer cells making it difficult for the pathologist to recognize their existence. (24) The latter would lead to a false increased rate of organ-confined tumors. With this data it is reasonable to conclude that the role of neoadjuvant hormonal therapy prior to radical prostatectomy remains to be determined.

Adjuvant Therapy

Considering that: a) appropriate patient selection is crucial for the success of combined therapy trials; b) current determinants of recurrence are based predominantly on pathologic findings and c) the fact that longer systemic therapy duration is likely to be necessary, it would seem quite logical to investigate adjuvant systemic therapy in patients with high risk localized prostate cancer. Current data which will be summarized in the ensuing paragraphs suggest that systemic therapy in the form of short course or permanent androgen deprivation results predominantly in prolongation of disease free survival, however, statistically significant survival improvements were demonstrated in only one study. A significant disease free survival advantage was noted at 5, 10, and 15 years in favor of diethylstilbestrol (DES) plus radiation therapy as compared with standard dose irradiation in 78 patients with locally advanced prostate cancer. (25) The lack of an overall survival advantage was attributed to the greater incidence of intercurrent disease-related mortality in the DES arm. The second study was conducted by the National Prostate Cancer Project (NPCP) in radical prostatectomy (NPCP-900, 184 patients) or radiation therapy (NPCP-1000, 253 patients) treated patients. (26) Following lymph node dissection, patients were randomized to observation, cyclophosphamide or estramustine. Recent update of the result with a 14.3 years follow-up indicate that the estramustine treated patients in both studies demonstrated improved progression free survival (PFS) especially in patients with T3 or T4 or Grade 3 tumors and in radiation treated patients with extensive nodal metastases.

The introduction of long acting reversible gonadal suppressing agents has fostered the development of a new generation of adjuvant therapy trials. Two randomized trials have been conducted comparing combined therapy to radiation alone, one by the Radiation Therapy Oncology Group (RTOG) and the other by the European Organization for Research and Treatment of Cancer (EORTC), in patients with locally advanced or node positive prostate cancer. The RTOG trial used life long or until progression androgen suppression with goserelin and the EORTC trial tested three years of adjuvant goserelin. (27, 28) With 945 evaluable patients in the former and 401 evaluable patients in the latter, combined modality therapy was superior with regard to disease-free survival in both trials. Overall survival superiority was observed only in the EORTC trial. However, for patients with centrally reviewed tumors with a Gleason score of 8 - 10, in the RTOG trial, the difference in actuarial five year survival was in favor of the adjuvant therapy arm (66% vs. 55%, P=0.03). The discrepancy in outcome with regard to survival between the two trials is unclear. It is interesting to note that the five year survival in the experimental arms of the two studies is comparable (75% and 79%, respectively), however the control arm in the RTOG study had a better survival than the EORTC study (71 % vs. 62%, respectively). This difference in

survival may be related, in part, to different patterns of clinical practice as they relate to timing of salvage hormonal therapy in the USA and Europe and differences in patients' characteristics.

With this background we organized a multidisciplinary consensus conference in April of 1997 to answer three specific questions: 1) Considering 1997 diagnosis and treatment standards, is prostate cancer a curable disease in the vast majority of patients undergoing radical prostatectomy for clinically localized prostate cancer?, 2) If not, can we identify the subset of patients that is likely to be at a high risk of relapse using current refined clinical/pathologic criteria?, 3) If a high risk subset can be defined, should adjuvant systemic therapy be investigated and what should the design be?

The conference recommendations were further endorsed by members of the Genitourinary Cancer Committee of the Southwest Oncology Group and the Prostate Committee of the Cancer and Leukemia Group-B (CALGB). These recommendations provide the basis for this proposal. The eligibility criteria used in this proposal are thought to identify a subset of patients with a 40% or greater risk of relapse. The primary endpoint is survival. Much discussion centered around the treatment arms. A "no therapy" arm versus hormonal therapy were both discussed as potential controls. However, the inherent difficulties in randomizing a high risk group to "no therapy" coupled with emerging data (discussed above) on early systemic therapy suggesting an advantage in at least the disease free survival, the fact that survival outcome from an adjuvant trial will not be ready for at least 10 years, with the desire to jump start the process and the awaited results of two major trials (the intergroup D1 adjuvant hormone trial and the adjuvant bicalutamide trial) led to choosing primary androgen deprivation as the control arm.

Therapy intensification using chemohormonal therapy was also deemed an important step based on proven successes of modestly active chemotherapy in other solid tumors such as colon, lung and melanoma when advanced to earlier stages, and attempting to change the paradigm in the management of this disease. Both estramustine and mitoxantrone based combination chemotherapy were considered. However, despite the apparent improved response rates with estramustine based combination chemotherapy, it was recognized that no large scale or Phase III data are currently available for these combinations in contrast to the mitoxantrone + prednisone combination therapy. (29 - 32) Although the latter combination had no impact on survival, the outcome from the two randomized trials indicate a higher proportion and duration of palliative, objective and PSA response rates in favor of the mitoxantrone/corticosteroid arm as compared with corticosteroid control, in addition to a favorable side effect profile. (31, 32)

With this background we propose a Phase III randomized trial targeting high risk surgically treated prostate cancer patients. A combined hormonal therapy arm will be compared with chemohormonal therapy arm.

The role of post prostatectomy radiation in patients with locally advanced disease is uncertain. Patients with margin, capsular, seminal vesicle, and lymph node involvement have a significant risk of local failure. Retrospective studies indicate that postoperative radiation could reduce the risk of local failure significantly. (33 - 35) It is unclear as to what degree this impacts on disease free and overall survival. (33 - 36) In 1987, the Southwest Oncology Group initiated a postprostatectomy study (**SWOG-8794**) that randomized patients with T3, N0, M0 disease to adjuvant radiation or none. The goal was to determine the effect of postoperative radiation on the disease free survival rate. The results of that study are to be reported in 2002. Accrual to the study was slower than expected, partially due to the increasing trust and dependence on PSA as a marker of failure. Since not all patients with T3 disease fail, it is appealing to wait for the disease to declare itself before initiating potentially morbid treatment. (37) On the other hand, there is some indication that earlier radiation might have a better chance of improving the outcome. (38, 39) Given that the question is uncertain, the Southwest Oncology Group will allow investigators to continue to utilize post-operative radiation to the prostate fossa at their discretion on this study.

Minority Participation

There is particular concern about prostate cancer in African American (AA) men where the incidence is higher and the prognosis appears to be worse. The issue in this trial is whether AA patients will have a different outcome as compared to non AA patients, and more specifically whether clinically meaningful arm-specific differences between AA and non AA patients can be detected. At this time there are no data suggesting that such a relationship exists. This study will provide an opportunity to perform exploratory analyses of the relationship of survival to AA status and adjuvant therapy. The Southwest Oncology Group experience in accruing AA patients to an early stage prostate cancer trial has been in **SWOG-8794** where 20% of the pathologic Stage C patients accrued are AA (which is considerably higher than that which would be expected based on the proportion of older AA men in the population).

Anticipated accrual to this study by race follows:

American Indian or Alaskan Native	Asian or Pacific Islander	Black, not of Hispanic Origin	Hispanic	White, not of Hispanic Origin	Other or Unknown	Total
1	5	313	41	1,000	0	1,360

As this is a prostate cancer study, no females will be registered.

3.0 DRUG INFORMATION

3.1 Bicalutamide (Casodex®) (NSC-0310-0705)

a. DESCRIPTION

Chemistry: Casodex® is a racemic mixture containing two enantiomers, (2RS)-4'-Cyano-3(4-fluorophenylsulphonyl)-2-hydroxy-2-methyl-3'-trifluoromethyl) propionanilide.

Casodex® is an active non-steroidal antiandrogen and its antiandrogen activity resides exclusively in the (-) or (R) enantiomer. Unlike flutamide, it is peripherally selective and does not cause a rise in serum LH or Testosterone in male rats and dogs. This peripheral selectivity may be because it penetrates poorly the CNS and Hypothalamus (the site of negative feedback of androgens). In humans, rises in LH, Testosterone and Estradiol concentrations were seen. These rises were not dose related. In 90%, testosterone levels remained within normal limits. There was no significant rise in mean serum FSH.

b. TOXICOLOGY

In rats, besides antiandrogenic changes, there was evidence of hepatocyte hypertrophy and basophilia. In dogs treated for 6 months, there was increased heart rate with decreased PR interval, transient decrease in circulating PMNs and increased plasma cholesterol. No cardiac pathology was found. In a mouse oncogenicity study, an increased incidence of hepatocellular carcinoma was observed in the top dose male group (75 mg/kg/day). The no effect dose level for hepatocellular carcinoma in this study was 15 mg/kg/day with steady state blood levels in excess of 10 µg/ml. The mechanism for this tumor formation is a non-genotoxic, phenobarbitone-type MFO induction and is not considered to represent a risk for humans. A two-year study in rats and female mice at similar doses did not show an increased incidence of hepatic tumors.



Casodex® has been given to over 3,500 men in 35 different clinical studies worldwide, in doses up to 600 mg daily. When Casodex® is given in combination with an LHRH analog, the pharmacologic adverse event profile is dominated by the LHRH analog and includes hot flashes (53%), gynecomastia (9%) and breast pain (6%). Other adverse events reported regardless of causality included diarrhea (12%), constipation (22%), nausea (15%) and abdominal pain (11%). Other adverse were reported, such as fatigue (22%), pain (35%), back pain (25%), pelvic pain (21%), infection (18%), peripheral edema (13%), dyspnea (13%), nocturia (12%), hematuria (12%), anemia (11%), dizziness (10%). Casodex® has been associated with changes in liver function, although these are infrequent (7%) and rarely occur with jaundice. Many of these changes improved or resolved despite continuation of bicalutamide therapy. There have been no reports of fatal hepatotoxicity associated with Casodex® therapy.

c. PHARMACOLOGY

Pharmacokinetics:

Animal studies: After oral single dose administration, absorption of the compound was slow with peak concentration occurring 3 - 12 hours and plateau between 2 and 48 hours. There was non-proportional increase in plasma levels with increasing doses. Elimination half life ranges from 17 - 28 hours in male rats, 21 - 29 hours in female rats and 5 - 7.5 days in dogs. 91 - 96% of Casodex® is bound to plasma protein.

Human studies: After single doses, mean time for peak plasma concentration was 6 hours at 10 and 30 mg, but at 50 mg, it was 16 hours. Mean plasma elimination half lives after 12 weeks of 10, 30, 50, 100 mg/day was 7 - 10 days. This finding was consistent with single dose data. In patients given daily doses of 50 mg, mean plasma concentration was 10 ug/ml at 12 weeks. After single doses, there was linear increase with doses between 10 and 50 mg, but became non-linear at doses of 50 - 100 mg. At 100 mg, the oral bioavailability is reduced by 30% but plasma elimination half life is unchanged. Casodex® is extensively metabolized and metabolites are excreted by both the biliary and urinary system.

Formulation: Casodex® is prepared as round, film-coated green or white tablets containing standard recipients and 50 mg of the drug.

Storage and stability: All packages of Casodex® should be stored securely in a dry place at room temperature.

Route of Administration: Casodex® is to be administered orally in tablet form as a once-daily oral dose. Patients should be instructed to take one tablet once daily.

Supplier: Casodex™ is commercially available, however for this study Astra Zeneca Pharmaceuticals, Inc. will supply the drug to UVI, Inc. for distribution. Casodex™ will be supplied as white tablets containing 50 mg each of micronized drug (F6625). Casodex™ will be provided in bottles of 100 tablets. Institutions are instructed to delay ordering the drug from the UVI, Inc. until they have a patient in mind for registration. Drug may be requested by contacting the clinical customer service staff at UVI, Inc. at Phone: 800/370-2508, Fax: 650/745-3877, Monday - Friday 8:00 a.m. - 5:00 p.m., PST. Please note that drug is shipped via UPS Ground and may take up to 5 business days for delivery. Drug must be ordered prior to 3:00 p.m. Eastern Time in order to be shipped that day. All unused drug supplies will be returned to UVI, Inc. for destruction using the Returned Medication Packing Slip (see Section 19.3), detailing the material being returned.

3.2 Goserelin Acetate (Zoladex[®]) D-Ser (But)⁶, Azgly¹⁰) (LH-RH) (ICI 118,630) (NSC-606864)

a. DESCRIPTION

Chemistry: The physical form of Zoladex is an off-white powder.

Chemical Structure:

pyro-Glu-His-Trp-Ser-Tyr-D-Ser (Bu^t)-Leu-Arg-Pro-Azgly-NH₂

Molecular Weight: 1269 (as base)

Solubility: Soluble in water, dimethylformamide and dimethylsulfoxide.

b. TOXICOLOGY

Animal Studies: In laboratory animals, the acute toxicity of ICI 118,630 was found to be very low in comparison to its pharmacologic potency. Intravenous doses of up to 6 mg/kg were without any adverse effects in rats undergoing LD50 studies. No significant pharmacological activity was apparent in the cardiovascular, respiratory, central nervous, renal and metabolic, coagulation or gastric acid secretory systems. In rats, but not the cat, mouse, dog or rabbit, long-term dosing of Zoladex has resulted in benign pituitary adenomas.

Human Toxicity: Most side effects attributed to LH-RH agonists have been due to testosterone withdrawal (e.g., hot flashes, sweats, impotence, breast enlargement, nausea and dizziness). Skin reaction and irritation at the injection site (rarely, < 2%) have also been observed. Tumor flares have been reported in a small number of patients receiving LH-RH agonists. Flare reactions usually consist of minor complications such as increased bone pain and therapy may be continued; however, potentially dangerous complications (e.g. incipient spinal cord compression or ureteral obstruction) must be averted by discontinuing Zoladex treatment and beginning corrective therapy immediately.

c. PHARMACOLOGY

Kinetics: Subcutaneous depot given on Days 1 and 29 to patients with prostatic cancer with normal renal and hepatic function revealed a peak concentration 12 to 15 days after administration, with peak values of 2.64 ng/ml and 2.44 ng/ml. There was no drug accumulation. In an aqueous formulation given daily to 8 patients with advanced prostatic cancer, peak serum concentration was 12.8 ng/ml and the half life was 6.1 hours. The mean area under the curve in the dosing interval was 65 ng h/ml and mean total body clearance was 120.1 ml/min.

Formulation: Zoladex is supplied as a 10.8 mg solid depot formulation preloaded in a disposable syringe device mounted on a #14 gauge hypodermic needle.

Storage and Stability: The sterile unit will be enclosed in a sealed light and moisture proof package. The package should be stored securely in a dry place at room temperature (not to exceed 25°C or 77°F). Before being opened, each package must be inspected for damage in which case the depot should not be used. Being sterile, the syringe should be removed from its package only immediately before required.

Administration: Zoladex will be injected every 3 months (13 weeks). No anesthetic is required; however, local anesthetics may be applied prior to injection if desired. After cleaning with an alcohol swab, a small area of skin on the anterior abdominal wall will be anesthetized by injecting 0.2 ml of 1.0% lidocaine hydrochloride intradermally or by applying topical ethyl chloride. Zoladex will then



be injected into the subcutaneous fat using aseptic technique. After injecting Zoladex depot, for the first time only, the overlying skin will be indelibly marked with a single spot. In the unlikely event of the depot needing to be surgically removed (e.g., severe anaphylaxis), this mark will facilitate such a procedure. After checking to ensure that the depot has been discharged, the used syringe will be broken and discarded in a safe manner.

Supplier: Zoladex™ is commercially available, however, for this study Astra Zeneca Pharmaceuticals, Inc. will supply the drug to UVI, Inc. for distribution. Zoladex™ for the study will be supplied in packages of one preloaded syringe, either the 3.6 mg solid depot or the 10.8 mg solid depot formulation. Participating institutions are instructed to delay ordering the drug from UVI, Inc. until they have a patient in mind for registration. Drug may be requested by contacting the clinical customer service staff at UVI, Inc. at Phone: 800/370-2508, Fax: 650/745-3877, Monday - Friday 8:00 a.m. - 5:00 p.m., PST. Please note that drug is shipped via UPS Ground and may take up to 5 business days for delivery. Drug must be ordered prior to 3:00 p.m. Eastern Time in order to be shipped that day. All unused drug supplies will be returned to UVI, Inc. for destruction using the Returned Medication Packing Slip (see Section 19.3), detailing the material being returned.

3.3 Mitoxantrone hydrochloride (Dihydroxyanthracenedione) (DHAD) (Novantrone®) (NSC-301739)

a. DESCRIPTION

Mitoxantrone is a synthetic antineoplastic anthracenedione. All of the aminoanthraquinones are potent inhibitors of DNA and RNA synthesis in vitro and bind strongly to DNA as evidenced by T_m values. It would appear, because not all of them have antitumor effects, that the antitumor activity is due to some mechanism other than, or in addition to, DNA binding and the inhibition of nucleic acid synthesis. Since a number of bis(substituted amino-alkyl amino) anthraquinones have been shown to be intercalating agents, mitoxantrone most likely acts through intercalation between base pairs of the DNA double helix.

b. TOXICOLOGY

Human Toxicology: The dose-limiting toxicities are myelosuppression and cardiotoxicity. Leukopenia and thrombocytopenia were maximal by day nine and both had resolved by Day 19 - 21. Other toxicities seen occasionally include stomatitis, nausea and vomiting, phlebitis, mild elevations in SGOT, alopecia, dyspnea, urticaria, rash, hypotension, arrhythmias, chest pains and green urine and serum. Cardiotoxicity may be more common in patients previously treated with anthracycline, mediastinal radiotherapy or preexisting cardiac disease. Mitoxantrone may cause fetal anomaly and is mutagenic in bacterial systems. Extravasation may cause local tissue necrosis.

c. PHARMACOLOGY

Kinetics: Pharmacologic studies done in dogs showed that the drug disappears rapidly from plasma (drug found only in the three-minute sample) and that $\leq 1\%$ appears in the urine in a 24-hour period. Initial clinical pharmacology studies in man show a rapid distribution half-life (eight minutes) and an elimination half-life of two hours. Most of the drug is probably excreted in the biliary system, as only about 10% of the drug is excreted in the urine. Additional experience at the University of Texas Health Science Center in San Antonio shows an every-three-week schedule to be tolerable.

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Formulation: Mitoxantrone is supplied as a dark blue sterile concentrated solution containing mitoxantrone hydrochloride equivalent to 2 mg/ml mitoxantrone free base. The concentrate is supplied in 12.5 ml vials **and must be diluted prior to injection.** Inactive ingredients include sodium acetate (0.0005% w/v) and acetic acid 0.046%, sodium chloride (0.800% w/v), and water for injection.

