Southwest
Oncology Group
A National Clinical Research Group

Faxed: September 27, 2000
Mailed: October 15, 2000

TO: ALL SOUTHWEST ONCOLOGY GROUP, CCOP, AND AFFILIATE MEDICAL ONCOLOGISTS AND PATHOLOGISTS, AND THE EASTERN COOPERATIVE ONCOLOGY GROUP

FROM: Calleleh "Cal" E. Bonugli, Protocol Coordinator

RE: **SWOG-9005 (ECOG-S9005)**, "Double Blind Randomized Trial of the Anti-Progestational Agent Mifepristone In The Treatment of Unresectable Meningioma, Phase III". Southwest Oncology Group Study Coordinators: Drs. S.M. Grunberg, J. Ahmadi and J. Townsend.

STATUS NOTICE

Study Coordinator: Steven M. Grunberg, M.D. Phone: 802/656-3827
E-mail: sgrunber@moose.uvm.edu

IRB Review Requirements

(√) Full board review required

( ) Expedited review allowed

( ) No review required

PERMANENT CLOSURE - CROSSOVER REGISTRATION

The Crossover Registration of the above-noted study is **permanently closed, effective October 15, 2000**, as there is no evidence of benefit from the study drug.

Please attach this notice to the front of your copy of the protocol.

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

cc: PROTOCOL AND INFORMATION OFFICE
Cathryn Rankin, M.S.
Laura Kingsbury
Lauren Crowley
Jean MacDonald - ECOG

Southwest
Oncology Group
A National Clinical Research Group

Mailed: July 1, 1998
Faxed: June 19, 1998

TO: ALL SOUTHWEST ONCOLOGY GROUP, CCOP, AND CGOP MEDICAL ONCOLOGISTS AND PATHOLOGISTS, M.D. ANDERSON CANCER CENTER, AND THE EASTERN COOPERATIVE ONCOLOGY GROUP

FROM: Patricia O'Kane, Protocol Coordinator

RE: **SWOG-9005 (ECOG-S9005)**, "Double Blind Randomized Trial of the Anti-Progestational Agent Mifepristone In The Treatment of Unresectable Meningioma, Phase III". Southwest Oncology Group Study Coordinators: Drs. S.M. Grunberg, J. Ahmadi and J. Townsend.

PERMANENT CLOSURE

The above-noted study will be **permanently closed to new patient registration, effective July 1, 1998** as a sufficient number of patients have been accrued to answer study objectives.

Please attach this notice to the front of your copy of the protocol.

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

cc: PROTOCOL AND INFORMATION OFFICE
Cathryn Rankin, M.S.
Dona Marrah
Jean MacDonald - ECOG Operations Office

Southwest
Oncology Group
A National Clinical Research Group

January 15, 1997

TO: ALL SOUTHWEST ONCOLOGY GROUP, CCOP, AND CGOP MEDICAL ONCOLOGISTS AND PATHOLOGISTS, M.D. ANDERSON CANCER CENTER, AND THE EASTERN COOPERATIVE ONCOLOGY GROUP

FROM: Patricia O'Kane, Protocol Coordinator

RE: **SWOG-9005 (ECOG-S9005)**, "Double Blind Randomized Trial of the Anti-Progestational Agent Mifepristone In The Treatment of Unresectable Meningioma, Phase III". Southwest Oncology Group Study Coordinators: Drs. S.M. Grunberg, J. Ahmadi and J. Townsend.

REVISION #8

The following revisions have been made in the above-noted study:

1. Dr. Grunberg's phone number has been updated on the Title page and in Section 8.5, and his fax number has been updated on page 20. Dr. Ahmadi's phone number and address have been corrected on the Title page and Dr. Russell's phone number has been revised in Section 8.5.

2. The Title page has been revised to reflect that Cathryn Rankin, M.S. is the biostatistician for this study. The Statistical Center's address has also been updated.

3. The M.D. Anderson Cancer Center (MDACC) is no longer a participant in this study. Therefore, Sections 12.1b, 12.2b, 13.2, 14.4 and, in Section 16.0, the second and third sentences of the paragraph entitled "Adverse Experiences", have been deleted. Dr. Levin's name and address have been removed from the Title page and the MDACC has been removed from the list of participants.

4. Section 12.2 has been revised to indicate that all CT or MRI scans and formal field examinations be submitted **directly to Jamshid Ahmadi** rather than to the Statistical Center.

A revised Title page and revised pages 11 and 16 - 20 are included for replacement into your copy of the protocol.

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

cc: PROTOCOL AND INFORMATION OFFICE
Cathryn Rankin, M.S.
Dona Marrah
Victor Levin, M.D. - M.D. Anderson
Jean MacDonald - ECOG Operations Office

Southwest
Oncology Group
A National Clinical Research Group

June 15, 1996

TO: ALL SOUTHWEST ONCOLOGY GROUP, CCOP, AND CGOP MEDICAL ONCOLOGISTS AND PATHOLOGISTS, M.D. ANDERSON CANCER CENTER, AND THE EASTERN COOPERATIVE ONCOLOGY GROUP

FROM: Patricia O'Kane, Protocol Coordinator

RE: **SWOG-9005 (ECOG-S9005)**, "Double Blind Randomized Trial of the Anti-Progestational Agent Mifepristone In The Treatment of Unresectable Meningioma, Phase III. Southwest Oncology Group Study Coordinators: Drs. S.M. Grunberg, J. Ahmadi and J. Townsend.