Storage and Stability: The product contains no preservatives and is stored at room temperature. Discard any unused drug after eight hours of entering the ampule. The expiration date for each ampule of mitoxantrone is provided on the label. When 2.5 mg of parenteral solution is admixed at room temperature with 500 cc of 5% Dextrose for injection, USP or sodium chloride injection, USP, the solutions maintain their potency for 48 hours.

Administration: Mitoxantrone should be given in a solution of 100 cc of D5W as an infusion into a well-running IV over 30 minutes. DO NOT GIVE IV PUSH.

Supplier: Mitoxantrone is commercially available however, for this study OSI Pharmaceuticals will supply and distribute the drug free of charge. Institutions are instructed to delay ordering the drug until after randomization. Drug may be requested by faxing an **S9921** Novantrone® Drug Request Form (see Section 19.4) to Priority Healthcare Corporation at 866/203-4684. Mitoxantrone will be shipped Monday through Wednesday. A minimum of two days notice is required.

The mitoxantrone shall be shipped to the Investigators in appropriately marked containers and shall be used solely for conducting **S9921**. Accurate records of all mitoxantrone received and dispensed shall be maintained by the Investigators, and all mitoxantrone shall be stored by the Investigators in a secure and locked location to prevent the theft or misuse. All used vials of mitoxantrone shall be discarded in accordance with applicable federal and state laws, rules and regulations. Upon the completion or termination of **S9921** or termination of the Agreement, whichever occurs first, all expired or unused Study Drug shall, at the direction of Company, either be returned to Company or discarded in accordance with all applicable federal and state laws, rules, and regulations.

3.4 Prednisone (NSC-10023)

a. DESCRIPTION

Prednisone is a glucocorticoid rapidly absorbed from the GI tract.

b. TOXICOLOGY

Human Toxicology: Possible adverse effects associated with the use of prednisone are: fluid and electrolyte disturbances, congestive heart failure in susceptible persons, hypertension, euphoria, personality changes, insomnia, mood swings, depression, exacerbation of infection (e.g., tuberculosis), exacerbation or symptoms of diabetes, psychosis, muscle weakness, osteoporosis, vertebral compression fractures, pancreatitis, esophagitis, peptic ulcer, dermatologic disturbances, convulsions, vertigo and headache, endocrine abnormalities, ophthalmic changes, and metabolic changes. Some patients have experienced itching and other allergic, anaphylactic or other hypersensitivity reactions. Withdrawal from prolonged therapy may result in symptoms including fever, myalgia and arthralgia. Phenytoin phenobarbital and ephedrine enhance metabolic clearance of corticosteroids.

Corticosteroids should be used cautiously in patients with hypothyroidism, cirrhosis, ocular herpes simplex, existing emotional instability or psychotic tendencies, nonspecific ulcerative colitis, diverticulitis, fresh intestinal anastomoses, peptic ulcer, renal insufficiency, hypertension, osteoporosis and myasthenia gravis. Immunization procedures (especially smallpox vaccination) should not be undertaken in patients on corticosteroids.

c. PHARMACOLOGY

Kinetics: Natural and synthetic glucocorticoids are readily and completely absorbed from the GI tract. Prednisone is very slightly soluble in water. Glucocorticoids have salt-retaining properties. The anti-inflammatory property of this drug is its ability to modify the body's immune system. On the other hand, glucocorticoids suppress the body's response to viral as well as bacterial infections. Equivalent doses are as follows:

Dexamethasone	Methyl-prednisolone and Triamcinolone	Prednisolone and Prednisone	Hydrocortisone	Cortisone
0.75 mg	4 mg	5 mg	20 mg	25 mg

Formulation: Prednisone is available in 2.5 mg, 5 mg, 10 mg, 20 mg and 50 mg tablets.

Storage and Stability: Prednisone should be stored at room temperature.

Administration: Prednisone is administered orally.

Supplier: Prednisone is commercially available and should be purchased by third party. Prednisone will not be supplied by the NCI.

4.0 **STAGING CRITERIA**

(TAKEN FROM THE MANUAL FOR STAGING OF CANCER, AJCC, FIFTH EDITION.)

DEFINITION OF TNM

Clinical Staging. Primary tumor assessment includes digital rectal examination of the prostate and histologic or cytologic confirmation of prostatic carcinoma.

Pathologic Staging. Histologic examination of the resected specimen is required. Total prostatectomy and pelvic lymph node dissection are required for pathologic staging.

Definition of TNM

Primary Tumor, Clinical (T)

- | | |
|-------|--|
| TX | Primary tumor cannot be assessed. |
| T0 | No evidence of primary tumor. |
| T1 | Clinically inapparent tumor not palpable or visible by imaging |
| T1a | Tumor incidental histologic finding in 5% or less of tissue resected |
| T1b | Tumor incidental histologic finding in more than 5% of tissue resected |
| T1c | Tumor identified by needle biopsy (e.g., because of elevated PSA) |
| <hr/> | |
| T2 | Tumor confined within the prostate* |
| T2a | Tumor involves one lobe |
| T2b | Tumor involves both lobes |
| <hr/> | |
| T3 | Tumor extends through the prostatic capsule** |
| T3a | Extracapsular extension (unilateral or bilateral) |
| T3b | Tumor invades the seminal vesicle(s) |
| <hr/> | |
| T4 | Tumor is fixed or invades adjacent structures other than the seminal vesicles: bladder neck, external sphincter, or rectum, levator muscles and/or pelvic wall |

*Note: Tumor found in one or both lobes by needle biopsy, but not palpable or reliably visible by imaging, is classified as T1c.

**Note: Invasion into the prostatic apex or into (but not beyond) the prostatic capsule is not classified as T3, but as T2.

Primary Tumor, Pathologic (pT)

- | | |
|--------|----------------|
| pT2*** | Organ confined |
| pT2a | Unilateral |
| pT2b | Bilateral |

-
- pT3 Extraprostatic extension
 pT3a Extraprostatic extension
 pT3b Seminal vesicle invasion
-

pT4 Invasion of bladder, rectum

***Note: There is no pathologic T1 classification.

Regional Lymph Nodes (N)

- NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Metastasis in a single lymph node or nodes.

Distant Metastasis* (M)**

- MX Distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis
 M1a Nonregional lymph node(s)
 M1b Bone(s)
 M1c Other site(s)

***NOTE: When more than one site of metastasis is present, the most advanced category is used. pM1c is most advanced.

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5.0 ELIGIBILITY CRITERIA

Each of the criteria in the following section must be met in order for a patient to be considered eligible for registration. Use the spaces provided to confirm a patient's eligibility. For each criterion requiring test results and dates, please record this information on the Prestudy Form and submit to the Data Operations Center in Seattle (see Section 14.0). Any potential eligibility issues should be addressed to the Data Operations Center in Seattle at 206/652-2267 prior to registration.

SWOG Patient No. _____

Patient's Initials (L, F, M) _____

- ____ 5.1 All patients must have a histologic diagnosis of adenocarcinoma of the prostate and must be considered to have **clinically localized disease (Stage T1-T3, N0, M0)**, and be considered operable for cure by their primary urologic surgeon.

Patients must have had a radical prostatectomy within 120 days prior to registration **and must fulfill one or more** of the following criteria (from pathologic analysis of the radical prostatectomy specimen) **check all that apply:**

- ____ a. Pathologic Gleason's sum of equal or greater than 8.
- ____ b. pT3b (seminal vesicle) or pT4 or N1.
- ____ c. Pathologic Gleason's sum of 7 and positive margin.
- ____ d. Patients who have either a preoperative serum PSA value of > 15 ng/ml, or a biopsy Gleason score > 7, or a serum PSA level of > 10 ng/ml and a biopsy Gleason score > 6 are eligible.

- ____ 5.2 Serum testosterone must be obtained within 28 days prior to registration.
- ____ 5.3 Patients must have a performance status of 0 - 1 by Southwest Oncology Group criteria (see Section 10.3).
- ____ 5.4 Prior neoadjuvant hormonal therapy (of ≤ 4 months duration) prior to radical prostatectomy is allowed provided that the patient has fulfilled the clinical eligibility criteria prior to hormonal treatment. Patients may have started hormonal therapy post-prostatectomy but prior to registration to this study (see Sections 5.2 and 5.5 for other requirements).

No other therapy aimed at the treatment of this diagnosis may have been given or may be planned while the patient is receiving protocol treatment. The use of low dose megace (< 40 mg/day) for the treatment of hot flashes is allowed.

Patients must not have received prior radiation therapy. If the treating physician wishes to have RT administered, then the patient should be registered to the study FIRST and then optional RT can be given on protocol. All RT should be documented on the **S9921** Treatment Form (Form #38859).



SWOG Patient No. _____

Patient's Initials (L, F, M) _____

- 5.5 a. **Patients who have not started post-surgical hormone therapy:** Patients must have a post-operative serum prostate specific antigen (PSA) less than or equal to 0.2 ng/ml documented after surgery and within 28 days prior to registration.
- b. **Patients who have already started post-surgical hormone therapy:** Patients must have a post-operative serum prostate specific antigen (PSA) \leq 0.2 ng/ml documented after surgery, but prior to the start of hormonal therapy. This may have been more than 28 days prior to registration.
- c. **Patients who started hormone therapy prior to prostatectomy:** Patients must have a post-operative serum prostatic specific antigen (PSA) \leq 0.2 ng/ml documented after surgery but prior to the start of post-surgical hormone therapy. This may have been more than 28 days prior to registration.
- 5.6 The institutional pathology report documenting eligibility for this study must be available for submission as outlined in Section 14.6.
- 5.7 All patients registered on or after June 15, 2006 must be offered the opportunity to consent for specimen banking per Section 15.0.

SWOG Patient No. _____

Patient's Initials (L, F, M) _____

- ____ 5.8 Patients with PSA at clinical diagnosis \geq 20 ng/ml must have a bone scan not suggestive of metastatic disease done within 180 days prior to registration.
- ____ 5.9 Patients with symptoms of distant metastatic disease must have appropriate tests to evaluate for metastatic disease within 56 days prior to registration. Patients with confirmed distant metastatic disease are ineligible.
- ____ 5.10 Patients must have a baseline EKG to rule out underlying cardiac disease within 42 days prior to registration. Patients with a history of cardiac disease, specifically CHF are ineligible unless their disease is well-controlled and they have LVEF \geq 50% by MUGA or 2-d echo within 42 days prior to registration.
- ____ 5.11 Patients known to be HIV positive are not eligible because of the potential to confound the study's endpoint, although patients will not routinely be screened for HIV.
- ____ 5.12 No other prior malignancy is allowed except for the following: adequately treated basal cell or squamous cell skin cancer, adequately treated Stage I or II cancer from which the patient is currently in complete remission, or any other cancer from which the patient has been disease-free for 5 years.
- 5.13 If Day 28, 42, 56, 120 or 180 falls on a weekend or holiday, the limit may be extended to the next working day.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday four weeks later would be considered Day 28. This allows for efficient patient scheduling without exceeding the guidelines.

- ____ 5.14 All patients must be informed of the investigational nature of this study and must sign and give written informed consent in accordance with institutional and federal guidelines.
- ____ 5.15 At the time of patient registration, the treating institution's name and ID number must be provided to the Data Operations Center in Seattle in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered into the data base.

6.0 STRATIFICATION FACTORS/RANDOMIZATION SCHEME

- 6.1 At the time of registration, patients will be randomly assigned to either Arm 1 or Arm 2 according to a dynamic allocation scheme. The treatment arms will be balanced with respect to the following factors:
- a. Pathologic stage of disease:
 1. organ confined (pT2a - pT2b with either ± surgical margins), but N0,
 2. not organ confined (\geq pT3), but N0,
 3. N1 (any T).
 - b. Gleason's sum: < 7, 7, > 7.
 - c. RT planned: Yes vs. No.

7.0 TREATMENT PLAN

For chemotherapy treatment or dose modification related questions, please contact Dr. L. Michael Glode at 303/724-3853 or Dr. Maha H. Hussain at 734/936-8906. For urology related questions, please contact Dr. David P. Wood, Jr. at 734/763-9269. For radiation therapy related questions, please contact Dr. Gregory P. Swanson at 210/616-5648. For dosing principles or questions, please consult the Southwest Oncology Group Policy #38 "Dosing Principles for Patients on Clinical Trials" at <http://swog.org> (then click on "Policies and Manuals" under the "Visitors" menu and choose Policy 38).

7.1 Good Medical Practice

The following pre-study tests should be obtained within 28 days prior to registration and the following guidelines should be met in accordance with good medical practice. Results of these tests do not determine eligibility and minor deviations would be acceptable if they do not impact on patient safety in the clinical judgement of the treating physician. The Study Coordinator must be contacted if there are significant deviations in the values of these tests.

- a. Patients should have AGC \geq 1,500 cells/mm³, and platelet count \geq 100,000 cells/mm³, SGOT \leq 2.5 X institutional upper limits of normal and serum bilirubin \leq institutional upper limit of normal done within 28 days prior to registration.
- b. Patients must have recovered from major infections and/or surgical procedures and, in the opinion of the investigator, not have significant active concurrent medical illness precluding protocol treatment or survival.

It is recommended that patients have a lymph node dissection in conjunction with the radical prostatectomy within 120 days prior to registration.

7.2 Patients will be randomized to:

Arm 1: Casodex® + Zoladex® for two years.

Arm 2: Chemotherapy (mitoxantrone + prednisone) x 6 cycles plus Casodex® + Zoladex® x 2 years.

7.3 Arm 1 - Hormonal therapy

- a. Zoladex 10.8 mg depot given subcutaneously once every 3 months (13 weeks) for a total of 8 injections given over 2 years, concurrent with Casodex 50 mg orally once daily everyday for two years.
- b. Neo-adjuvant or adjuvant hormonal therapy started prior to registration may be counted as protocol treatment if it included an LHRH agonist (e.g., goserelin acetate, leuprolide acetate, triptorelin) and there was no interruption in treatment. This could be either an LHRH agonist alone or in combination with antiandrogen, but antiandrogen alone will not be counted as pre-registration protocol treatment. Patients must receive a total of 2 years of treatment with LHRH agonist, where the treatment duration of any LHRH agonist received prior to registration may be counted as part of the 2 years of protocol treatment only if that treatment duration was continuous up to the date of registration. It is recommended that patients also complete 2 years of concurrent antiandrogen treatment, but if LHRH agonist was started alone prior to registration the duration of antiandrogen treatment can be shortened to the remaining time of hormonal deprivation after starting the protocol. For patients beginning LHRH agonist prior to registration, every effort should be made to conform to the LHRH agonist administration schedule that is specified in the study calendar, which may mean administering a few doses of single-month depot at the beginning to get on track. All prior hormonal therapy must be documented on the S9921 Local Prostate Carcinoma Prestudy (Form # 23968).

Treatment Schedule

Agent	Dose	Route	Days	ReRx Interval
<u>LHRH Agonist:</u> Goserelin acetate (Zoladex®)	10.8 mg	SC	1	q 3 months (13 weeks) x 8
<u>Anti-androgen:</u> Bicalutamide (Casodex®)	50 mg	Oral (once daily)		1-730 (2 years)

All continuous hormonal treatment counts towards protocol treatment.

7.4 Arm 2 Mitoxantrone and Prednisone + Hormonal Therapy

The administration of Casodex + Zoladex + mitoxantrone + prednisone will commence simultaneously.

- a. Hormonal therapy: Follow same guidelines as Arm 1.
- b. Mitoxantrone 12 mg/m² intravenously every 21 days, plus prednisone 5 mg/dose, BID orally given Days 1-21. A total of 6 courses will be administered. At the end of prednisone treatment (21 days after last mitoxantrone dose), prednisone should be tapered over 2 - 3 weeks at the discretion of the treating physician.

NOTE: Protocol treatment on Arm 2 is not considered complete until patients have completed the 2 years of hormonal therapy. Do not submit an Off Treatment Notice until patient is off **all** protocol treatment.

Agent	Dose	Route	Days	Interval
Mitoxantrone	12 mg/m ²	IV over 30 min	1	q 21 days X 6
Prednisone	5 mg/dose, BID	Oral	1 - 21	continuous q 21 days x 6

7.5 Radiation Therapy:

All RT must be recorded on the S9921 Treatment Form (Form #38859).

Radiation therapy will begin upon recovery from chemotherapy (ideally 3 - 6 weeks and no later than 8 weeks) for patients on Arm 2, and should begin no later than 4 weeks after the initiation of androgen ablation for patients on Arm 1.

Radiation therapy for patients on either arm of the study will be allowed at the physician's discretion following these suggested guidelines:

Doses: The target volume will be the prostate fossa and immediate periprostatic tissue. The minimum and maximum allowable doses will be 6,480 cGy and 7,100 cGy respectively at a dose of 180 - 200 cGy per day. Conedown of the fields at 4,400 - 4,600 cGy is allowed (see portals below).

Radiation Portals: Whole pelvis radiation is not allowed. Initial ports can have more generous margins than those outlined below, but after the initial 4,400 - 4,600 cGy should be coned down to those margins. The goal is to treat the prostate fossa. Treatment of the seminal vesicle (SV) fossa is left to the discretion of the treating physician. For SV negative patients it is probably not necessary. For SV positive patients, it is usually the base of the seminal vesicle that is involved and it may not be desirable to cover the whole SV fossa to the full dose out of concerns for toxicity. If a preoperative CT is available, it can be used in planning, with a margin of 1.5 cm around the prostate and if treated, the SV. For simulation, rectal and urethral or bladder contrast is required.

Four-field technique (recommended) can be planned with 3D conformal technique. IMRT is allowed as long as boundary parameters are met. The NCI's IMRT guidelines can be found on the Advanced Technologies Consortium website (<http://atc.wush.edu> under "News", then "NCI IMRT Letter").

AP/PA ports:

Inferior margin will be at or below the ischial tuberosity (or if urethrogram is used, > 0.5 cm below the narrowing of the urethra).

Lateral margin will be minimum of 1.0 cm lateral to the midpoint of the obturator foramen (usually a field width of 8 to 9 cm).

Superior margin for prostate only or to include the base of the SV is 2 cm above the pubic symphysis. For the entire SV is at the top of the femoral head.

Lateral ports:

Inferior margins as for the AP/PA ports.

Lateral margins - anterior: 1 cm anterior to the junction of the projection of the posterior pubic symphysis over the superior ramus of the pubis or at the tip of the pubic symphysis.

Posterior: 1 cm posterior to a line from the posterior acetabulum and posterior obturator foramen. As much rectum as possible needs to be spared, but at the minimum the anterior 1 cm will be included in the port. This would usually put the block in the mid rectum. A larger portion of the rectum may need to be covered if the rectum subluxed into the prostate fossa. The rectum above the midpoint of the femoral head can be blocked entirely.

Superior: margins for the prostate only and base of the SV would be as for the AP/PA ports. The anterior bladder can be blocked from a line 1 cm anterior to the junction of the projection of the pubic symphysis over the superior ramus of the pubis through the center of the femoral head. Unless the entire SV fossa is to be covered the area posterior to the acetabulum can be blocked.

Beam Energy: Megavoltage equipment with effective photon energies greater than 6 MV is required.

Treatment Distance: Minimum SSD and SAD distance is 80 cm.

Fractionation: 180 - 200 cGy per day five days a week with one set of portals treated each day.

Treatment Planning: Isodose distribution at the mid-transverse plane of the tumor volume and the central axis (if different).

Localization films: If a cone down is done, both fields can be on the same set of films if they are the basis for both treatment.

- a. Patients will be evaluated weekly for toxicity during radiotherapy and all toxicities documented on the S9921 Adverse Event Summary Form (Form #27242).
- b. Post radiation follow-up: Follow-up will be in accordance with the Study Calendar.
- c. Radiotherapy information will be recorded on the S9921 Treatment Form (Form #38859).

7.6 There is a tumor bank for this study for patients with adequate tissue available. In order to have tissue submitted, patients must consent to submission of tissue. Please see Section 15.0 for details of tissue submission.

7.7 Criteria For Removal From Protocol Treatment

- a. Unacceptable toxicity.
 - b. Completion of 2 years of hormonal therapy per protocol.
 - c. The patient may withdraw from the study at any time for any reason.
 - d. Disease progression.
- 7.8 All reasons for discontinuation of treatment must be documented in the Off Treatment Notice (Form #8756).
- 7.9 All patients will be followed 15 years or until death.

8.0 TOXICITIES TO BE MONITORED AND DOSAGE MODIFICATIONS

- 8.1 Patients will be evaluated and graded for toxicity every visit as specified on the Study Calendar for subjective/objective evidence of developing toxicities according to the NCI Common Toxicity Criteria version 2.X (see Section 19.1).
- 8.2 Arm 1 – Hormone therapy
- a. There are no dosage adjustments for hematologic toxicity.
 - b. The most common side effects of anti-androgen therapy are breast pain and gynecomastia. No dose modification is needed except in very severe cases (Grade 3 or higher). In such cases, the anti-androgen will be discontinued permanently and LHRH agonist therapy continued.
 - c. Antiandrogens may be omitted in the case of hepatic toxicity of any severity (at the discretion of the treating physician).
 - d. Hot flashes may develop in patients treated with LHRH agonists. In general, these will not require therapy as resolution is expected following completion of protocol treatment (termination of therapy).
- 8.3 Arm 2 – Mitoxantrone and prednisone + hormone therapy (follow guidelines in Section 8.2 for toxicities attributable to hormone therapy). If mitoxantrone is delayed due to toxicity, prednisone is given on schedule without dose reduction.

- a. Myelosuppression:

See table below for a summary of dose modifications for myelosuppression.

Grade 1, 2 and 3 myelosuppression (leukopenia, neutropenia, thrombocytopenia) and Grade 4 leukopenia or Grade 4 neutropenia except as defined below, with recovery within twenty-one days, does not require dose modification. Patients who do not recover WBC or platelet counts to ≤ CTC Grade 1 toxicity within 21 days should be reduced to dose level -1 for all subsequent courses.

In order to maximize dose intensity, patients with afebrile Grade 4 neutropenia ≥ 7 days or Grade 3 or 4 neutropenia associated with fever (one reading of oral temperature > 38.5°C, or three readings of oral temperature > 38.0°C in a 24-hour period) should be retreated after recovery at the dose level -1.

Grade 4 thrombocytopenia (platelet count < 25,000) at any time necessitates retreatment after recovery at the dose level -1.

G-CSF is not permitted.

Dose Modifications for Myelosuppression.

Dose Level	Mitoxantrone Dose (mg/m ²)
Starting Level	12
Level -1*	9

*This is a permanent dose reduction. Further dose reduction requires removing patient from protocol treatment.

b. Gastrointestinal

Appropriate symptomatic treatment of nausea and/or emesis, diarrhea, mucositis, and/or abdominal pain is permitted.

c. Cardiovascular

The total cumulative dose of mitoxantrone is anticipated to $\leq 72 \text{ mg/m}^2$; based on 6 cycles of 12 mg/m^2 ; EKG changes, arrhythmias, tachycardia, and/or chest pain should be managed based on the specific findings. Patients who have underlying cardiac disease or CHF, will undergo baseline ejection fraction determination echocardiogram or MUGA and this evaluation will be repeated for all patients every two courses. If MUGA decreases to below institutional limits (or $< 15\%$) discontinue protocol treatment.

d. Allergic:

Patients who experience Grade 3 or 4 hypotension, urticaria, or severe rash should be removed from protocol treatment.

e. Hepatic (\geq Grade 2):

Delay mitoxantrone treatment for up to 4 weeks until transient increases in SGOT or hyperbilirubinemia have resolved to Grade 1 or less. If toxicity has not resolved within 4 weeks discontinue protocol treatment.

f. Other:

If toxicities \leq Grade 2, manage symptomatically, if possible and retreat without dose reduction.

If toxicities \geq Grade 3, drug should be withheld (except for alopecia or anemia) until resolution to \leq Grade 1 or baseline if baseline was greater than Grade 1, then reinstated, if medically appropriate, at a dose of 9 mg/m^2 (permanent dose reduction).

8.4 For chemotherapy treatment or dose modification related questions please contact Dr. Glode at 303/724-3853 or Dr. Hussain at 734/936-8906. For urology related questions please contact Dr. Wood at 734/763-9269. For radiation therapy related questions please contact Dr. Swanson at 210/616-5648.

8.5 Unexpected or fatal toxicities (including suspected reactions) must be reported to the Operations Office, to the Study Coordinator, to the IRB and the NCI. The procedure for reporting adverse reactions is outlined in Section 16.0.

9.0 STUDY CALENDAR

9.1 Arm 1 Hormonal therapy alone

REQUIRED STUDIES	PRE	Mo	Ω						
	STUDY	1	4	7	10	13	16	19	22
PHYSICAL									
History and Physical Exam	X		X	X	X	X	X	X	X
Weight and Performance Status	X		X	X	X	X	X	X	X
Toxicity Notation		X	X	X	X	X	X	X	X
LABORATORY / TESTS									
PSA ¥	X		X	X	X	X	X	X	X
CBC/diff/platelets	X**								
Bilirubin	X**								
SGOT	X**								
Testosterone §	X			X		X		X	
Blood specimens π	X			X					
Tissue Specimen ™	X								
X-RAYS AND SCANS									
Bone Scan §	X								
CT/MRI abdomen and pelvis Σ	X								
OTHER X-RAYS/SCANS									
EKG	X								
MUGA or 2-d Echo	X*								
TREATMENT (Sect. 7.0)									
Radical Prostatectomy ∞	X								
Goserelin acetate (Zoladex®) #		X	X	X	X	X	X	X	X
Bicalutamide (Casodex®) √		X	X	X	X	X	X	X	X

NOTE: All forms to be used for this study are found in Section 18.0. Form submission guidelines are found in Section 14.0.

** Results of these tests do not determine eligibility but should be done prior to registration in accordance with good medical practice (see Section 7.1a). With the exception of blood counts, significant deviations in the values of these tests should be discussed with the Study Coordinator.

These tests are required during treatment as scheduled to assess toxicity.

π Blood specimens for patients opting to participate in the blood and tissue banking should be collected prestudy, between Weeks 24 and 28, and at progression (see Section 15.0).

Σ See Section 5.9. CT scan of abdomen and pelvis must be performed if patient has symptoms of distant metastatic disease.

Every 3 months.

√ Daily.

Ω Treatment and parameters will continue for a total of two years according to the schedule outlined above.

After off treatment, patients will be followed for disease status with Physical Exam and DRE (if PSA \geq 0.1 ng/ml), repeated at end of treatment and every six months for two years and annually thereafter for three additional years. All patients will be followed for 15 years or until death, and PSA will be collected as noted below.

* At prestudy, only for patients with underlying cardiac disease or CHF.

§ For patients with PSA \geq 20 ng/ml at diagnosis.

∞ Must be done within 120 days prior to registration.

™ For patients with adequate tissue and who consent to tissue banking (see Section 15.0 for details).

¥ Testosterone is collected every six months until it reaches the institutional lower limit of normal (ILLN).

PSA is collected every three months for five years, and then every 6 months until 15 years or death.

9.0 STUDY CALENDAR

9.2 Arm 2 Hormonal therapy + mitoxantrone + prednisone

	Cy 1	Cy 2	Cy 3	Cy 4	Cy 5	Cy 6	Ω
REQUIRED STUDIES	PRE	Mo					
STUDY	1	Day	Day	Day	Day	Day	
		15	22	36	43	57	
PHYSICAL							
History and Physical Exam	X		X	X	X	X	X X X X X X X X
Weight and Performance Status	X		X	X	X	X	X X X X X X X X
Toxicity Notation	X	X	X	X	X X	X X X	X X X X
LABORATORY / TESTS							
PSA \ddagger	X				X	X X	X X X X X X
CBC/diff/platelets	X**	X X X X X X X X	X X X X X X X X				
Bilirubin	X**	X X X X X X X X	X X X X X X X X				
SGOT	X**	X X X X X X X X	X X X X X X X X				
Testosterone \ddagger	X					X	X X
Blood specimens π	X					X	
Tissue Specimen $^{\text{TM}}$	X						
X-RAYS AND SCANS							
Bone Scan \S	X						
CT/MRI abdomen and pelvis Σ	X						
OTHER X-RAYS/SCANS							
EKG	X						
MUGA or 2-d Echo	X*		X*		X*		
TREATMENT (Sect. 7.0)							
Radical Prostatectomy ∞	X						
Mitoxantrone \P	X	X	X	X	X	X	
Prednisone f	X	X	X	X	X	X	
Goserelin acetate (Zoladex®) #	X				X	X X X X X X X X	
Bicalutamide (Casodex®) ∇	X X X X X X X X	X X X X X X X X	X X X X X X X X	X X X X X X X X			

NOTE: All forms to be used for this study are found in Section 18.0. Form submission guidelines are found in Section 14.0.

** Results of these tests do not determine eligibility but should be done prior to registration in accordance with good medical practice (see Section 7.1a). With the exception of blood counts, significant deviations in the values of these tests should be discussed with the Study Coordinator. These tests are required during treatment as scheduled to assess toxicity.

π Blood specimens for patients opting to participate in the blood and tissue banking should be collected prestudy, between Weeks 24 and 28, and at progression (see Section 15.0).

Σ See Section 5.9. CT scan of abdomen and pelvis must be performed if patient has symptoms of distant metastatic disease.

\P Mitoxantrone will be given on Day 1, every twenty-one days for six cycles.

f Prednisone will be given twice a day continuously for 6 twenty-one day cycles. At the end of prednisone treatment (21 days after last mitoxantrone dose), prednisone should be tapered over 2 - 3 weeks at the discretion of the treating physician.

Every 3 months.

\checkmark Daily.

Ω Treatment and parameters will continue for a total of two years according to the schedule outlined above.

After off treatment, patients will be followed for disease status with Physical Exam and DRE (if PSA \geq 0.1 ng/ml), repeated at end of treatment and every six months for two years and annually thereafter for three additional years. All patients will be followed for 15 years or until death, and PSA will be collected as noted below.

* At prestudy, only for patients with underlying cardiac disease or CHF. Follow-up MUGA or 2-d echo is only needed for those patients who required one at baseline.

\ddagger For patients with PSA \geq 20 ng/ml at diagnosis.

∞ Must be done within 120 days prior to registration.

$^{\text{TM}}$ For patients with adequate tissue and who consent to tissue banking (see Section 15.0 for details).

\ddagger Testosterone is collected every six months until it reaches the institutional lower limit of normal (ILLN).

PSA is collected every three months for five years, and then every 6 months until 15 years or death.

10.0 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS

- 10.1 Overall Survival: Measured from date of randomization to date of death from any cause. Patient known to be alive are censored at date of last contact.
- 10.2 Disease-Free Survival: Measured from date of randomization to date of first observation of recurrence or death due to any cause. Patients without recurrence are censored at date of last contact.
- 10.3 **Performance Status:** Patients will be graded according to the current Southwest Oncology Group grading scale:
- | <u>GRADE</u> | <u>SCALE</u> |
|---------------------|---|
| 0 | Fully active; able to carry on all predisease activities without restriction. |
| 1 | Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work. |
| 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. |
| 3 | Capable of only limited self-care; confined to bed or chair more than 50% of waking hours. |
| 4 | Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. |
| 5 | Dead |
- 10.4 PSA Progression: A serum PSA level of > 0.2 ng/mL measured on 3 consecutive occasions or in the absence of increasing PSA, a positive bone scan result or other radiographic or histologic evidence of progression will be used. Date of progression will be the date that the first measure of increasing PSA is noted in the series of 3. (40)
- 10.5 PSA Progression-Free Survival: Measured from date of randomization to date of PSA progression or death due to any cause.

11.0 STATISTICAL CONSIDERATIONS

- 11.1 The primary objective of this study is to compare the overall survival in prostate cancer patients treated with combined androgen blockade (LHRH agonist and anti-androgen) with that in patients treated with the combination of combined androgen blockade and mitoxantrone plus prednisone. Mitoxantrone, prednisone and combined androgen blockade would be judged superior to the standard regimen of combined androgen blockade if the true increase in median survival is 30%.
- 11.2 It was initially anticipated that 250 eligible patients per year would be accrued to this study. However, accrual has been slower than expected. Instead of the original accrual period estimate of 5.5 years, we now anticipate a period of 9.5 years in order to randomize 680 eligible patients per arm.
- 11.3 A median survival of 10 years is anticipated on combined androgen blockade. Assuming exponential survival, 9.5 years of patient accrual, and an additional 4 years of follow-up, a sample size of 680 patients per arm, this study has .92 power to detect a 30% increase in median survival, using a one-sided test with 0.05 significance level.
- 11.4 This study will be monitored throughout the accrual and follow-up periods by the Southwest Oncology Group Data and Safety Monitoring Committee (DSMC). The DSMC will be approved by CTEP and will include members both from within the Group and from outside the Group. A majority of the DSMC will be outside members, and at least one outside member will be a patient advocate and at least one will be a statistician. The

Group Statistician and two representatives of CTEP will be non-voting members. The Group Chair may not be on the DSMC. The DSMC will be provided with administrative reports every 6 months by the Study Statistician, and will discuss the reports if necessary at a meeting held in conjunction with the Southwest Oncology Group Meeting. The DSMC and study statistician will be the only individuals with regular access to the primary outcome data and this information will be provided to the DSMC on a regular basis.

- 11.5 In addition to the study monitoring mentioned above, three formal interim analyses will be done. The decision to terminate accrual early will be made by the DSMC, and will consider disease-free survival, toxicities, and other factors in addition to survival. Additionally, the Southwest Oncology Group Statistical Center will closely monitor throughout the trial whether there is differential use of optional radiotherapy between the two treatment groups and this information will be provided to the DSMC at regular intervals.
- 11.6 The first formal interim analysis will be done after 700 patients have been entered, approximately 6 years after the study opens. Evidence suggesting early termination of the trial would be if the alternative hypothesis of a 30% improvement in survival with the MP + CZ combination arm is rejected at the 0.005 level, using an extension of the logrank test that allows for testing a relative risk not equal to 1. In addition, the null hypothesis of no difference in survival will be tested at the one-sided level of 0.005. The second interim analysis will be performed after 50% of the total expected deaths (275 deaths) will have occurred. Testing will be done as above at the 0.005 level. A third interim analysis will be performed 2.5 years after accrual has been completed. This testing will also be done at the alpha=0.005 level. The final analysis will be performed at the 0.045 significance level, approximately 4 years after accrual has been completed.
- 11.7 Secondary analyses will also be done regarding disease-free survival and toxicities. With 680 patients per arm, toxicity rates can be estimated to within at \pm 4% (95% confidence interval).

12.0 DISCIPLINE REVIEW

There will be no discipline review for this study.

13.0 REGISTRATION GUIDELINES

- 13.1 Patients must be registered prior to initiation of protocol treatment (no more than ten working days prior to planned start of treatment).
- 13.2 For either phone or web registration, the individual registering the patient must have completed the appropriate Southwest Oncology Group Registration Form. The completed form must be referred to during the registration but should not be submitted as part of the patient data.

The individual registering the patient must also be prepared to provide the treating institution's name and ID number in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered into the data base. Patients will not be registered if the IRB approval date has not been provided or is > 365 days prior to the date of registration.

13.3 Registration Procedures

- a. You may register patients from Member, CCOP, UCOP and approved Affiliate institutions to a therapeutics study using the SWOG Registration program. To access the Registration program go to the SWOG Web site (<http://swog.org>) and click on the *Logon* link to go to the SWOG Members Area logon page (<https://swog.org/visitors/logon.asp>). This Web program is available at any time except for periods listed **under Down Times**. Log on as an Individual User using your SWOG Roster ID Number and individual web user password. Help for the logon process may be found at <https://swog.org/visitors/logonhelp.asp>. After you have logged on, click on the *Clinical Trials* link and then the *Patient Reg* link to go to the Entry Page for the Patient Registration program. If you are a Registrar at an institution with Internet access you are encouraged to register this way. For new users, the link to a "Starter Kit" of help files may be found by clicking on **Starter Kit link at the logon page**.

To register a patient the following must be done (in order):

1. You are entered into the Southwest Oncology Group Roster and issued a SWOG Roster ID Number,
2. You are associated as an investigator or CRA/RN to the institution where a registration is occurring, and
3. You are granted permission to use the Patient Registration program at that institution.

For assistance with points 1 and 2 call the SWOG Operations Office at 210/677-8808. For point 3 you must contact your Web User Administrator. Each SWOG institution has one or more Web User Administrators who may set up Web Users at their institution and assign permissions and passwords to these users. For other password problems or problems with the Patient Registration program, please e-mail webreghelp@crab.org. Include your name, Roster ID Number, and telephone number, when the problem occurred, and exactly what you were doing.