REVISION #7

The Study Calendar for the above-noted study has been revised to indicate that after the second year of treatment, follow-up CT/MRI scans and Formal Visual Field exams are only required annually, rather than twice a year.

Additionally, the area code for the Pharmaceutical Management Branch has been corrected in Section 7.1a.1.

Revised pages 8 and 12 are included for replacement into your copy of the protocol.

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

cc: PROTOCOL AND INFORMATION OFFICE
Dorothy Rector, M.S.
Joseph M. Unger, M.S.
Dona Marrah
Victor Levin, M.D. - M.D. Anderson
Jean MacDonald - ECOG Operations Office

Southwest
Oncology Group
A National Clinical Research Group

March 15, 1996
Effective: March 1, 1996

TO: ALL SOUTHWEST ONCOLOGY GROUP, CCOP, AND CGOP MEDICAL ONCOLOGISTS AND PATHOLOGISTS, M.D. ANDERSON CANCER CENTER, AND THE EASTERN COOPERATIVE ONCOLOGY GROUP

FROM: Patricia O'Kane, Protocol Coordinator

RE: **SWOG-9005 (ECOG-S9005)**, "Double Blind Randomized Trial of the Anti-Progestational Agent Mifepristone In The Treatment of Unresectable Meningioma, Phase III. Southwest Oncology Group Study Coordinators: Drs. S.M. Grunberg, J. Ahmadi and J. Townsend.

REVISION #6

Effective March 1, 1996, the Pharmaceutical Management Branch (PMB) will discontinue its Electronic Clinical Drug Request system, and will accept drug orders only by FAX or mail. To ensure efficiency and accuracy of drug ordering, the Statistical Center will no longer perform initial drug orders for patients registered on study **SWOG-9005**. Instead, the institution registering the patient will be responsible for placing the initial drug order. These orders must be placed using PMB's Clinical Drug Request Form (NIH Form 986).

If further clarification is needed, please contact the PMB directly by phone at 310/496-5725 or fax 301/402-4870.

Since **SWOG-9005** is a double-blind study, the blinded drug for each patient is identified by a coded treatment preparation identification number. This number is provided by the Statistical Center to the caller during the telephone registration (see Section 13.4 of the protocol); it should be written down at that time so that it can be entered on the Clinical Drug Request Form.

Page 4 of the Eligibility Checklist for Step 1 and page 3 of the Checklist for Crossover Registration and, Section 7.1a have been revised, and Section 13.4 has been added to reflect the change in drug ordering procedures.

Revised pages 8, 18 and the Eligibility Checklists are included for replacement into your copy of the protocol.

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

cc: PROTOCOL AND INFORMATION OFFICE
Dorothy Rector, M.S.
Joseph M. Unger, M.S.
Angela Ribble, B.A.
Victor Levin, M.D. - M.D. Anderson
Jean MacDonald - ECOG Operations Office

Southwest
Oncology Group
A National Clinical Research Group

February 1, 1996

TO: ALL SOUTHWEST ONCOLOGY GROUP, CCOP, AND CGOP MEDICAL ONCOLOGISTS AND PATHOLOGISTS, M.D. ANDERSON CANCER CENTER, AND THE EASTERN COOPERATIVE ONCOLOGY GROUP

FROM: Patricia O'Kane, Protocol Coordinator

RE: **SWOG-9005 (ECOG-S9005)**, "Double Blind Randomized Trial of the Anti-Progestational Agent Mifepristone In The Treatment of Unresectable Meningioma, Phase III. Southwest Oncology Group Study Coordinators: Drs. S.M. Grunberg, J. Ahmadi and J. Townsend.

REVISION #5

Sections 12.1, 14.3d, and 14.4 of the above-noted study have been revised to indicate that Southwest Oncology Group institutions and the M.D. Anderson Cancer Research Office must submit pathology materials **directly to the pathology reviewers,** rather than the Southwest Oncology Group Pathology Office.

Pathology slides are to be sent to Dr. Peter C. Burger as described in Section 12.1a. Tissue blocks, however, are to be submitted to Dr. Andy E. Sherrod, as described in Section 12.1a.

Please note that materials must be identified with a hot pink "SWOG Pathology Materials" label affixed to the outside of each package. If this label is missing, the materials will not be able to be reviewed, rendering the patient ineligible. An initial supply of labels, will be sent to your institution for your use. To obtain additional labels, please call 206/ 667-4623 and ask for the Data Operations Technical Manager.

ECOG institutions will continue to submit pathology materials to the ECOG Pathology Coordinating Office. Do not send materials directly to the reviewers.