4. If the Web Reg program is not used, the registration must be done by phone.

Member, Affiliate, CCOP, and UCOP Institutions

Registration by phone of patients from member, affiliate and CCOP institutions must be done through the Southwest Oncology Group Data Operations Center in Seattle by telephoning 206/652-2267, 6:30 a.m. to 4:00 p.m. Pacific Time, Monday through Friday, excluding holidays.

- 13.4 **CALGB Institutions:** Confirm all eligibility criteria as listed in Section 5.0. Registration will be accepted through institutions with direct registration privileges. Call the CALGB Registrar (919/286-4704, Monday - Friday, 9:00 AM - 4:30 PM, Eastern Time) with the following information:

Study

Name of Group (CALGB)
Name of institution where patient is being treated
Name of treating physician
Naming of treating physician or responsible CRA
CALGB patient ID#, if applicable
Patient's first name, middle initial, and last name
Patient's Social Security number, date of birth and hospital ID number
Patient's gender
Patient's height, in centimeters
Patient's weight, in kilograms
Patient's race
CTC performance status (optional, if required by CDUS)
Type of insurance (method of payment)
Disease, type and stage, if applicable
Patient's Postal Code, if applicable
Treatment start date
Date of signed consent
Eligibility criteria met (yes, no)
Stratification factors (Surgical extent of disease, Gleason Sum, RT planned; see Section 6.1)

The CALGB Registrar will then contact the Southwest Oncology Group Statistical Center for treatment assignment, after which the CALGB Registrar will inform the institution of the treatment assignment. The Southwest Oncology Group will forward a confirmation of treatment assignment to the CALGB Registrar, who will subsequently forward the confirmation of treatment assignment to the main member institution.

Patients entered on this study may not be cancelled (see Section 13.6).

13.5 **CTSU REGISTRATION/RANDOMIZATION**

Prior to the recruitment of a patient for this study, investigators must be registered members of the CTSU. Each investigator must have an NCI investigator number and must maintain an "active" investigator registration status through the annual submission of a complete investigator registration packet (FDA Form 1572 with original signature, current CV, Supplemental Investigator Data Form with signature, and Financial Disclosure Form with original signature) to the Pharmaceutical Management Branch, CTEP, DCTD, NCI. These forms are available on the CTSU registered member Web site or by calling the PMB at 301-496-5725 Monday through Friday between 8:30 a.m. and 4:30 p.m. Eastern time.

Each CTSU investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can enroll patients. Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU member web site at <http://members.ctsu.org>.

All forms and documents associated with this study can be downloaded from the **S9921** Web page on the CTSU registered member Web site (<https://members.ctsu.org>). Patients can be registered only after pre-treatment evaluation is complete, all eligibility criteria have been met, and the study site is listed as 'approved' in the CTSU RSS.

Requirements for S9921 site registration:

- CTSU IRB Certification
- CTSU IRB/Regulatory Approval Transmittal Sheet

Prestudy requirements for patient enrollment on S9921

- Patient must meet all inclusion criteria, and no exclusion criteria should apply
- Patient has signed and dated all applicable consents and authorization forms
- All baseline laboratory tests and prestudy evaluations performed.

CTSU Procedures for Patient Enrollment

1. Contact the CTSU Patient Registration Office by calling 1-888-462-3009. Leave a voicemail to alert the CTSU Patient Registrar that an enrollment is forthcoming. For immediate registration needs, e.g. within one hour, call the registrar cell phone at 1-301-704-2376.
 2. Complete the following forms:
 - CTSU Patient Enrollment Transmittal Form
 - Eligibility Criteria Checklist (Section 5.0 of the protocol)
 - SWOG Registration Form (Complete all sections of form except for SWOG-specific data fields)
 3. Fax these forms to the CTSU Patient Registrar at 1-888-691-8039 between the hours of 8:00 a.m. and 8:00 p.m., Mon-Fri, Eastern Time (excluding holidays). The CTSU registrar will check the investigator and site information to ensure that all regulatory requirements have been met. The registrar will also check that forms are complete and follow-up with the site to resolve any discrepancies.
 4. Once investigator eligibility is confirmed and enrollment documents deemed complete, the CTSU registrar will contact the Southwest Oncology Group to obtain assignment of a treatment arm and assignment of a unique patient ID (to be used on all future forms and correspondence). The CTSU registrar will convey this information to the enrolling site and follow up with a confirmation via e-mail or fax.
- 13.6 For either method of registration, exceptions to Southwest Oncology Group registration policies will not be permitted.
- a. Patients must meet all eligibility requirements.
 - b. Institutions must be identified as approved for registration.
 - c. Registrations may not be cancelled.
 - d. Late registrations (after initiation of treatment) will not be accepted.

14.0 DATA SUBMISSION SCHEDULE

- 14.1 Data must be submitted according to the protocol requirements for **ALL** patients registered, whether or not assigned treatment is administered, including patients deemed to be ineligible. Patients for whom documentation is inadequate to determine eligibility will generally be deemed ineligible.
- 14.2 Master forms are included in Section 18.0 and (with the exception of the sample consent form and the Registration Form) must be photocopied for data submission to the Data Operations Center in Seattle. Alternatively, data from approved SWOG institutions may be submitted on-line via the web; see Section 14.3a for details.

CLOSED EFFECTIVE 01/12/2007

14.3 Southwest Oncology Group Institutions

Data Submission Procedures. Please select **one** option for submitting specific data. Data submitted electronically or via facsimile should **not** be followed up with a mailed version.

- a. Southwest Oncology Group Member Institutions, CCOPs, UCOPs and approved Affiliate institutions may submit data electronically via the Web by using the SWOG CRA Workbench. To access the CRA Workbench, go to the SWOG Web site (<http://swog.org>) and logon to the Members Area. After you have logged on, click on the *CRA Workbench* link to access the home page for CRA Workbench website. Next, click on the *Data Submission* link and follow the instructions. If you are a CRA at an institution with Internet access, you are encouraged to submit data this way. For new users, the link to a "Starter Kit" of help files may be found by clicking on the **Starter Kit** link at the Members" logon page.

To submit data via the web the following must be done (in order):

1. You are entered into the Southwest Oncology Group Roster and issued a SWOG Roster ID Number,
2. You are associated as an investigator or CRA/RN at the institution where the patient is being treated or followed, and
3. Your Web User Administrator has added you as a web user and has given you the appropriate system permissions to submit data for that institution.

For assistance with points 1 and 2 call the Operations Office at 210/677-8808. For point 3, contact your local Web User Administrator (refer to the "Who is my Web User Administrator?" function on the swog.org Members logon page). For other difficulties with the CRA Workbench, please email technicalquestion@crab.org.

- b. Alternatives to the CRA Workbench/web based data submission option are: submission via facsimile, surface, or express mail.

For facsimile submission: Member, CCOPs, UCOPs and approved Affiliate institutions may submit data via facsimile to 800/892-4007 or 206/342-1680 locally. Please do not use cover sheet for faxed data. Facsimile submission is the 2nd preferred option for data submission.

For surface or express mail: Group Member Institutions, CCOPs, UCOPs and approved Affiliate institutions must submit one copy of all data forms directly to the Southwest Oncology Group Data Operations Center in Seattle at the address below. Affiliates must submit (number of copies to be determined by the Group member) copies of all forms to their Group member institution for forwarding to the Southwest Oncology Group Data Operations Center in Seattle at the following address:

Southwest Oncology Group Data Operations Center
Cancer Research And Biostatistics
1730 Minor Ave, STE 1900
Seattle, WA 98101-1468

14.4 CALGB Institutions

CALGB participants should submit data forms as listed in this section at the required intervals to:

Southwest Oncology Group Data Operations
Cancer Research And Biostatistics
1730 Minor Avenue, Suite 1900
Seattle, WA 98101-1468

Include the Southwest Oncology Group protocol number and patient number, as well as the CALGB study number and patient number.

14.5 CTSU DATA SUBMISSION AND RECONCILIATION

1. All case report forms (CRFs) associated with this study must be downloaded from the **S9921** Web page located on the CTSU registered member Web site (<https://members.ctsu.org>). Sites must use the current form versions and adhere to the instructions and submission schedule outlined in the protocol.
2. Submit all completed CRFs (with the exception of patient enrollment forms), clinical reports, and transmittals directly to the Southwest Oncology Data Operations Office. The preferred method of sending data is via fax at 800/892-4007. Do NOT include a cover sheet for faxed data.
3. The Southwest Oncology Group Data Operations Office will send query notices and delinquency reports directly to the site for reconciliation. Please fax query responses and delinquent data to the Southwest Oncology Group Data Operations Office and do not copy the CTSU Data Operations. When faxing data, include the query sheet that was originally sent from the Southwest Oncology Group.
4. Each site should have a designated CTSU Administrator and Data Administrator and **must keep their CTEP AMS account contact information current**. This will ensure timely communication between the clinical site and the Southwest Oncology Group Data Operations Office.

14.6 WITHIN 14 DAYS OF REGISTRATION:

Submit copies of the following:

S9921 Local Prostate Carcinoma Prestudy (Form #23968)

Pathology Report

14.7 AFTER CYCLE 3 AND CYCLE 6 OF CHEMOTHERAPY FOR ARM 2:

Submit copies of the **S9921** Adverse Event Summary Form (Form #27242) and the **S9921** Chemotherapy Treatment Form (Form #61544) summarizing adverse event and chemotherapy treatment information for the 3 cycles of chemotherapy being reported.

14.8 EVERY THREE MONTHS WHILE ON PROTOCOL TREATMENT (INCLUDING HORMONAL THERAPY) FOR BOTH ARM 1 AND ARM 2:

Submit the **S9921** Adverse Event Summary Form (Form #27242) and the **S9921** Treatment Form (Form #38859).

14.9 EVERY THREE MONTHS FOR FIVE YEARS, THEN EVERY SIX MONTHS UNTIL 15 YEARS OR DEATH:

Submit the **S9921** PSA Reporting Form (Form #59255).

14.10 EVERY SIX MONTHS UNTIL TESTOSTERONE LEVELS REACH INSTITUTIONAL LOWER LIMIT OF NORMAL (ILLN):

Submit the **S9921** Testosterone Reporting Form (Form #25939).

14.11 WITHIN 14 DAYS OF DISCONTINUATION OF ALL TREATMENT (INCLUDING HORMONAL THERAPY):

Submit copies of the Off Treatment Notice (Form #8756), final **S9921** Adverse Event Summary Form (Form #27242), and final **S9921** Treatment Form (Form #38859).

14.12 AFTER OFF ALL PROTOCOL TREATMENT, EVERY SIX MONTHS FOR TWO YEARS AND ANNUALLY THEREAFTER:

Submit the Follow-Up Form (Form #64587).

14.13 WITHIN 4 WEEKS OF KNOWLEDGE OF DEATH:

Submit copies of the Notice of Death (Form #49467). Also submit a **final S9921** Adverse Event Summary Form (Form #27242) and **S9921** Treatment Form (Form #38859) (if patient was still on protocol treatment) or Follow-Up Form (Form #64587) (if patient was off protocol treatment) documenting death information.

15.0 SPECIAL INSTRUCTIONS

15.1 Specimen Banking for Southwest Oncology Group Institutions

a. Specimens Requested and Patient Consent

It is strongly recommended that with the patient's additional consent on the "Consent Form for Use of Specimens for Research" that a formalin-fixed, paraffin-embedded tissue block from a representative area of the primary tumor be submitted as outlined in Section 15.1d below for banking.

It is strongly recommended that with the patient's additional consent that blood specimens be obtained at pre-study (after registration, but prior to receiving first dose of treatment), between Weeks 24 and 28, and at progression for banking. Instructions for the processing of these specimens are found in Section 15.1c below.

Material will be kept at the Southwest Oncology Group Repository.

- b. General Specimen Submission Instructions
1. Southwest Oncology Group Specimen Tracking System Guidelines

All specimen submissions for patients registered on this study must be entered and tracked using the Southwest Oncology Group Online Specimen Tracking System. Southwest Oncology Group members may log on to the Specimen Tracking System via the CRA Workbench (<https://gill.crab.org/txwb/logon.aspx>) using their Southwest Oncology Group roster identification numbers and passwords. First-time non-Southwest Oncology Group users must refer to start-up instructions located at <https://gill.crab.org/SpecTrack/>.

In the online Specimen Tracking System, laboratory ID numbers are used to identify the laboratories to which specimens are shipped. The laboratory ID number for this study is:

Lab # 107: U of Cincinnati/Path and Lab Correlates
Contact: Chris Hackett/Dr. Fenoglio-Preiser
Phone: 513/558-4675 or 513/558-4500

ALL SPECIMENS MUST BE LOGGED VIA THIS SYSTEM; THERE ARE NO EXCEPTIONS. To report technical problems with Specimen Tracking, such as database errors or connectivity issues, please send an email to technicalquestion@crab.org. For procedural help with logging and shipping specimens, there is an introduction to the system on the Specimen Tracking main page (<http://dnet.crab.org/SpecTrack/Documents/SpecTPrimer-Insts.pdf>); or contact the Data Operations Center at 206/667-2267 to be routed to the Data Coordinator for further assistance.

A copy of the Shipment Packing List produced by the Specimen Tracking System should be printed and placed in the pocket of the specimen bag if it has one, or in a separate resealable bag.

The bags should then be shipped in a standard Styrofoam shipping container which the sites can supply. PLEASE PACK TUBES CAREFULLY. Cardboard express mail envelopes alone are NOT ADEQUATE—please additionally pack the tubes in Styrofoam or with extra padding. If freezing conditions or extreme heat conditions are anticipated, insulated containers are recommended.

All submitted specimens must be labeled with the protocol number (**S9921**), SWOG patient number, patient's initials, and date and time of specimen collection.

All paraffin-embedded tissue samples should be mailed at **ambient (room) temperature** or placed on ice packs if shipped from warm climate areas.

Blood, serum, and plasma should be shipped on **dry ice** by overnight carrier Monday through Wednesday only.

Saturday, Sunday and Holiday Deliveries: Specimens will NOT be accepted on Saturdays, Sundays, and holidays.

2. **The Federal guidelines for shipment are as follows:**

- a. The specimen must be wrapped in an absorbable material.
- b. The specimen must be placed in an AIRTIGHT container (like a resealable bag).

- c. Pack the resealable bag and specimen in a Styrofoam shipping container.
 - d. Pack the Styrofoam shipping container in a cardboard box.
 - e. The cardboard box must be marked as "BIOHAZARD".
- c. Blood Specimen Submission for Banking

If the patient consents, please draw an additional blood sample at prestudy (after registration, but prior to receiving first dose of treatment), between Weeks 24 and 28, and at progression for submission to the Southwest Oncology Group Repository per instructions above.

Instructions for Processing of Blood Specimens

1. Blood samples should be collected using standard venipuncture technique.
2. A total of 20 mL of whole blood drawn in 3 separate tubes will be collected prior to treatment (at prestudy), between Weeks 24 and 28, and at progression. Follow instructions in #3, 4 and 5 below.
3. Serum: 10 ml of whole blood will be collected in red top vacutainer tubes (anticoagulant-free) and allowed to clot for approximately 30 minutes. Serum must be separated from cells within 45 - 60 minutes of venipuncture.
 - a. Serum is separated from clotted blood by centrifugation at 3,000 RPM for ten minutes. Alternatively, serum can be separated by centrifugation at 3500 rpm for 30 minutes if the blood is being run with blood tubes for plasma samples (see below).
 - b. Using a pipette, serum should then be equally aliquoted into three plastic storage/transport or cryotubes, and shipped according to the instructions below. Avoid disturbing the cell or clot layer during the pipeting procedure. Prolonged exposure to light, especially sunlight, should be avoided, but routine processing is not affected by normal, artificial laboratory lighting. Label cryovials with Patient ID#, cycle information and contents (e.g. plasma, serum, whole blood).
4. Whole Blood: Draw 5 mL of whole blood into an EDTA Lavender Top Tube, shake gently, and then separate sample equally into two (2) cryovials. Sample may be stored at -20° to -70°C and shipped with aliquots from serum sample and plasma sample.
5. Plasma: Process sample within 30 minutes of blood draw. Draw 5 ml of whole blood into an EDTA lavender top tube, invert gently, then centrifuge at 3500 rpm for 30 minutes. Divide plasma into three cryovials in ~ 1.0 ml aliquots, and then freeze the samples immediately at -70°C. Samples MUST be shipped as soon as possible and sent by overnight courier, DO NOT ALLOW SAMPLES TO THAW. If a -70°C freezer is not available plasma samples may be stored at -20°C until shipped. Label cryovials with Patient ID#, cycle information and contents (e.g. plasma, serum, whole blood).

NOTE: If you need cryovials, please contact the Southwest Oncology Group Repository at 513/558-4675.

d. **Tissue Submission for Banking**

With the patient's additional consent on the "Consent Form for Use of Specimens for Research," within 28 days of obtaining specimens, submit a biopsy specimen. Specimens of paraffin-embedded tissue should be shipped in appropriate mailing containers with adequate wrapping or cushioning to protect the specimens. These should be sent at ambient temperature, not on wet or dry ice (see instructions above).

15.2 CTSU Investigators - Special Materials or Substudies

All specimens submitted for this study must be entered and tracked using the Southwest Oncology Group on-line Specimen Tracking System, as specified in protocol Section 15.0. You can also access the Tracking System from the CTSU Member Web Site. Go to the **S9921** protocol page and click on the link provided under the Case Report Forms header.

Follow instructions as outlined in protocol Section 15.1.

15.3 CALGB Institutions

The following should be submitted to:

CALGB Pathology Coordinating Office
The Ohio State University
320 West 10th Avenue
M364 Starling-Loving Hall
Columbus, Ohio 43210
Phone: 614/293-7073
Fax: 614/293-7967

- a. Within one month of patient randomization submit:
1. One formalin-fixed, paraffin-embedded block from a representative area of the primary tumor along with:
 - i. Patient's name
 - ii. CALGB patient number and Southwest Oncology Group patient number
 - iii. CALGB study number and Southwest Oncology Group study number
 2. Original completed CALGB Form C-490
 3. A copy of the responsible pathologist's surgical pathology report from the TREATING institution, and, if applicable, the REFERRING institution.

If the institution is unable to submit a tumor block, submit C-490 to the CALGB Pathology Coordinating Office (copy to the CALGB DMC) with letter from institutional pathologist stating reason why block will not be sent. If patient does not consent to tissue submission, CALGB Form C-490 should be returned marked "Patient refused".

These tissue blocks will be stored at 4°C and sectioned by the CALGB Pathology Reference Laboratory according to companion protocol guidelines for studies which are approved by the Intergroup GU Cancer Correlative Sciences Committee.

- b. At prestudy (after registration, but prior to receiving first dose of treatment), between Weeks 24 and 28, and at progression submit blood specimens as outlined in Section 15.1c.

16.0 ETHICAL AND REGULATORY CONSIDERATIONS

The following must be observed to comply with Food and Drug Administration regulations for the conduct and monitoring of clinical investigations; they also represent sound research practice:

Informed Consent

The principles of informed consent are described by Federal Regulatory Guidelines (Federal Register Vol. 46, No. 17, January 27, 1981, part 50) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46). They must be followed to comply with FDA regulations for the conduct and monitoring of clinical investigations.

Institutional Review

This study must be approved by an appropriate institutional review committee as defined by Federal Regulatory Guidelines (Ref. Federal Register Vol. 46, No. 17, January 27, 1981, part 56) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46).

Drug Accountability

For each drug supplied for a study, an accountability ledger containing current and accurate inventory records covering receipt, dispensing, and the return of study drug supplies must be maintained. Drug supplies must be kept in a secure, limited access storage area under the recommended storage conditions. During the course of the study, the following information must be noted on the accountability ledger; the identification code of the subject to whom drug is dispensed, the date(s) and quantity of drug dispensed to the subject, and the date(s) and quantity of drug returned by the subject; subjects should return empty containers to the investigator, with the return noted on the ledger. These Accountability Forms must be readily available for inspection and are open to FDA or NCI inspection at any time.

Monitoring

This study will be monitored by the Clinical Data Update System (CDUS) version 1.1. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31.

16.1 Adverse Event Reporting Requirements

a. Purpose

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. (Directions for routine reporting are provided in Section 14.0.) Additionally, certain adverse events must be reported in an expedited manner to allow for more timely monitoring of patient safety and care. The following guidelines prescribe expedited adverse event reporting for this protocol. See also Appendix 19.5 for general and background information about expedited reporting.

b. Reporting methods

This study requires that expedited adverse event reporting use the NCI's Adverse Event Expedited Reporting System (AdEERS). The NCI's guidelines for AdEERS can be found at <http://ctep.cancer.gov>. An AdEERS report must be submitted to the Southwest Oncology Group Operations Office by one of the following methods:

- Electronically submit the report via the AdEERS Web-based application located at <http://ctep.cancer.gov>, or
- Only if submitting electronically is not possible, fax the completed NCI Adverse Event Expedited Report – Single Agent or Multiple Agents – paper template, located at <http://ctep.cancer.gov>, to 210/677-0006. Once Internet connectivity is restored, an AE report submitted on a paper template must be entered electronically into AdEERS by the original submitter at the site.

c. When to report an event in an expedited manner

When the adverse event requires expedited reporting, submit the report within 10 calendar days of learning of the event.

d. Other recipients of adverse event reports

The Operations Office will forward reports and documentation to the appropriate regulatory agencies and drug companies as required.

Adverse events determined to be reportable must also be reported according to local policy and procedures to the Institutional Review Board responsible for oversight of the patient.

e. **Expedited reporting for commercial agents**

Commercial reporting requirements are provided in Table 16.2. If there is any question about the reportability of an adverse event or if on-line AdEERS cannot be used, please telephone or email the SAE Program at the Operations Office, 210/677-8808 or adr@swog.org, before preparing the report.

Table 16.2. Expedited reporting requirements for adverse events experienced by patients who have received commercial drug(s) on this study.

Attribution	Grade 4		Grade 5^a	
	Unexpected	Expected	Unexpected	Expected
Unrelated or Unlikely			AdEERS	AdEERS
Possible, Probable, Definite	AdEERS		AdEERS	AdEERS
AdEERS: Indicates an expedited report is to be submitted using the NCI AdEERS Commercial Drug pathway within 10 calendar days of learning of the event.				
^a This includes all deaths within 30 days of the last dose of treatment with a commercial agent(s), regardless of attribution. Any death that occurs more than 30 days after the last dose of treatment with a commercial agent(s) and is attributed (possibly, probably, or definitely) to the agent(s) and is not due to cancer recurrence must be reported according to the instructions above.				

f. **Reporting secondary AML/MDS/ALL**

All cases of acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), and acute lymphocytic leukemia (ALL) that occur in patients on NCI-sponsored trials following chemotherapy for cancer must be reported using the NCI/CTEP Secondary AML/MDS Report Form in lieu of AdEERS. The following supporting documentation must also be submitted within 30 days:

- a copy of the pathology report confirming the AML/MDS/ALL diagnosis;
- and
- (if available) a copy of the cytogenetics report.

Submit the Report and documentation to:

Investigational Drug Branch **and** Southwest Oncology Group
by fax at 301-230-0159 ATTN: SAE Program
14980 Omicron Drive
San Antonio, Texas 78245-3217

NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the AML/MDS Report must be submitted for the most recent trial.

Adverse Reaction Reporting Requirements for CALGB Institutions:

CALGB participants should employ definitions of adverse events as described above. **Adverse reactions, both written and telephone reports, should be made directly to the Southwest Oncology Group and the NCI according to the institutions in those sections. A copy of written AERs should also be sent to the CALGB Regulatory Affairs Coordinator:**

CALGB Central Office
Attn: Regulatory Affairs, Coordinator
208 South LaSalle Street, Suite 2000
Chicago, IL 60604-1104
Fax: 312/345-0117

Institutions are responsible for notifying their IRBs of toxicities reported as adverse events under these guidelines.

Adverse Event (AE) Reporting for CTSU Investigators:

1. CTSU sites must comply with the expectations of their local Institutional Review Board (IRB) regarding documentation and submission of adverse events. Local IRBs must be informed of all reportable serious adverse reactions.
2. CTSU sites will assess and report adverse events according to the guidelines and timelines specified in the protocol. You may navigate to the CTEP Adverse Event Expedited Report System (AdEERS) from either the Adverse Events tab of the CTSU member homepage (<https://members.ctsu.org>) or by selecting Adverse Event Reporting Forms from the document center drop down list on the **S9921** Web page.
3. Do not send adverse event reports to the CTSU.
4. Secondary AML/MDS/ALL reporting: Report occurrence of secondary AML, MDS, or ALL via the NCI/CTEP AML-MDS Report Form in lieu of AdEERS. Submit the completed form and supporting documentation as outlined in the protocol.

17.0 BIBLIOGRAPHY

1. Bagshaw MA, Cox RS, Hancock SL. Control of prostate cancer with radiotherapy. Long term results. *J Urol* 152:1781-1785, 1994.
2. Zincke H, Utz DC. Observation on surgical management of carcinoma of the prostate with limited nodal metastases. *Urology* 24:107, 1984.
3. Hussain M. Future directions in prostate cancer treatment: An oncologist's perspective. *Prostate Supp* 6:26-30, 1996.
4. Stein A, Dekernion JB, Smith RB, et al. Prostate specific antigen levels after radical prostatectomy in patients with organ confined and locally extensive prostate cancer. *J Urol* 147:942-946, 1992.
5. Partin AW, Pound CR, Clemens JQ, et al. Serum PSA after anatomic radical prostatectomy: The Johns Hopkins experience after 10 years. *Urol Clin N Amer* 20(4):713-725, 1993.
6. Partin AW, Lee BR, Carmichael M, et al. Radical prostatectomy for high-grade disease: A re-evaluation 1994. *J Urol* 151:1583-1586, 1994.
7. Ohori M, Goad JR, Wheeler TM, et al. Can radical prostatectomy alter the progression of poorly differentiated prostate cancer?. *J Urol* 152:1843-1849, 1994.
8. Epstein JI, Pizov G, Walsh PC. Correlation of pathologic findings with progression after radical retropubic prostatectomy. *Cancer* 71(11):3582-3593, 1993.
9. Fisher B, Fisher ER, Redmond C. Ten-year results from the NSABP clinical trial evaluation the use of L-phenylalanine mustard (L-PAM) in the management of primary breast cancer. *JCO* 4:9290941, 1996.
10. Moertel CG, Fleming TR, Macdonald JS, et al. Levamisole and fluorouracil for adjuvant therapy of resected colon carcinoma. *NEJM* 322:352-358, 1990.
11. Ginsberg RJ, Vokes EE, Raben A. Non-small cell lung cancer. Section 30.2. In *Principles and Practice of Oncology*. DeVita VT, Hellman S, Rosenberg SA, eds. 5th ed. Philadelphia: Lippencott-Raven, 1997, pp. 858-911.
12. Kirkwood JM, Strawderman MH, Ernstaff MS, et al. Interferon alfa-2b adjuvant therapy of high risk resected cutaneous melanoma: The Eastern Cooperative Oncology Group Trial EST 1684. *JCO* 14:7-17, 1998.
13. Pilepich MV, Sause WT, Shipley WU, et al. Androgen deprivation with radiation therapy compared with radiation therapy alone for locally advanced prostatic carcinoma: a randomized comparative trial of the Radiation Therapy Oncology Group. *Urology* 45:616-623, 1995.
14. Porter AT, Elhilali M, Manji M, et al. A Phase III randomized trial to evaluate the efficacy of neoadjuvant therapy prior to curative radiotherapy in locally advanced prostate cancer patients: A Canadian Urologic Oncology Group study. *Proc ASCO* 16:315, #1123, 1997.
15. Walsh PC, Partin AW, Epstein JI. Cancer control and quality of life following anatomical radical retropubic prostatectomy for prostate cancer – results at 10 years. *J Urol* 152:1831-1836, 1994.
16. Catalona WJ, Smith DS. Five-year tumor recurrence rates after anatomical radical retropubic prostatectomy for prostate cancer. *J Urol* 152:1837-1842, 1994.
17. Soloway MS, Sharifi R, Wajsman Z, McLeod D, Wood DP Jr., Puras-Baez A. Randomized prospective study comparing radical prostatectomy alone versus radical prostatectomy preceded

- by androgen blockade in clinical stage B2 (T2bNxM0) prostate cancer. J Urol 154:424-428, 1995.
18. Witjes WP, Schulman CC, Debruyne FM. Preliminary results of a prospective randomized study comparing radical prostatectomy versus radical prostatectomy associated with neoadjuvant hormonal combination therapy in T2-T3N0M0 prostatic carcinoma. The European Study Group on Neoadjuvant Prostate Cancer. Urology 49(3A Supplement):65-69, 1997.
19. Fair WR, Cookson MS, Stroumbakis N, Cohen D, Aprikian AG, Want Y, Russo P, Soloway SM, Sogani P, Sheinfeld J, Herr H, Dalgabni G, Begg CB, Heston DW and Reuter VE. The indications, rationale and result of neoadjuvant androgen deprivation in the treatment of prostatic cancer: Memorial Sloan-Kettering Cancer Center results. Urology 49(3A Supplement):46-55, 1997.
20. Labrie F, Dupont A, Cusan L, Gomez JL, Diamond P, Suburu R, Lemay M, Tetu B, Fradet Y, Belanger A, Candas B. Neoadjuvant hormonal therapy: The Canadian experience. Urology 49(3A Supplement):56-64, 1997.
21. Goldberg SL, Klotz LH, Sprigley J, Jewett MAS, Mador D, Fradet Y, Barkin J, Chin J, Paquin JM, Bullock MJ, Laplante S and Canadian urologic oncology group. Randomized, prospective controlled study comparing radical prostatectomy alone and neoadjuvant androgen withdrawal in the treatment of localized prostate cancer. J Urol 156:873-877, 1996.
22. Soloway MS, Sharifi R, Wajsman Z, McLeod D, Wood DP, Jr. Radical prostatectomy alone vs. radical prostatectomy preceded by androgen blockade in cT2b prostate cancer. J Urol 157:160, 1997 (Abstract).
23. Harris J, Morrow M, Norton L. Malignant tumors of the breast. . In Principles and Practice of Oncology. DeVita VT, Hellman S, Rosenberg SA, eds. 5th ed. Philadelphia: Lippencott-Raven, 1997, pp. 1557-1616.
24. Murphy WM, Soloway MS, Barrows GH. Pathologic changes associated with androgen deprivation therapy for prostate cancer. Cancer 68:821-828, 1991.
25. Zagars GK, Johnson DE, Von Eschenbach AC, et al. Adjuvant estrogen following radiation therapy for stage C adenocarcinoma of the prostate: long-term results of a prospective randomized study. Int J Rad Onc Biol Phys 14:1085-1091, 1988.
26. Schmidt JD, Gibbons RP, Murphy GP, Bartolucci A. Adjuvant estramustine phosphate treatment for localized prostate cancer. PPO updates 11(10):1-9, 1997.
27. Pilepich MV, Caplan R, Byhardt RW et al. Phase III trial of androgen suppression using goserelin in unfavorable prognosis carcinoma of the prostate treated with definitive radiotherapy: report of Radiation Therapy Oncology Group protocol 85-31. J Clin Oncol 15:1013-1021, 1997.
28. Bolla M, Gonzalez D, Warde P, et al. Improved survival in patients with locally advanced prostate cancer treated with radiotherapy and goserelin. NEJM 337:295-300, 1997.
29. Pienta KJ, Redman B, Hussain M, et al. Phase II evaluation of oral estramustine and oral etoposide in hormone refractory adenocarcinoma of the prostate. J Clin Onc 12:2005-2012, 1994.
30. Hudes GR, Nathan F, Khater C, et al. Phase II trial of 96-hour paclitaxel plus oral estramustine phosphate in metastatic hormone-refractory prostatic cancer. JCO 15:3156-3163, 1997.
31. Tannock IF, Osoba D, Stockler M, et al. Chemotherapy with mitoxantrone plus prednisone or prednisone alone for symptomatic hormone resistant prostate cancer. A Canadian randomized trial with palliative endpoints. J Clin Onc 14:1756-1764, 1996.
32. Kantoff PW, Conoway M, Winer E, et al. Hydrocortisone with or without mitoxantrone in patients with hormone refractory prostate cancer; Preliminary results from a prospective randomized



Cancer and Leukemia Group B study (9182) comparing chemotherapy to best supportive care. Proc Am Soc Clin Onc 15:25 (addendum), abstr #2013, 1996.

33. Gibbons RP, Cole BS, Richardson RG, Correia RJ Jr., Brannen GE, Mason JT, Taylor WJ, Hafermann MD. Adjuvant radiotherapy following prostatectomy: results and complications. J Urol 135(1):65-68, 1986.
34. Anscher MS, Prosnitz LR. Postoperative radiotherapy for patients with carcinoma of the prostate undergoing radical prostatectomy with positive surgical margins, seminal vesicle involvement and/or penetration through the capsule. J Urol 138(6):1407-1412, 1987.
35. Eusbrycg A, Perez CA, Roessler EH, Lockett MA. Adjuvant irradiation after prostatectomy for carcinoma of the prostate with positive surgical margins. Cancer 73(2):384-388, 1994.
36. Paulson DF, Moul JW, Robertson JE, Walther PJ. Postoperative radiotherapy of the prostate for patients undergoing radical prostatectomy with positive margins, seminal vesicle involvement and/or penetration through the capsule. J Urol 143(6):1178-1182, 1990.
37. Walsh PC. Adjuvant radiotherapy after radical prostatectomy: is it indicated? J Urol 138(6):1427-1428, 1987.
38. Ray GR, Bagshaw MA, Freiha F. External beam radiation salvage for residual or recurrent local tumor following radical prostatectomy. J Urol 132(5):926-930, 1984.
39. Morris MM, Dallow KC, Zietman AL, Park J, Althausen A, Heney NM, Shipley WU. Adjuvant and salvage irradiation following radical prostatectomy for prostate cancer. Int J Radiat Oncol Biol Phys 38(4):731-736, 1997.
40. Pound CR, Partin AW, Eisenberger MA, Chan DW, Pearson JD, Walsh PC. Natural History of Progression After PSA Elevation Following Radical Prostatectomy. JAMA 281(17):1591-1597, 1999.

18.0 **MASTER FORMS SET**

This section includes copies of all data forms which must be completed for this study. These include:

- 18.1 Model Consent Form (to be reviewed and approved by the Institutional Review Board prior to patient registration on the study).
- 18.2 Southwest Oncology Group Registration Form (Form #26636) (3/15/06) and Guidelines
- 18.3 **S9921** Local Prostate Carcinoma Prestudy (Form #23968) (3/15/06)
- 18.4 **S9921** PSA Reporting Form (Form #59255) (3/15/06)
- 18.5 **S9921** Testosterone Reporting Form (Form #25939) (3/15/06)
- 18.6 **S9921** Treatment Form (Form #38859) (3/15/06)
- 18.7 **S9921** Chemotherapy Treatment Form (Form #61544) (3/15/06)
- 18.8 **S9921** Adverse Event Summary Form (Form #27242) (3/15/06)
- 18.9 Follow-Up Form (Form #64587) (9/15/03)
- 18.10 Off Treatment Notice (Form #8756) (9/1/03)
- 18.11 Notice of Death (Form #49467) (9/1/03)

This model informed consent form has been reviewed by the DCT/NCI and is the official consent document for this study. Local IRB changes to this document are allowed. (Institutions should attempt to use sections of this document which are in bold type in their entirety.) Editorial changes to these sections may be made as long as they do not change information or intent. If the institutional IRB insists on making deletions or more substantive modifications to the risks or alternatives sections, they may be justified in writing by the investigator and approved by the IRB. Under these circumstances, the revised language, justification and a copy of the IRB minutes must be forwarded to the Southwest Oncology Group Operations Office for approval before a patient may be registered to this study.

Readability Statistics: Flesch Reading Ease 61.3 (targeted above 55)
Flesch-Kincaid Grade Level 8.2 (targeted below 8.5)

S9921, "Adjuvant Androgen Deprivation versus Mitoxantrone Plus Prednisone Plus Androgen Deprivation in Selected High Risk Prostate Cancer Patients Following Radical Prostatectomy"

PHASE III

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 family and friends.

You are being asked to take part in this study because you have prostate cancer considered to be high risk, and your prostate has been removed by surgery.