The Pathology Submission Form currently in the protocol should be discarded and replaced with the new protocol specific Pathology Submission Forms which include the protocol number. (Please note that there is a form for slide submission and a separate form for tissue submission.) The protocol specific Pathology Submission form referenced in Sections 12.1d.3, 12.1e.2, and 18.2c, will be used by all Groups. Section 12.1f has been deleted.

The Title page has been updated to include Dorothy Rector, M.S. as the primary Statistician.

Section 16.0 (page 20), has been updated to include guidelines for reporting cases of secondary AML or MDS.

A revised Title page and pages 16, 16a, 19, 20, 22 and the protocol specific Pathology Submission Forms are included for replacement into your copy of the protocol.

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

cc: PROTOCOL AND INFORMATION OFFICE
Dorothy Rector, M.S.
Joseph M. Unger, M.S.
Angela Ribble, B.A.
Victor Levin, M.D. - M.D. Anderson
Jean MacDonald - ECOG Operations Office

May 1, 1995

TO: ALL SOUTHWEST ONCOLOGY GROUP, CCOP, AND CGOP MEDICAL ONCOLOGISTS AND PATHOLOGISTS, M.D. ANDERSON CANCER CENTER, AND THE EASTERN COOPERATIVE ONCOLOGY GROUP

FROM: Patricia Gutierrez, Protocol Coordinator

RE: **SWOG-9005 (ECOG-S9005)**, "Double Blind Randomized Trial of the Anti-Progestational Agent Mifepristone In The Treatment of Unresectable Meningioma, Phase III. Southwest Oncology Group Study Coordinators: Drs. S.M. Grunberg, J. Ahmadi and J. Townsend.

REVISION #4

Section 12.1c of the above-noted study has been revised to reflect the new address of the ECOG Pathology Coordinating Office.

Revised page 16 is included for replacement into your copy of the protocol.

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

cc: PROTOCOL AND INFORMATION OFFICE
Dorothy Rector, M.S.
Laura Loll, M.S.
Angela Ribble, B.A.
Victor Levin, M.D. - M.D. Anderson
Jean MacDonald - ECOG Operations Office

January 15, 1995

TO: ALL SOUTHWEST ONCOLOGY GROUP, CCOP, AND CGOP MEDICAL ONCOLOGISTS AND PATHOLOGISTS, M.D. ANDERSON CANCER CENTER, AND THE EASTERN COOPERATIVE ONCOLOGY GROUP

FROM: Patricia Gutierrez, Protocol Coordinator

RE: **SWOG-9005 (ECOG-S9005)**, "Double Blind Randomized Trial of the Anti-Progestational Agent Mifepristone In The Treatment of Unresectable Meningioma, Phase III. Southwest Oncology Group Study Coordinators: Drs. S.M. Grunberg, J. Ahmadi and J. Townsend.

REVISION #3

Section 5.19b of the above-noted study has been revised as:

"b. Patients must satisfy the criteria in Sections 5.1, 5.3 and 5.5 - 5.18 at the time of re-registration. The CT or MRI scan for the crossover registration must be obtained within 60 days prior to registration."

Also, the address for the Southwest Oncology Group Statistical Center which was inadvertently deleted in Amendment #5, has been added in Section 12.2a.

Revised pages 7 and 16a and the revised Eligibility Checklist for the Crossover Registration are included for replacement into your copy of the protocol.

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

cc: PROTOCOL AND INFORMATION OFFICE
Dorothy Rector, M.S.
Angela Ribble, B.A.
Victor Levin, M.D. - M.D. Anderson
Patt Anderson - ECOG Operations Office

October 1, 1994

TO: ALL SOUTHWEST ONCOLOGY GROUP, CCOP, AND CGOP MEDICAL ONCOLOGISTS AND PATHOLOGISTS, M.D. ANDERSON CANCER CENTER, AND THE EASTERN COOPERATIVE ONCOLOGY GROUP

FROM: Patricia Gutierrez, Protocol Coordinator

RE: **SWOG-9005 (ECOG-S9005)**, "Double Blind Randomized Trial of the Anti-Progestational Agent Mifepristone In The Treatment of Unresectable Meningioma, Phase III. Southwest Oncology Group Study Coordinators: Drs. S.M. Grunberg, J. Ahmadi and J. Townsend.

AMENDMENT #5

Section 5.2 of the above-noted study has been revised as follows:

"Patients must have active meningioma, which is defined to be one of the following:

a. Progressive disease within the past 2 years.

For patients with measurable disease, progressive disease is defined as an increase of over 25% in the cross sectional area of the meningioma on CT/MRI scan (using the same scan technique to document this increase) during this two year period.

For patients with evaluable disease, progressive disease is defined as disease that is not measurable, such that there has been a significant increase in the tumor mass, as judged by two independent observers, within the past two years.

b. Recurrent Disease, as defined by the reappearance of a previously completely resected meningioma, within the past two years.

c. New disease, defined as a diagnosis of meningioma within the previous two years .

(5.2a, b or c must be documented on the initial Flow Sheet)."

The Eligibility Checklist for the first registration has been revised. Spaces have been provided to record tumor measurements when there is measurable, progressive disease.

Section 5.7 has been revised to reflect that the time frame for performing lab tests has been extended to 28 days prior to registration rather than 14 days.

Section 5.19a has been revised as:

"Patients who progress on placebo will be eligible to begin open-label mifepristone **provided** that all of the following criteria are met:

a. Patients must have been eligible for the initial registration;

b. Patients must satisfy the criteria in Sections 5.1, 5.3, and 5.5 - 5.18 at the time of re-registration;

c. There must be documentation of disease progression (per Section 10.1d.5); and

d. If placebo was discontinued prior to progression, discontinuation must have been due to unacceptable toxicity (e.g., per Sections 8.3 - 8.4 or Section 16.0)."

e. Patients treated with surgery following progression on placebo are eligible provided there is evidence of residual disease.

f. Patients treated with RT following progression on placebo are eligible. However, if the interim RT covered the entire tumor field, this treatment must have been completed more than one year prior to re-registration with documented progressive disease since completion of RT.

A sentence has been added to the 5th paragraph under Section II of the Model Informed Consent Form informing patients that lab tests must be repeated prior to mifepristone therapy if crossing over due to progression on placebo.

The Eligibility Checklist for the Cross-over Registration has been revised.

"...following appearance of symptoms" has been deleted from Section 6.1c to be consistent with Section 5.2.

"...(and the blind is not broken)." has been added to the end of the sentence in Section 7.1c.

Sections 10.3 and 10.7 have been updated to be consistent with the Southwest Oncology Group standard definitions of Best Response and Treatment Failure.

Section 12.0 has been revised to clarify that both slides and tissue blocks (if available) must be sent to the Group's Pathology Office. Slides will be reviewed to verify histologic diagnosis. Tissue analysis is to confirm or determine hormone receptor status.

Financial support is available to help defray the cost of specimen shipment. Each investigator requesting reimbursement must submit the **SWOG-9005** Sample Submission Reimbursement Form, which is included with this amendment, to the Southwest Oncology Group Operations Office. This form must be filled out entirely and signed by the investigator. This form is not a part of the Master Forms Set, and should not be submitted to the Statistical Center. Each investigator will be reimbursed a flat fee of $10.00 for shipment of tissue blocks. Section 12.1g has been added to provide instruction for reimbursement from the Operations Office.

Dori Rector, M.S. has been added to the title page as the secondary statistician for this study.

A revised title page and revised pages 6, 7, 7a, 8, 9, 14 - 16, 16a, 23 and the revised Eligibility Checklists are included for replacement into your copy of the protocol. Pages 7a and 16a have been added to prevent extensive repagination.

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

cc: PROTOCOL AND INFORMATION OFFICE
Christine Upchurch, M.S.
Dorothy Rector, M.S.
Angela Ribble, B.A.
Victor Levin, M.D. - M.D. Anderson
Patt Anderson - ECOG Operations Office

SWOG-9005 SAMPLE SUBMISSION
REIMBURSEMENT FORM (MANDATORY SHIPMENTS ONLY)

(reimbursement will be made for the shipment of paraffin blocks)

TODAY'S DATE: _____

PATIENT NUMBER: _____

PATIENT NAME: _____

DATE SAMPLES SENT TO THE SOUTHWEST ONCOLOGY GROUP (SWOG INSTITUTIONS) OR EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG INSTITUTIONS) PATHOLGY OFFICE _____

INVESTIGATOR'S NAME (print): _____

AND MAILING ADDRESS _____

_____

_____

FUNDS PAYABLE TO: _____

TAX ID # : _____

INVESTIGATOR'S SIGNATURE: _____

My signature confirms that the shipment referenced above has been sent to my cooperative group's pathology office.

Please mail/fax to:

Marjorie A. Godfrey
Southwest Oncology Group
Operations Office
14980 Omicron Drive
San Antonio, Texas 78245-3217
Phone: 210/677-8808
FAX: 210/677-0006

FOR INTERNAL USE ONLY:

Date: _____
Acct. #: 2-401-075-133-4-001
Amount: $10.00
Initials: _____

August 1, 1994

TO: ALL SOUTHWEST ONCOLOGY GROUP, CCOP, AND CGOP MEDICAL ONCOLOGISTS AND PATHOLOGISTS, M.D. ANDERSON CANCER CENTER, AND THE EASTERN COOPERATIVE ONCOLOGY GROUP

FROM: Patricia Gutierrez, Protocol Coordinator

RE: **SWOG-9005 (ECOG-S9005)**, "Double Blind Randomized Trial of the Anti-Progestational Agent Mifepristone In The Treatment of Unresectable Meningioma, Phase III. Southwest Oncology Group Study Coordinators: Drs. S.M. Grunberg, J. Ahmadi and J. Townsend.

AMENDMENT #4

The fourth paragraph of Section 3.1d and the second paragraph of Section III of the Model Informed Consent Form of the above-noted study have been revised to reflect the observation of adenomatous hyperplasia of the endometrium in patients receiving long term mifepristone therapy.

Revised pages 5 and 24 are included for replacement into your copy of the protocol.