*It is suggested that CTSU institutions incorporate the following paragraph in their consent form:
(7/1/01)*

You have been asked to participate in a research study because you have **[INSERT BRIEF DESCRIPTION OF DISEASE BEING STUDIED]**. This study is being performed by the doctors at **[INSERT INSTITUTION NAME]** who are members of the National Network of participating physicians and sponsored by the National Cancer Institute's Cancer Trial Support Unit. *(paragraph added 6/1/00)*

Why Is This Study Being Done?

The purpose of this study is to compare the effects (good and bad) of the addition of chemotherapy (mitoxantone and prednisone) to a standard hormone therapy with hormone therapy given alone on you and your prostate cancer to see which is better.



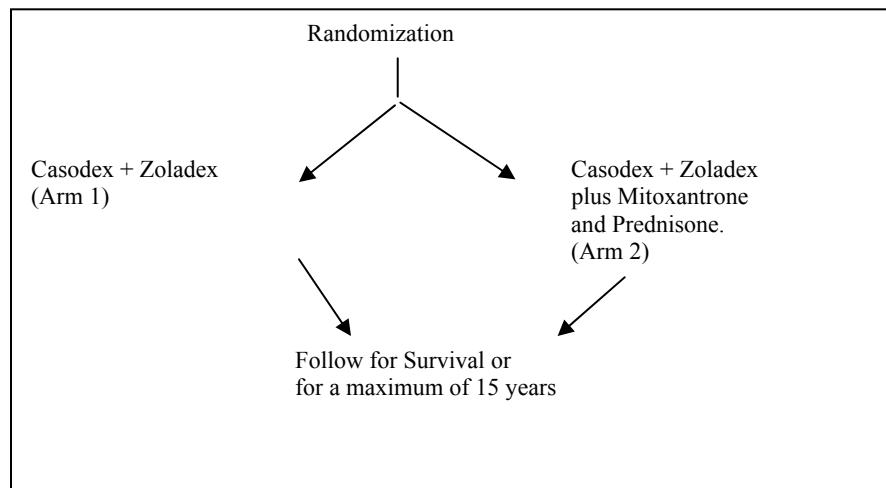
(2/14/06)

How Many People Will Take Part in the Study

Nationally, about 1,360 people will take part in this study.

(paragraphs deleted 2/14/06)

What Is Involved in the Study?



You will be "randomized" into one of the study groups described above. 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 any group.

If you take part in this study you will be randomized to either Arm 1 or Arm 2 as described in the chart above. Depending on which arm you are placed in you will receive treatment as described in the following sections:

ARM 1 (Hormonal Therapy)

Medical Tests:

The following tests may be done to make sure that you are eligible for this study. None of these tests are experimental. They are routine. You may not need to have all of these tests done. Depending on when you last had them, you may need to repeat some of these tests:

- Blood Tests
- Bone Scan
- CAT scan of your abdomen/lower abdomen
- Electrocardiogram
- A special x-ray to study the heart (MUGA scan)

Many of the tests will also be repeated during the study. If you participate in this study, some of these tests may be done more frequently than if you were not taking part in this research study.

Procedures (treatment):

If you are eligible and agree to take part in this study you will receive:

- Goserelin Acetate (Zoladex[®]) as an injection every 3 months for two years.
(2/14/06)
- Bicalutamide (Casodex[®]) is taken once a day for two years.
- **ARM 2 (Hormonal Therapy Plus Mitoxantrone Plus Prednisone)**

Medical Tests:

The following tests may be done to make sure that you are eligible for this study. None of these tests are experimental. They are routine. You may not have to have all of these tests done. Depending on when you last had them, you may need to repeat some of these tests:

- Blood Tests

- Bone Scan
- CAT scan of your abdomen/lower abdomen
- Electrocardiogram
- A special x-ray to study the heart (MUGA scan)

Many of the tests will also be repeated during the study. If you participate in this study, some of these tests may be done more frequently than if you were not taking part in this research study.

Procedures (treatment):

If you are eligible and agree to take part in this study you will receive:

- Goserelin Acetate (Zoladex[®]) as an injection every 3 months for two years.
(2/14/06)
- Bicalutamide (Casodex[®]) every day for two years. Bicalutamide is taken once a day for two years.
- Mitoxantrone and prednisone 6 times. Mitoxantrone is given through a needle in a vein on the first day of each 21 day cycle. Prednisone is given twice per day by mouth every day until the 6 cycles are finished. Each dose regimen will be 21 days apart.

How Long Will I Be in the Study?

Your hormonal therapy will last 2 years. We would like to keep track of your medical condition for fifteen years to look at the long-term effects of the study.

The researcher may decide to take you off this study if your disease gets worse despite the treatment; the side effects of the treatment are too dangerous for you; new information about the treatment becomes available and this information suggests the treatment will be ineffective or unsafe for you.

What Are the Risks of the Study?

While on the study, you are at risk for these side effects. You should discuss these with the researcher and/or your regular doctor. There also may be other side effects that we cannot predict. Other drugs will be given to make side effects less serious and uncomfortable. Many side effects go away shortly after the drugs are stopped, but in some cases side effects can be serious or long-lasting or permanent.



Side effects of Hormonal Therapy with Goserelin Acetate (Zoladex®) and Bicalutamide (Casodex®):

ARM 1: (*text bolded 2/14/06*)

Very likely:

- **Hot flashes**
- **Nausea**
- **Dizziness**
- **Diarrhea**
- **Constipation**
- **Fatigue**
- **Pain (back, abdominal, pelvic or in general)**
- **Swelling of hands or feet**
- **Impotence**
- **Loss of bone mineral density (2/14/06)**

Less likely:

- **Breast tenderness and swelling**
- **Mild skin rash**
- **Decreased testicular size**
- **Weakness (items added 2/14/06)**
- **Anemia**
- **Increased liver enzymes (blood tests)**
- **Weight gain**
- **Osteoarthritis**

Side effects of Hormonal Therapy plus Mitoxantrone plus Prednisone:

ARM 2: (*text bolded 2/14/06*)

Very likely:

- **Lowered white blood count may lead to an infection**
- **Lowered platelets may lead to an increase in bruising or bleeding**
- **Nausea, vomiting, or diarrhea**
- **Constipation**
- **Fatigue**
- **Temporary complete hair loss**
- **Loss of appetite**
- **High or low blood pressure**
- **Numbness or tingling in fingers or toes**
- **Pain in muscles and joints**
- **Muscle weakness**
- **Swelling of the feet, abdomen, or face (fluid retention)**
- **Impotence**
- **Urine color changes (blue-green)**
- **Dizziness/lightheadedness**
- **Rash**
- **Hot flashes**
- **Pain (back, abdominal, pelvic or in general)**

Less likely: (*text bolded 2/14/06*)

- **Breast tenderness and swelling**
- **Allergic reactions (may happen during injection)**
- **Irregular heartbeat**
- **Weakening of heart muscle**
- **Whites of eyes slightly bluish**
- **Lowered red blood cells may lead to anemia, tiredness, or shortness of breath**
- **Decreased testicular size**
- **Mild skin rash**
- **Infection** (*items from here on added 2/14/06*)
- **Weight gain**
- **Weight loss**
- **Fever without infection**
- **Shortness of breath**
- **Nail bed changes**
- **Mouth or lip sores**
- **Sweats**
- **Mood changes (anxiety, depression, irritability)**
- **Cough**
- **Heartburn**

Rare, but Serious: *(added 2/14/06)*

Mitoxantrone has been reported to cause leukemia.

(paragraph deleted 2/14/06)

Are There Benefits to Taking Part in the Study?

We cannot and do not guarantee you will benefit if you take part in this study. The treatment you receive may even be harmful. Your doctors feel that your participation in this study will give you at least as good a chance as you might expect from other treatments. We hope the information learned from this study will benefit other patients with prostate cancer in the future.

(paragraph deleted 2/14/06)

What Other Options Are There?

**Instead of being in this study, you have these options:
Other types of chemotherapy, radiation or no anti-cancer treatment at this time (with care to help you feel more comfortable).**

You can get treatment for prostate cancer without being on this study. All of the treatment on this study may be available at this center or at other locations.

Please talk to your regular doctor about these and other options.

What about Confidentiality?

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. 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 National Cancer Institute, a qualified representative of the drug manufacturers, the Food and Drug Administration, CALGB and the Southwest Oncology Group. (5/15/00)

If we publish the information we learn from this study in a medical journal, you will not be identified by name or in any other way.

FOR CTSU INVESTIGATORS ONLY

While you are participating in this study a record of your progress on this study will be kept in a confidential form at [INSERT NAME OF INSTITUTION] and sent to the sponsor who will add this information to a computer file. The confidentiality of any central computer record will be carefully guarded and no information by which you can be identified will be released or published. You have been informed that authorized representatives of [INSERT GROUP NAME and the CLINICAL TRIALS SUPPORT UNIT], the National Cancer Institute, The Food and Drug Administration (FDA), and [INSERT NAME OF INSTITUTION AND INSTITUTIONAL REVIEW BOARD HERE] may inspect and copy the records. ([Optional, if applicable] *An authorized representative of the manufacturers of the drugs used in this study may also have access to your study records.*) Your identity will remain confidential and your records will be used by these authorized representatives only in connection with carrying out their obligations relating to the clinical trial and they shall not be used for any other purpose or disclosed to any third party except with your express permission. (Paragraph added 6/1/00)

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. (local institutions must choose the option that best fits the hospital's situation)

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.

Administration of the drug will be (provided free of charge/charged in the usual way). The goserelin acetate (Zoladex[®]) and the bicalutamide (Casodex[®]) will be provided free of charge for this study by the manufacturer (Astra Zeneca). (4/15/00) The mitoxantrone will be provided free of charge for this study by OSI Pharmaceuticals. (4/15/00, 2/14/06) The prednisone is commercially available and will be charged in the usual way. The parts of the research consisting of keeping research records will be paid by those organizing and conducting the research. The research requires that you receive certain standard medical tests and examinations.



(Repagination page 6/01/00)

These standard tests and examinations will be (charged in the usual way/provided at a reduced rate). (local institutions must choose the option that best fits the hospital's situation)

What Are My Rights as a Participant?

Taking part in this study is voluntary. You may choose not to 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. 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.

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

Whom Do I Call if I Have Questions or Problems?

For questions about the study or a research-related injury, contact the researcher name(s) _____ at _____ telephone number _____.

For questions about your rights as a research participant, contact the name of center Institutional Review Board (which is a group of people who review the research to protect your rights) at _____ telephone number _____. [And, if available, list patient representative (or other individual who is not on the research team or IRB)].

(section added 2/14/06)

Please note: This section of the informed consent form is about additional research studies that are being done with people who are taking part in the main study. You may take part in these additional studies if you want to. You can still be a part of the main study even if you say 'no' to taking part in any of these additional studies.

You can say "yes" or "no" to each of the following studies. Please mark your choice for each study.

*[The following example of tissue consent has been taken from the NCI Cancer Diagnosis Program's model tissue consent form found at the following url
<http://www.cancerdiagnosis.nci.nih.gov/specimens/model.pdf>]*

Consent Form for Use of Specimens for Research (2/14/06)

About Using Specimens for Research

You have had a prostatectomy (surgery to remove the prostate). Your doctor has removed some body tissue to do some tests. The results of these tests will be given to you by your doctor and will be used to plan your care. If you agree, you will have about 2 tablespoons of blood drawn before your first treatment, again between Weeks 24 and 28 of treatment, and when you go off protocol treatment.

We would like to keep some of the tissue and blood for future research. If you agree, these specimens will be kept and may be used in research to learn more about cancer and other diseases. Please read the information sheet called "How are Specimens Used for Research" to learn more about specimen research.

Your specimens will be kept at:

Cecilia M. Fenoglio-Preiser, M.D.
University of Cincinnati
231 Albert Sabin Way
PO Box 670529
Cincinnati, OH 45267-0529
Phone: 513/558-4500
FAX: 513/558-2289
E-mail: cecilia.fenogliopreiser@uc.edu

The research that may be done with your specimens is not designed specifically to help you. It might help people who have cancer and other diseases in the future.

Reports about research done with your specimens will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care.

Things to Think About

The choice to let us keep the left over specimens for future research is up to you. No matter what you decide to do, it will not affect your care.

If you decide now that your specimens can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your specimens. Then any specimens that remain will no longer be used for research.

In the future, people who do research may need to know more about your health. While the Southwest Oncology Group may give them reports about your health, it will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Sometimes specimens are used for genetic research (about diseases that are passed on in families). Even if your specimens are used for this kind of research, the results will not be put in your health records.

Your specimens will be used only for research and will not be sold. The research done with your specimens may help to develop new products in the future.

Benefits

The benefits of research using specimens include learning more about what causes cancer and other diseases, how to prevent them, and how to treat them.

Risks

The greatest risk to you is the release of information from your health records. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone else is very small.



Making Your Choice

Please read each sentence below and think about your choice. After reading each sentence, circle "Yes" or "No." If you have any questions, please talk to your doctor or nurse, or call our research review board at IRB's phone number.

No matter what you decide to do, it will not affect your care.

- 1. My specimens may be kept for use in research to learn about, prevent, treat or cure cancer.**

Yes No

- 2. My specimens may be kept for use in research about other health problems (for example: diabetes, Alzheimer's disease, or heart disease).**

Yes No

- 3. Someone may contact me in the future to ask me to allow other uses of my specimens.**

Yes No

If you decide to withdraw your specimens from a Southwest Oncology Group Specimen Repository in the future, a written withdrawal of consent should be submitted through your treating physician to the Southwest Oncology Group Operations Office. Please designate in the written withdrawal whether you would prefer to have the specimens destroyed or returned to the treating physician.

Where Can I Get More Information?

[To IRB/Investigators: Attach information materials and checklist of attachments. Signature page should be at the end of package. You may also wish to include the following informational resources].

You may call the NCI's Cancer Information Service at 1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

Visit the NCI's Web sites...

Cancer Trials: comprehensive clinical trials information
<http://cancertrials.nci.nih.gov>.

CancerNet™: accurate cancer information including PDQ
<http://cancernet.nci.nih.gov>.

You will get a copy of this form. You may also request a copy of the protocol (full study plan).



SIGNATURE

You are deciding whether or not to take part in this study. If you sign, it means that you have decided to volunteer to take part in this study, and that you have read and understood all the information on this form.

Participant _____ Date _____

(section deleted 2/14/06)

CLOSED EFFECTIVE 01/12/2007

Specimen Consent Supplemental Sheets (added 2/14/06)

How are Specimens Used for Research?

Where do specimens come from?

A specimen may be from a blood sample or from bone marrow, skin, toenails or other body materials. People who are trained to handle specimens and protect donors' rights make sure that the highest standards of quality control are followed by the Southwest Oncology Group. Your doctor does not work for the Southwest Oncology Group, but has agreed to help collect specimens from many patients. Many doctors across the country are helping in the same way.

Why do people do research with specimens?

Research with specimens can help to find out more about what causes cancer, how to prevent it, how to treat it, and how to cure it. Research using specimens can also answer other health questions. Some of these include finding the causes of diabetes and heart disease, or finding genetic links to Alzheimer's.

What type of research will be done with my specimen?

Many different kinds of studies use specimens. Some researchers may develop new tests to find diseases. Others may develop new ways to treat or even cure diseases. In the future, some of the research may help to develop new products, such as tests and drugs. Some research looks at diseases that are passed on in families (called genetic research). Research done with your specimen may look for genetic causes and signs of disease.

How do researchers get the specimen?

Researchers from universities, hospitals, and other health organizations conduct research using specimens. They contact the Southwest Oncology Group and request samples for their studies. The Southwest Oncology Group reviews the way that these studies will be done, and decides if any of the samples can be used. The Southwest Oncology Group gets the specimen and information about you from your hospital, and sends the specimen samples and some information about you to the researcher. The Southwest Oncology Group will not send your name, address, phone number, social security number or any other identifying information to the researcher.

Will I find out the results of the research using my specimen?

You will not receive the results of research done with your specimen. This is because research can take a long time and must use specimen samples from many people before results are known. Results from research using your specimen may not be ready for many years and will not affect your care right now, but they may be helpful to people like you in the future.

Why do you need information from my health records?

In order to do research with your specimen, researchers may need to know some things about you. (For example: Are you male or female? What is your race or ethnic group? How old are you? Have you ever smoked?) This helps researchers answer questions about diseases. The information that will be given to the researcher may include your age, sex, race, diagnosis, treatments and family history. This information is collected by your hospital from your health record and sent to the Southwest Oncology Group. If more information is needed, the Southwest Oncology Group will send it to the researcher.

Will my name be attached to the records that are given to the researcher?

No. Your name, address, phone number and anything else that could identify you will be removed before they go to the researcher. The researcher will not know who you are.

How could the records be used in ways that might be harmful to me?

Sometimes, health records have been used against patients and their families. For example, insurance companies may deny a patient insurance or employers may not hire someone with a certain illness (such as AIDS or cancer). The results of genetic research may not apply only to you, but to your family members too. For disease caused by gene changes, the information in one person's health record could be used against family members.

How am I protected?

The Southwest Oncology Group is in charge of making sure that information about you is kept private. The Southwest Oncology Group will take careful steps to prevent misuse of records. Your name, address, phone number and any other identifying information will be taken off anything associated with your specimen before it is given to the researcher. This would make it very difficult for any research results to be linked to you or your family. Also, people outside the research process will not have access to results about any one person which will help to protect your privacy.

What if I have more questions?

If you have any questions, please talk to your doctor or nurse, or call our research review board at (Insert IRB's Phone Number).

CLOSED EFFECTIVE 01/12/2007



Southwest Oncology Group Data Operations Center
C/o Cancer Research And Biostatistics
1730 Minor Ave, Suite 1900
Seattle, WA 98101-1468
Patient Registration:
via WebReg at: <http://swog.org>

Southwest Oncology Group Operations Office
14980 Omicron Drive
San Antonio, TX 78245-3217
Phone: (210) 677-8808
Fax: (210) 677-0006

(24 hours a day, 7 days a week, excluding downtimes for maintenance)
or call 206-652-2267 (Mon-Fri, 6:30am-4:00pm Pacific Time, excluding holidays)

Southwest Oncology Group Registration Form

SWOG Study No.

S | 9 | 9 | 2 | 1

Registration Step

1

Assigned Treatment Arm

Activation Date: October 15, 1999

Last Amended Date: March 15, 2006

Adjuvant Androgen Deprivation Versus Mitoxantrone Plus Prednisone Plus Androgen Deprivation in Selected High Risk Prostate Cancer Patients Following Radical Prostatectomy, Phase III

Patient's Name _____

SWOG Patient ID

Other Group Patient ID

Other Group Name/
Protocol Number _____

INSTRUCTIONS: All of the information on this Registration Form and the Protocol Eligibility Section must be answered appropriately for a patient to be considered eligible for registration. This Registration Form must be entirely filled out and referred to during the registration. Do NOT submit this form as part of the patient data.

Caller's SWOG Roster ID

IRB Approval Date

/ /

Date Informed Consent Signed

/ /

SWOG Investigator Number

OR

Other Group Investigator Name and Number

/ _____

SWOG Treating Institution Number

OR

Other Group Treating Institution Name and Number

/ _____

Please indicate how the patient answered the following questions on the consent form:

1. My specimens may be kept for use in research to learn about, prevent, treat or cure cancer.

Yes No

2. My specimens may be kept for use in research about other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

Yes No

3. Someone may contact me in the future to ask me to allow other uses of my specimens.

Yes No

Patient's Date of Birth: / /

Patient's Sex: Female Male

Method of Payment:

Patient's Ethnicity:

Patient's Race (select all that apply):

White or Caucasian Native Hawaiian or Other Pacific Islander American Indian or Alaska Native
 Black or African American Asian Unknown

If a U.S. resident:

Patient's Social Security Number: - -

Country of Residence, if not USA: _____

If a resident of Canada: Social Insurance Number: - - - - Postal Code: - -

Stratification Factors:

Height: cm

Weight: . kg

BSA: . m²

Performance Status:

Pathologic stage of disease: Organ confined Not organ confined, but N0 N1

Gleason's Sum: <7 7 >7 RT intended: Yes No

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3/15/2006



Southwest Oncology Group Registration Form Code Sheet

12/8/2004

Race code definitions:

White or Caucasian: a person having origins in any of the original peoples of Europe, Middle East, or North Africa

Black or African American: a person having origins in any of the black racial groups of Africa.

Native Hawaiian or Other Pacific Islander: a person having origins in any of the original peoples of Hawaii, Guam, Samoa and other Pacific islands.

Asian: a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent. Including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand and Vietnam.

American Indian or Alaska Native: a person having origins in any of the original peoples of North, Central or South America, and who maintains tribal affiliations or community attachment.

Ethnicity (Spanish/Hispanic Origin) codes:

- | | |
|-----------------------|---------------------------|
| 0 - Unknown | 5 - Yes, Central American |
| 1 - No (not Spanish) | 6 - Yes, South American |
| 2 - Yes, Mexican | 7 - Yes, Other |
| 3 - Yes, Puerto Rican | 8 - Yes, NOS |
| 4 - Yes, Cuban | |

Method of Payment codes:

- | | |
|------------------------------|-------------------------------------|
| 01 - Private | 08 - No insurance (no means) |
| 02 - Medicare | 09 - Other, specify at registration |
| 03 - Medicare and Private | 10 - Unknown |
| 04 - Medicaid | 11 - Veterans Admin |
| 05 - Medicaid and Medicare | 12 - Military |
| 07 - No insurance (self-pay) | |

Other Group codes for use in the Web Registration program:

- | | |
|---------------|--------------|
| 9977 - ACOSOG | 9984 - GOG |
| 9982 - CALGB | 9996 - NCCTG |
| 9976 - CTSU | 9981 - NCIC |
| 9995 - ECOG | 9983 - NSABP |
| 9979 - EPP | 9997 - RTOG |

SOUTHWEST ONCOLOGY GROUP
S9921 LOCAL PROSTATE CARCINOMA PRESTUDY

Page 1 of 3

SWOG Patient ID

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SWOG Study No. S 9 9 2 1

Registration Step 1

Patient Initials _____ (L, F M)

Institution/Affiliate _____ Physician _____

Participating Group: Group Name/Study No./Patient ID _____ / _____ / _____

Instructions: All dates are MONTH, DAY, YEAR. Explain any blank fields or blank dates in the **Comments** section. Place an in appropriate boxes. Circle **AMENDED** items in red and write **AMENDED** across the top of the form.

PATIENT CHARACTERISTICS

Performance status: Is patient known to be HIV-positive? No Yes

Does patient have a history of cardiac disease? No Yes, specify: _____

Date of EKG:

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 /

--	--	--

 /

--	--	--	--	--

If measured, LVEF by MUGA or 2d ECHO:

--	--

% Date of LVEF measurement:

--	--	--

 /

--	--	--

 /

--	--	--	--	--

DISEASE DESCRIPTION

Date of First Pathologic Diagnosis:

--	--

 /

--	--

 /

--	--	--	--	--

Clinical Stage of Primary Tumor (T-stage): T1a T1b T1c T2a T2b T3a T3b

Pathologic Stage of Primary Tumor (pT-stage): pT2a pT2b pT3a pT3b pT4

Regional Lymph Nodes (N-stage)

NX (Regional lymph nodes cannot be assessed)

N0 (No regional lymph node metastases)

N1 (Metastasis in a regional lymph node or nodes)

Is there seminal vesicle involvement? No Yes

If PSA at clinical diagnosis \geq 20 ng/ml, was a bone scan performed? No Yes

Date of bone scan:

--	--

 /

--	--

 /

--	--	--	--	--

Was the bone scan suggestive of metastatic disease? No Yes

Does the patient have symptoms of metastatic disease? No Yes

If Yes, date of test to evaluate for metastatic disease:

--	--	--

 /

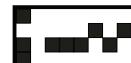
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 /

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Was metastatic disease confirmed? No Yes

continued on next page



**SOUTHWEST ONCOLOGY GROUP
S9921 LOCAL PROSTATE CARCINOMA PRESTUDY**

Page 2 of 3

SWOG Patient ID

SWOG Study No. S | 9 | 9 | 2 | 1

Registration Step 1

Patient Initials (L, F M)

DISEASE DESCRIPTION, *continued*

Gleason's Score:

Based on biopsy (including TURP)

Primary: (1-5)

These are the two components that are combined to obtain the Gleason sum.

Secondary: (1-5)

Gleason sum: (2-10)

98 = unsatisfactory

99 = no grade possible

Number of cores:

Number positive:

Based on surgical specimen

Primary: (1-5)

These are the two components that are combined to obtain the Gleason sum.

Secondary: (1-5)

Gleason sum: (2-10)

98 = unsatisfactory

99 = no grade possible

Histologic Grade:

- Grade cannot be assessed, GX
- Well differentiated (slight anaplasia), G1
- Moderately differentiated (moderate anaplasia), G2
- Poorly differentiated, G3
- Undifferentiated (marked anaplasia), G4

continued on next page

3/15/2006

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SOUTHWEST ONCOLOGY GROUP
S9921 LOCAL PROSTATE CARCINOMA PRESTUDY

Page 3 of 3

SWOG Patient ID

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SWOG Study No. S 9 9 2 1

Registration Step 1

Patient Initials _____ (L, F M)

PRIOR TREATMENT RELATED TO THIS CANCER

Did the patient have a radical prostatectomy (MUST be Yes for patient to be eligible)? No Yes

Date of radical prostatectomy:

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 /

--	--

 /

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 Were margins positive? No Yes

Did the patient receive hormonal therapy prior to radical prostatectomy? No Yes

Description: _____

Did the patient receive hormonal therapy after radical prostatectomy but prior to S9921 registration?

No Yes, description: _____

Did the prior hormonal therapy include an LHRH analog?

No Yes, description: _____

Date of first treatment with LHRH analog:

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 /

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 /

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Date of most recent LHRH analog injection:

--	--

 /

--	--

 /

--	--	--	--

Specified dose duration of most recent LHRH analog injection: _____

1 month 3 month 4 month Other, specify _____

Was LHRH analog treatment continuous from first administration to S9921 registration?

Yes No, explain _____

Did the patient receive any prior radiation therapy in the treatment of this cancer (MUST be No for patient to be eligible)? No Yes

LABORATORY VALUES

PSA value prior to radical prostatectomy:

--	--	--	--	--	--

.

--

 ng/ml

Date of PSA prior to radical prostatectomy:

--	--

 /

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 /

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PSA value after radical prostatectomy (prior to the start of post-surgical hormone therapy if already started OR within 28 days prior to registration if post-surgical hormone therapy not already started):

--	--	--	--	--

.

--

 ng/ml

Date of PSA after radical prostatectomy:

--	--

 /

--	--

 /

--	--	--	--

Testosterone:

--	--	--	--

 ng/dl (within 28 days prior to registration) Testosterone ILLN:

--	--	--	--

 ng/dl

Date of testosterone:

--	--

 /

--	--

 /

--	--	--	--

If patient had prior hormonal therapy, testosterone value prior to therapy:

--	--	--	--

 ng/dl

Date of testosterone:

--	--

 /

--	--

 /

--	--	--	--

Comments:

3/15/2006



**SOUTHWEST ONCOLOGY GROUP
S9921 PSA REPORTING FORM**

Page 1 of 1

SWOG Patient ID

SWOG Study No. S 9 2 1

Registration Step 1

Patient Initials _____ (L, F M)

Institution / Affiliate _____

Physician _____

Participating Group: Group Name/Study No./Patient ID _____ / _____ / _____

Instructions: Include all measurements of PSA taken since the last reported form. See the Study Calendar (Section 9.0) for collection schedules of PSA. Note PSA measurements taken prior to S9921 registration on the S9921 Prestudy form. All dates are MONTH, DAY, YEAR. Explain any blank fields or dates in the **Comments** section. Please mark **AMENDED** data in red and write **AMENDED** at the top of the form.

PSA

Date of assessment(s)

1. / /

PSA value(s) (ng/ml)

.

2. / /

.

3. / /

.

4. / /

.

5. / /

.

6. / /

.

Comments:



SOUTHWEST ONCOLOGY GROUP
S9921 TESTOSTERONE REPORTING FORM

Page 1 of 1

SWOG Patient ID

SWOG Study No. S 9 9 2 1

Registration Step 1

Patient Initials _____ (L, F M)

Institution / Affiliate _____

Physician _____

Participating Group: Group Name/Study No./Patient ID _____ / _____ / _____

Instructions: Include all measurements of Testosterone taken since the last reported form. See the Study Calendar (Section 9.0) for collection schedules of Testosterone. Note Testosterone measurements taken prior to S9921 registration on the S9921 Prestudy form. All dates are MONTH, DAY, YEAR. Explain any blank fields or dates in the **Comments** section. Please mark **AMENDED** data in red and write **AMENDED** at the top of the form.

Testosterone

Date of assessment(s)

1. / /

Testosterone value(s) (ng/dl)

2. / /

3. / /

Comments:



**SOUTHWEST ONCOLOGY GROUP
S9921 TREATMENT FORM**

Page 1 of 1

SWOG Patient ID

SWOG Study No.

Registration Step 1

Patient Initials (L, F M)

Institution/Affiliate

Physician

Participating Group: Group Name/Study No./Patient ID _____ / _____ / _____

Instructions: This form is for both Arm 1 and Arm 2. Please complete this form and submit after every 3 months of protocol hormonal therapy. Note hormonal therapy given prior to S9921 registration on the S9921 Prestudy form. Note the S9921 Chemotherapy Treatment Form must also be submitted for Arm 2 patients while on chemotherapy. All dates are **MONTH, DAY, YEAR**. Explain any blank dates or fields in the **Comments** section. Place an in appropriate boxes. Circle **AMENDED** items in red and write **AMENDED** across top of form.

STATUS Vital Status: Alive Dead Date of Last Contact or Death: / /
(submit Notice of Death)

Has the patient progressed per the definition in Section 10.0 of the protocol? No Yes
(submit Follow-Up Form)

TREATMENT

Reporting interval start date: / /

Reporting interval stop date: / /

Were there any dose modifications or additions/ omissions to protocol treatment?

No Yes, planned (per protocol guidelines)
(specify in comments) Yes, unplanned (not per protocol guidelines)
(specify in comments)

LHRH Analogue (Zoladex): (Report injections received in this reporting period. Patient may have received 1-3 injections depending on dose used.)

1. Injection Date: / / Dose: . mg

2. Injection Rate: / / Dose: mg

2. Injection Date: [] / [] / [] Dose: [] . [] mg
[] [] [] []

Anti-Androgen (Casodex):

Has the patient been receiving daily anti-androgen during the specified interval?

Yes No, explain:

Radiotherapy:

Has patient received any radiotherapy to date while on study? Yes No

If RT initiated in this reporting interval, start date: / /

If RT completed in this reporting interval, date of completion: / /

Total dose received in this reporting period: cGy

Comments:



**SOUTHWEST ONCOLOGY GROUP
S9921 CHEMOTHERAPY TREATMENT FORM**

Page 1 of 1

SWOG Patient ID

SWOG Study No.

Registration Step 1

Patient Initials (L, F M)

Date Form Completed: / /

Institution/Affiliate

Physician

Participating Group: Group Name/Study No /Patient ID / /

Instructions: This form is for Arm 2 patients during the chemotherapy phase of protocol treatment. Please complete this form and submit following the 3rd and 6th cycles of chemotherapy (1 cycle = 21 days). Note that the S9921 Treatment Form must also be completed every 3 months while on protocol hormonal therapy. All dates are **MONTH, DAY, YEAR**. Explain any blank dates or fields in the **Comments** section. Place an **X** in appropriate boxes. Circle **AMENDED** items in red and write **AMENDED** across top of form.

STATUS Vital Status: Alive Dead Date of Last Contact or Death: / /
(submit Notice of Death)

Has the patient progressed per the definition in Section 10.0 of the protocol? No Yes
(submit Follow-Up Form)

CHEMOTHERAPY (Report cycles 1-3 or 4-6)

Were there any dose modifications or additions/ omissions to protocol treatment?

No Yes, planned (per protocol guidelines)
(specify in comments) Yes, unplanned (not per protocol guidelines)
(specify in comments)

Cycle Number:

Did the patient receive mitoxantrone this cycle? Yes No

If Yes, Date of injection: / / Total dose: mg BSA: . m²

Did the patient receive prednisone this cycle? Yes No

Cycle Number:

Did the patient receive mitoxantrone this cycle? Yes No

If Yes, Date of injection: / / Total dose: mg BSA: . m²

Did the patient receive prednisone this cycle? Yes No

Cycle Number:

Did the patient receive mitoxantrone this cycle? Yes No

If Yes, Date of injection: / / mg BSA: . m²

Did the patient receive prednisone this cycle? Yes No

Comments:

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3/15/2006



(TX9921C)

SOUTHWEST ONCOLOGY GROUP
S9921 ADVERSE EVENT SUMMARY FORM

Page 1 of 1

SWOG Patient ID

SWOG Study No. S 9 9 2 1

Registration Step 1

Patient Initials _____ (L, F M)

Institution/Affiliate _____ Physician _____

Participating Group: Group Name/Study No./Patient ID _____ / _____ / _____

Instructions: **Arm 1** - Please complete this form and submit after every 3 months of protocol hormonal therapy.

Arm 2 - Please complete and submit this form after the 3rd and 6th cycles of chemotherapy (1 cycle = 21 days) summarizing all cycles in the reporting period. Continue to complete and submit this form every 3 months while on protocol hormonal therapy.

Report all adverse events observed. Document the worst Grade seen during the reporting period. Do not code a condition existing prior to registration as an adverse event unless it worsens. Category lists may not include all adverse events from that category.

Record any observed adverse events not listed on the blank lines at the end. All dates are MONTH, DAY, YEAR. Explain any blank dates or fields in the **Comments** section. Place an in appropriate boxes. Circle **AMENDED** items in red and write **AMENDED** across top of form.

TOXICITY Were toxicities assessed during this time period?

No Yes Date of most recent toxicity assessment: / /

Mark box if toxicities were assessed but none were seen. Otherwise indicate grades below.

CTC 2.0 Code	Toxicity	Grade (1 - 5)	Treatment Relation*	CTC 2.0 Code	Toxicity	Grade (1 - 5)	Treatment Relation*
CA50	Hypertension	<input type="checkbox"/>	<input type="checkbox"/>	MS31	Arthritis	<input type="checkbox"/>	<input type="checkbox"/>
CA51	Hypotension	<input type="checkbox"/>	<input type="checkbox"/>	NR12	Anxiety/agitation	<input type="checkbox"/>	<input type="checkbox"/>
EN20	Gynecomastia	<input type="checkbox"/>	<input type="checkbox"/>	NR13	Depression	<input type="checkbox"/>	<input type="checkbox"/>
EN30	Hot flashes	<input type="checkbox"/>	<input type="checkbox"/>	NR60	Sensory neuropathy	<input type="checkbox"/>	<input type="checkbox"/>
FL30	Sweating	<input type="checkbox"/>	<input type="checkbox"/>	NR92	Insomnia	<input type="checkbox"/>	<input type="checkbox"/>
FL40	Fatigue/malaise/lethargy	<input type="checkbox"/>	<input type="checkbox"/>	PA00	Headache	<input type="checkbox"/>	<input type="checkbox"/>
GI00	Nausea	<input type="checkbox"/>	<input type="checkbox"/>	PA30	Abdominal pain/cramping	<input type="checkbox"/>	<input type="checkbox"/>
GI10	Vomiting	<input type="checkbox"/>	<input type="checkbox"/>	PA40	Chest pain, not cardio or pleur	<input type="checkbox"/>	<input type="checkbox"/>
GI20	Diarrhea without colostomy	<input type="checkbox"/>	<input type="checkbox"/>	PA99	Pain - other	<input type="checkbox"/>	<input type="checkbox"/>
GI30	Constipation/bowel obstruction	<input type="checkbox"/>	<input type="checkbox"/>	SK11	Rash/desquamation	<input type="checkbox"/>	<input type="checkbox"/>
GI60	Stomatitis/pharyngitis	<input type="checkbox"/>	<input type="checkbox"/>	SK90	Alopecia	<input type="checkbox"/>	<input type="checkbox"/>
GU00	Incontinence	<input type="checkbox"/>	<input type="checkbox"/>	SX00	Libido loss	<input type="checkbox"/>	<input type="checkbox"/>
GU03	Urinary frequency/urgency	<input type="checkbox"/>	<input type="checkbox"/>	SX60	Erectile impotence	<input type="checkbox"/>	<input type="checkbox"/>
HE00	Leukopenia	<input type="checkbox"/>	<input type="checkbox"/>	Other Toxicities (specify):			
HE30	Neutropenia/granulocytopenia	<input type="checkbox"/>	<input type="checkbox"/>	<hr/> <hr/> <hr/>			
ME31	Hyperglycemia	<input type="checkbox"/>	<input type="checkbox"/>	<hr/> <hr/> <hr/>			
MS00	Muscle weakness (not neuro)	<input type="checkbox"/>	<input type="checkbox"/>	<hr/> <hr/> <hr/>			

* Treatment Relation codes: 1-unrelated

2-unlikely

3-possible

4-probable

5-definite

Comments: (Please explain any "other" adverse events reported above, e.g., PA99 Pain-other)

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SOUTHWEST ONCOLOGY GROUP

FOLLOW UP FORM

Page 1 of 1

SWOG Patient ID

SWOG Study No. S

Registration Step

Patient Initials _____ (L, F M)

Institution / Affiliate _____ Physician _____

Participating Group: Group Name/Study No./Patient ID _____ / _____ / _____

Instructions: Please submit at each follow up after completion of treatment until relapse or progression, at time of relapse or progression, and at protocol-specified intervals after relapse or progression. Also submit at time of diagnosis of second primary. All dates are MONTH, DAY, YEAR. Answer all questions and explain any blank fields or blank dates in the **Comments** section. Place an **X** in appropriate boxes. Circle AMENDED items in red.