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

cc: PROTOCOL AND INFORMATION OFFICE
Christine Upchurch, M.S.
Dorothy Rector, M.S.
Angela Ribble, B.A.
Victor Levin, M.D. - M.D. Anderson
Patt Anderson - ECOG Operations Office

January 1, 1994

TO: ALL SOUTHWEST ONCOLOGY GROUP, CCOP, AND CGOP MEDICAL ONCOLOGISTS AND PATHOLOGISTS, M.D. ANDERSON CANCER CENTER, AND THE EASTERN COOPERATIVE ONCOLOGY GROUP

FROM: Patricia Gutierrez, Protocol Coordinator

RE: **SWOG-9005**, "Double Blind Randomized Trial of the Anti-Progestational Agent Mifepristone In The Treatment of Unresectable Meningioma, Phase III. Southwest Oncology Group Study Coordinators: Drs. S.M. Grunberg, J. Ahmadi and J. Townsend.

AMENDMENT #3

The Eastern Cooperative Oncology Group has been added as a participant to this study. The following changes have been made:

1. The Eligibility Checklists have been revised to include the ECOG study number (ECOG-S9005).

2. The Title page has been revised to include the ECOG study number and Dr. Lynn Feun has been added as the Study Coordinator for the Eastern Cooperative Oncology Group.

3. Instructions for the submission of pathology materials have been added as Section 12.1c. Subsequent sections were renumbered.

4. Instructions for the routing of radiology materials have been added as Section 12.2c. Subsequent sections were renumbered.

5. Registration guidelines for ECOG institutions have been added as Section 13.3

6. Instructions for submission of forms by ECOG institutions have been added as Section 14.5.

7. Adverse Drug Reaction reporting guidelines for ECOG institutions have been added to Section 16.0.

Additionally, Sections 5.1 and 12.1e have been revised to reflect that the submission of tissue blocks for immunohistochemical staining is mandatory (if available). Tissue blocks must be sent to the Pathology Office within 30 days of registration.

Also, a definition of "menopausal status" has been added to Section 6.1.

Section 7.1a.1 has been revised to indicate that treatment should start within 2 working days of receipt of drug at the individual institution. This section is now consistent with Section 13.1.

A typographical error has been corrected in Section 10.1d.5. The reference for neurologic deterioration is Section 10.5 not 10.4.

The revised Eligibility Checklists for the Initial Registration and Crossover Registration, the Title page and pages 6, 8, 13, and 16 - 19a are included for replacement into your copy of the protocol.

A complete copy of the protocol has been sent to the Eastern Cooperative Oncology Group for distribution to their institutions.

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

cc: PROTOCOL AND INFORMATION OFFICE
Christine Upchurch, M.S.
Dorothy Rector, M.S.
Angela Ribble
John VanDamme, B.S.
Mischelle Stricker - ECOG

September 15,1993

TO: ALL SOUTHWEST ONCOLOGY GROUP, CCOP, AND CGOP MEDICAL ONCOLOGISTS AND PATHOLOGISTS, AND M.D. ANDERSON CANCER CENTER

FROM: Patricia Gutierrez, Protocol Coordinator

RE: **SWOG-9005**, "Double Blind Randomized Trial of the Anti-Progestational Agent Mifepristone In The Treatment of Unresectable Meningioma, Phase III. Southwest Oncology Group Study Coordinators: Drs. S.M. Grunberg, J. Ahmadi and J. Townsend.

REVISION #2

Dr. Grunberg has relocated to the Medical Center Hospital of Vermont. His address and phone number have been updated on the face page and Sections 8.4 and 16.0.

The revised face sheet and pages 11 and 20 are included for replacement into your copy of the protocol.

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

cc: PROTOCOL AND INFORMATION OFFICE
Christine Upchurch, M.S.
Dorothy Rector, M.S.
Angela Ribble
Susan Beatty

July 1,1993

TO: ALL SOUTHWEST ONCOLOGY GROUP, CCOP, AND CGOP MEDICAL ONCOLOGISTS AND PATHOLOGISTS, AND M.D. ANDERSON CANCER CENTER

FROM: Patricia Gutierrez, Protocol Coordinator

RE: **SWOG-9005**, "Double Blind Randomized Trial of the Anti-Progestational Agent Mifepristone In The Treatment of Unresectable Meningioma, Phase III. Southwest Oncology Group Study Coordinators: Drs. S.M. Grunberg, J. Ahmadi and J. Townsend.

AMENDMENT #2

The following changes have been made in the above-noted study:

1. The phrase "recurrent mass must have a diameter of at least 1 cm" has been deleted from Section 5.2a. Since this study allows both measurable and evaluable disease, specification of a minimum lesion size is not necessary.

2. Section 5.13 has been deleted as an eligibility requirement. Subsequent sections have been renumbered. The restriction on patients with a personal or family history of breast cancer was originally included due to early reports of marked elevation of serum estadiol after treatment with mifepristone and concern about the long term effects of unopposed estrogen. However, a recent publication (Grunberg SM, Weiss MH, Spitz IM, Zaretsky S, Kletzky O, Groshen S. Long-Term Treatment with the Oral Antiprogestational Agent Mifepristone. In: Salmon SE (ed). Adjuvant Therapy of Cancer VII. Philadelphia, JB Lippencott Co., (In Press), 1993) reports that the observed elevated estrogen appears to be a false positive lab result caused by cross-reaction of mifepristone in the assay. Therefore, there is no longer any reason for this restriction. Annual PAP and mammograms will continue to be requested.

3. Section 5.18 has been added to indicate that patients with other prior or concurrent malignancy within the preceding 5 years, except surgically treated squamous or basal cell skin cancer or cervical cancer *in situ*, are not eligible.

4. The definition of meningiomatosis has been added to Section 5.10.

5. Section 7.1d, footnote £ in the Study Calendar and paragraph 4 in Section II of the Model Informed Consent Form (page 23), have been added to include information regarding warning cards that will be distributed to patients registered to this study. As you know, mifepristone is being used as a progesterone receptor blocking agent in this study, however it also causes blockade of the glucocorticoid receptor resulting in higher levels of endogenous cortisol. In a worst case scenario, a patient involved in an accident and sustaining serious injuries theoretically might not be able to increase endogenous cortisol levels high enough to effectively act as stress level steroids past the glucocorticoid blockade, and this situation might not be obvious to medical personnel. We will therefore ask all patients to carry a wallet card stating that they might have adrenal insufficiency. It must be explained to the patients, however, that they do not really have adrenal insufficiency. In case of an emergency, finding

this card in a patients wallet would lead medical personnel to administer a large bolus of corticosteroids, causing no harm to the vast majority of patients and possibly being of significant benefit to others. Information contained on the patient warning card has been added to the Model Informed Consent Form. The cards will be distributed from the Southwest Oncology Group Statistical Center to the institution once the patient is registered. For those patients already registered prior to this amendment, during the next month these cards will be sent to the registering institution for distribution to the patients.

6. The Omega footnote on the Study Calendar has been revised to state that the prestudy PAP and mammogram should be performed within 1 year prior to registration.

7. Additionally, Section 15.0 has been revised to specify the temperature for freezing serum samples.

Revised pages 6 - 9, 12, 19 and 23 are included for replacement into your copy of the protocol.

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

cc: PROTOCOL AND INFORMATION OFFICE
Christine Upchurch, M.S.
Dorothy Rector, M.S.
Angela Ribble
Susan Beatty

December 1, 1992

TO: ALL SOUTHWEST ONCOLOGY GROUP, CCOP, AND CGOP MEDICAL ONCOLOGISTS AND PATHOLOGISTS, AND M.D. ANDERSON CANCER CENTER

FROM: Patricia Gutierrez, Protocol Coordinator

RE: **SWOG-9005**, "Double Blind Randomized Trial of the Anti-Progestational Agent Mifepristone In The Treatment of Unresectable Meningioma, Phase III. Southwest Oncology Group Study Coordinators: Drs. S.M. Grunberg, J. Ahmadi and J. Townsend.

AMENDMENT #1

M.D. Anderson Cancer Center (MDACC) has been added as a participant to the above noted study. The following sections of the protocol have been revised to reflect this change.

1. The Study Coordinator for M.D. Anderson Cancer Center, Victor A. Levin, M.D. has been added to the face sheet.

2. Section 13.0 has been revised to include registration instructions for MDACC.

3. Section 14.0 has been revised to include data submission schedule for MDACC.

4. Section 16.0 has been revised to include instructions for reporting of adverse drug reactions by MDACC.

The Study Calendar (page 12) and page 1 of the Flow Sheet have been revised to clarify that serum samples for cortisol and thyroid function test are NOT to be run during blinded treatment. They are to be collected, centrifuged, frozen and stored at the individual institutions until the randomization code is broken.

Additionally, Section 13.1 has been revised. Patients should start treatment within 2 working days of receipt of drug at the individual institutions.

The address and phone number of the Southwest Oncology Group Operations office has been updated on pages 19 and 20.

Revised pages for the face page and pages 12, 16-19a and page 1 of the Flow Sheet are included for replacement into your copy of the protocol. Page 19a was added to prevent extensive repagination of the protocol.

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

cc: PROTOCOL AND INFORMATION OFFICE
Christine Upchurch, M.S.
Danni Daniels, M.S.

October 1, 1992

TO: ALL SOUTHWEST ONCOLOGY GROUP, CCOP AND CGOP MEDICAL ONCOLOGISTS AND PATHOLOGISTS

FROM: Patricia Gutierrez, Protocol Coordinator

RE: **SWOG-9005,** "Double Blind Randomized Trial of the Anti-Progestational Agent Mifepristone In The Treatment of Unresectable Meningioma, Phase III".
Study Coordinators: Drs. S.M. Grunberg, J. Ahmadi and J. Townsend

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REVISION #1

The following sentence has been added to Section 12.1a:

"Slides from all cases are to be forwarded within 30 days to:"

The address for the Pathology Office remains unchanged but it is now listed under Section 12.1a.

The following sentence has been added as Section 12.1b:

"Submission of paraffin blocks from all cases is encouraged and should be submitted to the Pathology Office within 30 days."