VITAL STATUS

Vital Status: Alive Dead Date of last contact or death: / /

If vital status is Dead, complete and submit Notice of Death form.

DISEASE FOLLOW UP STATUS

Has the patient had a documented clinical assessment for this cancer (since submission of the previous follow-up form)?

No Yes If Yes, Date of Last Clinical Assessment: / /

NOTICE OF FIRST RELAPSE OR PROGRESSION

Has the patient developed a first relapse or progression that has not been previously reported?

No Yes If Yes, Date of Relapse or Progression: / /

Site(s) of Relapse or Progression: _____

NOTICE OF NEW PRIMARY

Has a new primary cancer or MDS (myelodysplastic syndrome) been diagnosed that has not been previously reported?

No Yes If Yes, Date of Diagnosis: / /

New Primary Site: _____

NON-PROTOCOL TREATMENT

Has the patient received any non-protocol cancer therapy (prior to progression/relapse) not previously reported?

No Yes If Yes, Date of First Non-Protocol Therapy: / /

Agent Name(s): _____

LONG TERM ADVERSE EVENT

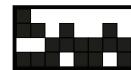
Has the patient experienced (prior to treatment for progression or relapse or a second primary, and prior to non-protocol treatment) any severe (grade ≥ 3) long term toxicity that has not been previously reported?

No Yes If Yes, Adverse Events and Grades: _____

Comments:

64587

9/15/2003



SOUTHWEST ONCOLOGY GROUP
OFF TREATMENT NOTICE

Page 1 of 1

SWOG Patient ID

--	--	--	--	--	--

SWOG Study No. S

--	--	--	--	--

Registration Step

--

Patient Initials _____ (L, F M)

Institution / Affiliate _____ Physician _____

Participating Group: Group Name/Study No./Patient ID _____ / _____ / _____

Instructions: For each registration step, submit this form within 2 weeks after completion (or discontinuation) of treatment.

Systemic Therapy: List regimens, start and end dates. For multidrug regimens, do not list individual drugs separately; end date would be the date all drugs in the regimen were discontinued.

Surgery: List type of surgery, and in the "end date" column, the date of surgery.

Radiation: List sites, start and end dates (inclusive of boosts and implants).

All dates are **MONTH, DAY, YEAR**. Explain any blank fields or blank dates in the **Comments** section.

Place an **X** in appropriate boxes. Circle **AMENDED** items in red.

Treatment Start Date

Treatment End Date

Regimen or Procedure or Site(s)

_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____

(If more room is needed, please continue on a separate page)

Off Treatment Reason (select one):

- Treatment completed per protocol criteria
- Medically required, due to toxicity, specify: _____
- Patient refused, due to toxicity, specify: _____
- Patient refused, other than toxicity, specify: _____
- Progression or relapse. Sites: _____
- Death (submit Notice of Death form)
- Other, specify: _____

Off Treatment Date

Date of completion, progression, death or decision to discontinue therapy:

--	--	--	--	--	--

 /

--	--	--	--	--	--

 /

--	--	--	--	--	--

Will patient receive further treatment?

- No Yes, specify: _____
- Unknown

Date of Last Contact (or death):

--	--	--	--	--	--

 /

--	--	--	--	--	--

 /

--	--	--	--	--	--

Vital Status: Alive Dead (submit Notice of Death form)

Comments:

8756

9/1/2003



SOUTHWEST ONCOLOGY GROUP
NOTICE OF DEATH

Page 1 of 1

SWOG Patient ID

Most Recent SWOG Study No. S

Patient Initials _____ (L, F M)

Institution / Affiliate _____ Physician _____

Participating Group: Group Name/Study No./Patient ID _____ / _____ / _____

Instructions: Answer all questions and explain any blank fields or blank dates in the **Comments** section.

Place an **X** in appropriate boxes. Circle **AMENDED** items in red.

Date of Death: / / (month / day / year)

CAUSES OF DEATH

Any cancer (select one):

No Primary Cause Contributory Possible Unknown

If cancer was the primary cause or if cancer possibly or definitely contributed to death, and the patient had had multiple tumor types, specify those which were causes of death:

Cancer of most recent SWOG study, specify cancer: _____

Cancer of other SWOG study, specify cancer: _____

Other cancer, specify: _____

Toxicity from disease related treatment (select one):

No Primary Cause Contributory Possible Unknown

If Primary Cause, Contributory or Possible, specify treatment and toxicity:

Non-cancer and non-treatment related causes (select one):

No Primary Cause Contributory Possible Unknown

If Primary Cause, Contributory or Possible, specify:

Autopsy? No Yes Unknown

Source(s) of death information:

- Autopsy report
- Medical record / Death certificate
- Physician
- Relative or friend
- Other, specify: _____

Comments:

49467

9/1/2003



19.0 APPENDIX

- 19.1 This study will utilize the CTC (NCI Common Toxicity Criteria) version 2.X for toxicity and Adverse Event reporting. A copy of the CTC version 2.X can be downloaded from the CTEP home page (<http://ctep.info.nih.gov>). **All appropriate treatment areas should have access to a copy of the CTC version 2.X.**
- 19.2 Expanded Participation Project (EPP) Instructions
- 19.3 Returned Medication Packing Slip
- 19.4 **S9921 Novantrone® Drug Request Form**
- 19.5 Determination of Expedited Adverse Event Reporting Requirements
- 19.6 CTSU Regulatory and Monitoring Guidelines

CLOSED EFFECTIVE 01/12/2007

19.2 Expanded Participation Project (EPP) Instructions.

**ADJUVANT ANDROGEN DEPRIVATION VERSUS MITOXANTRONE PLUS PREDNISONE
PLUS ANDROGEN DEPRIVATION IN SELECTED HIGH RISK PROSTATE CANCER PATIENTS
FOLLOWING RADICAL PROSTATECTOMY**

PHASE III

1.0 EPP Randomization and Registration Procedures

- I. EPP institutions will enroll a patient on-line through the Clinical Trials Management Unit (CTMU). Questions pertaining to eligibility criteria should be directed to the CTMU, medical questions should be directed to the Study Chair.
- II. A signed HHS 310 form documenting the Institutional Review Board (IRB) approval for this study must be on file at the CTMU before the EPP institution can enter a patient. IRB approval date must be less than one year prior to the date of registration.
- III. Once eligibility is confirmed, the CTMU will contact SWOG to randomize the patient. The CTMU will notify the institution by an email upon successful registration with SWOG. In addition SWOG will forward confirmation of randomization and treatment assignment to the CTMU for routing to the participating institutions. Please check for errors, and submit any corrections in writing to the CTMU. Treatment should start within one working day after registration.

2.0 EPP Data Submission

Data must be submitted electronically directly to the CTMU according to the following schedule:

FORM	TIME OF SUBMISSION
1. SWOG Registration Form	At enrollment
2. Prostate Cancer Prestudy Form** (Pathology Report*)	Within 14 days of enrollment
3. EPP Toxicity Form	Months 1, 2, 3, and every three months while on protocol therapy
4. EPP Follow-up Form**	Every 3 months while on protocol treatment and every 6 months after completion of protocol treatment until death
5. EPP Recurrence Form	At the time of recurrence

FORM	TIME OF SUBMISSION
6. EPP Chemotherapy/Immunotherapy/Hormonal Therapy Form	At the completion of protocol therapy
7. EPP Off-Treatment Form**	At the completion of all protocol therapy
8. EPP Notice of Secondary Malignancy Form	Within 10 days of diagnosis
9. EPP Death Form	Within 7 days of knowledge of event

* Fax a copy of the Pathology Report to the CTMU Attn: EPP Protocol Monitor 301-299-3991

** These forms are to be submitted according to the above schedule for all patients who never started treatment.

3.0 EPP Adverse Drug Reaction

For EPP Institutions, all ADR's are to be faxed to the CTMU (Attn: EPP Protocol Monitor 301-299-3991) using the Adverse Reaction (ADR) Form for Investigational Drugs. These reports will be reviewed and directed to the Southwest Oncology Group and appropriate regulatory offices. ADR reporting is based on the revised NCI Common Toxicity Criteria (version 2.X).

+

ADRs will be faxed to the CTMU based on the following adverse event reporting requirements table:

AGENTS	GRADE				
	1	2	3	4	5
Commercial Agents Expected AE	-----	-----	-----	-----	-----
Commercial Agents Unexpected AE	-----	-----	-----	ADR	ADR

ADR = Adverse Drug Reaction Report (within 7 days)

ADR reports should be submitted via fax within 7 days of the event. These will be forwarded to the NCI and the Coordinating Group within 3 working days. All ADRs should be reported to the local IRB.

For commercially available drugs, written reporting of any increased incidence of a known ADR is also required in addition to grade 4 and 5 toxicities.

All toxicities, including those with separate reporting requirements described above, must be reported on the Toxicity Form. Deaths are required to be reported via the Death Form within 7 days of knowledge of the event.

4.0 EPP Secondary Malignancy Reporting

Investigators are required to report secondary malignancies occurring on or following treatment on NCI-sponsored protocols using commercial drugs. Reporting of cases of secondary AML/MDS is to be performed using the NCI/CTEP Secondary AML/MDS Report Form. This form should be used in place of DCT Adverse Reaction (ADR) Form for reporting this toxicity. All other secondary malignancies should be reported using the form DCT Adverse Reaction Form. The EPP Notice of Secondary Malignancy must also be completed for all cases of secondary malignancy.



RETURNED MEDICATION PACKING SLIP

Institution: _____

Address: _____

Principal Investigator: _____ Phone No.: _____

Phone No.: _____

Study No: _____ **Cooperative Group No.:** _____

Cooperative Group No.: _____

Study Title: _____

Instructions:

Per FDA requirements, please retain a copy of this completed form for your files. Drug being returned for any reason should be sent, together with this original form, to UVI, Inc., c/o Livingston Healthcare Services, Inc., 11698 San Marino Drive, Rancho Cucamonga, CA 91730. Questions may be directed to (800) 370-2508, Monday through Friday 8:00 am - 5:00 pm, Pacific Standard Time. Voice Mail is available at all other times.

Study open to patient accrual at your site?

Person Shipping Drug:

Yes No

Drug being returned by:

Are there any patients at your site still receiving treatment?

Fed Ex UPS US Mail

Yes No

Date: _____ No. of cartons: _____

Reason drug returned? (Please check one)

Data Manager's/Pharmacist's Signature:

Drug Expired

Date: _____

Unused drug being returned

Fax number:

DESCRIPTION OF RETURN SHIPMENT

Comments:

TO BE COMPLETED AT WAREHOUSE

Returned shipment received on _____ and checked by _____
(Date) (Name)

Appended 4/15/00
Revised 5/15/00
Amended 7/1/00
Revised 7/15/01

Revised 11/1/02
Revised 5/15/03
Revised 9/1/03

S9921
Page 62
Amended 2/14/06

S9921 APPENDIX 19.4

Novantrone Drug Request Form

Requested By:

Dr. _____ Dr.'s State License #* _____

Institution _____ Current IRB Approval Date _____

Principal Investigator _____

Institution Contact _____

Telephone _____ Fax _____

*Note: Actual copy of license is required from physicians from Delaware, the District of Columbia, South Dakota, Mississippi and Puerto Rico. For other states, please indicate # only.

**Novantrone will be shipped Monday through Wednesday.
A minimum of two days notice is required.**

Date Drug Needed By:

Ship to:

Name _____

Address* _____

*Please do not use PO Box numbers

Novantrone (25mg)

SWOG Patient Sequence Number(s) REQUIRED FOR ALL DRUG SHIPMENTS	# of Vials Required	Signature
		Date

**Fax completed, signed and dated form to: Priority Healthcare Corporation
866-203-4684**

Questions? Please call Charlie Drayton at 407/804-6743
or Greg Friedman at 407/833-4500 (Priority Healthcare)



19.5 Determination of Expedited Adverse Event Reporting Requirements

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. (Directions for routine reporting are provided in Section 14.0.) Additionally, certain adverse events must be reported in an expedited manner to allow for more timely monitoring of patient safety and care. Expedited adverse event reporting principles and general guidelines follow; specific guidelines for expedited adverse event reporting on this protocol are found in Section 16.0.

Reporting requirements may include the following considerations: 1) whether the patient has received an investigational or commercial agent; 2) the characteristics of the adverse event including the *grade* (severity), the *relationship to the study therapy* (attribution), and the *prior experience* (expectedness) of the adverse event; 3) the Phase (I, II, or III) of the trial; and 4) whether or not hospitalization or prolongation of hospitalization was associated with the event.

An investigational agent is a protocol drug administered under an Investigational New Drug Submission (IND). In some instances, the investigational agent may be available commercially, but is actually being tested for indications not included in the approved package label.

Commercial agents are those agents not provided under an IND but obtained instead from a commercial source. The NCI, rather than a commercial distributor, may on some occasions distribute commercial agents for a trial.

When a study includes both investigational and commercial agents, the following rules apply.

- *Concurrent administration:* When an investigational agent(s) is used in combination with a commercial agent(s), the combination is considered to be investigational and expedited reporting of adverse events would follow the guidelines for investigational agents.
- *Sequential administration:* When a study includes an investigational agent(s) and a commercial agent(s) on the same study arm, but the commercial agent(s) is given for a period of time prior to starting the investigational agent(s), expedited reporting of adverse events that occur prior to starting the investigational agent(s) would follow the guidelines for commercial agents. Once therapy with the investigational agent(s) is initiated, all expedited reporting of adverse events should follow the investigational guidelines.

Steps to determine if an adverse event is to be reported in an expedited manner

Step 1: Identify the type of event using the NCI Common Terminology Criteria for Adverse Events (CTCAE). The CTCAE provides descriptive terminology and a grading scale for each adverse event listed. A copy of the CTCAE can be downloaded from the CTEP home page (<http://ctep.cancer.gov>). Additionally, if assistance is needed, the NCI has an Index to the CTCAE that provides help for classifying and locating terms. All appropriate treatment locations should have access to a copy of the CTCAE.

Step 2: Grade the event using the NCI CTCAE version specified.

Step 3: Determine whether the adverse event is related to the protocol therapy (investigational or commercial). Attribution categories are as follows: Unrelated, Unlikely, Possible, Probable, and Definite.

Step 4: Determine the prior experience of the adverse event. Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered *unexpected*, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in

- the current NCI Agent-Specific Adverse Event List (for treatments using agents provided under an NCI-held IND);
- the drug package insert (for treatments with commercial agents only);
- Section 3.0 of this protocol.

Step 5: Review Table 16.1 in the protocol to determine if there are any protocol-specific requirements for expedited reporting of specific adverse events that require special monitoring.

Step 6: Determine if the protocol treatment given prior to the adverse event included an investigational agent(s), a commercial agent(s), or a combination of investigational and commercial agents.

NOTE: If the patient received at least one dose of investigational agent, follow the guidelines in Table 16.1. If no investigational agent was administered, follow the guidelines in Table 16.2.

NOTE: This includes all events that occur within 30 days of the last dose of protocol treatment. Any event that occurs more than 30 days after the last dose of treatment and is attributed possibly, probably, or definitely to the agent(s) must be reported according to the instructions above.

19.6 CTSU Regulatory and Monitoring Guidelines

Study Audit

To assure compliance with Federal regulatory requirements [CFR 21 parts 50, 54, 56, 312, 314 and HHS 45 CFR 46] and National Cancer Institute (NCI)/ Cancer Therapy Evaluation Program (CTEP) Clinical Trials Monitoring Branch (CTMB) guidelines for the conduct of clinical trials and study data validity, all protocols approved by NCI/CTEP that have patient enrollment through the CTSU are subject to audit.

Responsibility for assignment of the audit will be determined by the site's primary affiliation with a Cooperative Group or CTSU. For Group-aligned sites, the audit of a patient registered through CTSU will become the responsibility of the Group receiving credit for the enrollment. For CTSU Independent Clinical Research Sites (CICRS), the CTSU will coordinate the entire audit process.

For patients enrolled through the CTSU, you may request the accrual be credited to any Group for which you have an affiliation provided that Group has an active clinical trials program for the primary disease type being addressed by the protocol. (e.g., NSABP members may only request credit for protocols pertaining to breast or colorectal cancers). Registrations to protocols for other disease sites may still take place through CTSU without receiving credit for your NSABP activities. Per capita reimbursement will be issued directly from CTSU.

Details on audit evaluation components, site selection, patient case selection, materials to be reviewed, site preparation, on-site procedures for review and assessment, and results reporting and follow-up are available for download from the CTSU Operations Manual located on the CTSU Member Web site.

Health Insurance Portability and Accountability Act of 1996 (HIPAA)

The HIPAA Privacy Rule establishes the conditions under which protected health information may be used or disclosed by covered entities for research purposes. Research is defined in the Privacy Rule referenced in HHS 45 CFR 164.501. Templatized language addressing NCI-U.S. HIPAA guidelines are provided in the HIPAA Authorization Form located on the CTSU website.

The HIPAA Privacy Rule does not affect participants from outside the United States. Authorization to release Protected Health Information is NOT required from patients enrolled in clinical trials at non-US sites.

Clinical Data Update System (CDUS) Monitoring

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. The sponsoring Group fulfills this reporting obligation by electronically transmitting to CTEP the CDUS data collected from the study-specific case report forms.