Additionally, Dr. Grunberg's phone number has been corrected in Section 8.5.

Revised pages 11 and 16 are included for replacement into your copy of the protocol.

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

cc: PROTOCOL AND INFORMATION OFFICE
Christine Upchurch, M.S.
Danni Daniels, M.S.
Kathy Sears

August 15, 1992

TO: ALL SOUTHWEST ONCOLOGY GROUP, CCOP AND CGOP MEDICAL ONCOLOGISTS AND PATHOLOGISTS

FROM: Patricia Gutierrez, Protocol Coordinator

RE: **SWOG-9005,** "Double Blind Randomized Trial of the Anti-Progestational Agent Mifepristone In The Treatment of Unresectable Meningioma, Phase III".
Study Coordinators: Drs. S.M. Grunberg, J. Ahmadi and J. Townsend

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ACTIVATION

The above referenced study is now open to patient registration.

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

cc: PROTOCOL AND INFORMATION OFFICE
Christine Upchurch, M.S.
Danni Daniels, M.S.
Kathy Sears

Southwest Oncology Group

Operations Office
14980 Omicron Drive
San Antonio, TX 78245-3217
(210) 677-8808

August 15, 1992

SWOG Patient No.	
Treatment No.	
Other Group Patient No.	
Other Group Name	

SWOG Statistical Center
Fred Hutchinson Cancer Research Center
1124 Columbia Street MP557

Seattle, WA 98104-2092
Patient registration (206) 667-4623

Investigator No.		PATIENT NAME (last,first,middle)	
Investigator		Patient's sex and race	
Institution		Patient's birthdate	
Date of IRB approval		Patient's Soc. Sec. No.	
Date of informed consent		Patient's zip code	
Projected start date of treatment		Method of payment	

SWOG 9005 ECOG S9005 Double Blind Randomized Trial of the Anti-Progestational Agent Mifepristone in the Treatment of Unresectable Meningioma

Eligibility Checklist

Each of the questions in the following two sections must be answered appropriately for a patient to be considered eligible for registration. The checklist should be entirely filled out and should be referred to during the phone registration. A copy must be submitted with the prestudy form and initial flow sheet.

Criteria for Eligibility (All responses must be ***Yes***)

Yes ***No***

____ ____ 1. Does the patient have a histologically documented primary, recurrent, or residual meningioma which is unresectable?

____ ____ 2. Will slides be submitted for pathology review?

____ ____ 3. Will tissue blocks be submitted (if available) for immunohistochemical staining?

Note: If tissue blocks are not available, answer "N/A."

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Eligibility Checklist
SWOG 9005 ECOG S9005

SWOG Patient No.	
Other Group Patient No.	

____ ____ 4. Does the patient have active meningioma which is defined as one of the following:

_____ ***Progressive disease*** within the past two years:

For patients with **measurable** disease, progressive disease is defined as an increase of over 25% in the cross sectional area of the meningioma on CT or MRI scan (using the same scan technique to document this increase). Indicate the dates and bidimensional measurements of the two scans being compared:

Tumor meas. _____ x _____ = _____ cm Date _____

Tumor meas. _____ x _____ = _____ cm Date _____

For patients with **evaluable** (non-measurable) disease, progressive disease is defined as a significant increase in the tumor mass as judged by two independent observers.

_____ ***Recurrent disease*** as defined by the reappearance of a previously completely resected meningioma within the past two years.

_____ ***New disease*** as defined as a diagnosis of meningioma within the past two years.

____ ____ 5. If the patient has meningioma of the base of the brain, cavernous sinus or optic nerve or has visual symptoms, was a formal visual field examination done within 28 days prior to this registration?

Note: Answer "N/A" if the patient does not have meningioma of the base of the brain, cavernous sinus or optic nerve or visual symptoms.

Date of exam _____

____ ____ 6. Does the patient have measurable or evaluable disease which has been documented on CT or MRI scan obtained within 28 days prior to this registration?

Date Obtained _____

____ ____ 7. Has the patient received radiotherapy?

Note: Patients should have had radiotherapy unless radiotherapy was inappropriate due to tumor location(s) or radiotherapy was refused after discussion with the patient's physician. If radiotherapy was not given due to one of these reasons, answer "N/A."

____ ____ 8. If the patient received prior radiotherapy, has it been more than one year since the patient was treated with radiotherapy and is there documented progressive disease since completion?

Note: If the patient has not had prior radiotherapy, answer "N/A."

____ ____ 9. Is the patient 18 years of age or older?

____ ____ 10. Does the patient have a SWOG performance status of 0-2?

____ ____ 11. Does the patient have a serum creatinine, SGOT, and bilirubin ≤ 2 times the institutional upper limit of normal obtained within 28 days prior to registration?

Serum Creatinine _____ ULN _____

SGOT _____ ULN _____

Bilirubin _____ ULN _____

Date Obtained _____

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Eligibility Checklist

SWOG 9005 ECOG S9005

SWOG Patient No.	
Other Group Patient No.	

____ ____ 12. If the patient requires simultaneous administration of corticosteroids for cerebral edema, have they been receiving a stable dose for at least 4 weeks prior to the registration?

Note: Answer "N/A" if the patient does not require simultaneous administration of corticosteroids for cerebral edema.

____ ____ 13. If the patient has reproductive potential, has the patient agreed to use an effective local contraceptive method (such as condom, diaphragm, or IUD) or abstinence during and for 3 months after study therapy?

Note: Answer "N/A" if the patient does not have reproductive potential.

Criteria for Exclusion (All responses must be ***No***)

Yes ***No***

____ ____ 1. Has the patient received prior cytotoxic chemotherapy for meningioma?

____ ____ 2. Does the patient have meningiomatosis (diffuse meningeal infiltration resulting in only non-evaluable meningeal thickening)?

Note: Multiple measurable or evaluable meningioma tumor masses are allowed.

____ ____ 3. Does the patient have a malignant meningioma?

____ ____ 4. Has the patient had additive or ablative modulation of sex hormone or glucocorticoid pathways within the preceding 3 months (not including stable corticosteroid therapy for cerebral edema)?

____ ____ 5. Has the patient had prior mifepristone therapy for meningioma?

____ ____ 6. Does the patient have a serious intercurrent medical illness; that is, any illness that in the opinion of the investigator would prevent the patient from following the study regimen?

____ ____ 7. Does the patient have clinical adrenal insufficiency requiring exogenous corticosteroid replacement?

____ ____ 8. Does the patient have a known allergy to mifepristone?

____ ____ 9. Does the patient have another prior or concurrent malignancy within the preceding 5 years (except surgically treated squamous or basal cell skin cancer or cervical cancer in situ)?

____ ____ 10. If the patient is female, is she pregnant or lactating?

Note: If the patient is male, answer "N/A."

Stratification Factors (Response does not affect eligibility)

1. Menopausal Status

   _____ Male

   _____ Female/pre-menopausal

   _____ Female/post-menopausal

2. Prior radiotherapy

   _____ Yes

   _____ No

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Eligibility Checklist

SWOG 9005 ECOG S9005

SWOG Patient No.	
Other Group Patient No.	

3. Disease status

   _____ Documented progressive disease or recurrence

   _____ New diagnosis

Descriptive Factors

1. Progesterone receptor status

   _____ < 5 fmol/mg protein

   _____ ≥ 5 fmol/mg protein

   _____ Unknown

Additional Information (This information is required to register)

NCI Investigator number _____

Investigator name _____

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August 15, 1992

SWOG Patient No.	
Treatment No.	
Other Group Patient No.	
Other Group Name	

SWOG Statistical Center
Fred Hutchinson Cancer Research Center
1124 Columbia Street MP557
Seattle, WA 98104-2092
Patient registration (206) 667-4623

Investigator No.		PATIENT NAME (last,first,middle)	
Investigator		Patient's sex and race	
Institution		Patient's birthdate	
Date of IRB approval		Patient's Soc. Sec. No.	
Date of informed consent		Patient's zip code	
Projected start date of treatment		Method of payment	

SWOG 9005 ECOG S9005 Double Blind Randomized Trial of the Anti-Progestational Agent Mifepristone in the Treatment of Unresectable Meningioma.

Eligibility Checklist - Crossover

Each of the questions in the following two sections must be answered appropriately for a patient to be considered eligible for registration. The checklist should be entirely filled out and should be referred to during the phone registration. A copy must be submitted with the prestudy form and initial flow sheet.

Criteria for Eligibility (All responses must be ***Yes***)

Yes ***No***

____ ____ 1. Was the patient eligible for the initial registration to SWOG 9005?

____ ____ 2. Does the patient have a histologically documented primary, recurrent, or residual meningioma which is unresectable?

____ ____ 3. Does the patient have documentation of progression (per sect. 10.1d.5 of the protocol)?

Note: Patients treated with surgery following progression on placebo are eligible provided there is evidence of residual disease.

Note: Patients treated with radiation therapy following progression on placebo are eligible. However, if the interim radiation therapy covered the entire tumor field, this treatment must have been completed more than one year prior to re-registration with documented progressive disease since completion of radiation therapy.

____ ____ 4. Was the patient originally assigned to placebo?

Note: If the initial registration treatment assignment has not yet been unblinded, this will be determined during the crossover registration phone call to the Statistical Center.

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Eligibility Checklist - Crossover
SWOG 9005 ECOG S9005

SWOG Patient No.	
Other Group Patient No.	

____ ____ 5. If placebo was discontinued prior to progression, was the discontinuation due to unacceptable toxicity?

Note: If placebo was not discontinued prior to progression, answer "N/A."

____ ____ 6. Does the patient have measurable or evaluable disease which has been documented on CT or MRI scan obtained within 60 days prior to this registration?

Date Obtained _____

____ ____ 7. If the patient has meningioma of the base of the brain, cavernous sinus or optic nerve or has visual symptoms, was a formal visual field examination done within 28 days prior to this registration?

Note: Answer "N/A" if the patient does not have meningioma of the base of the brain, cavernous sinus or optic nerve or visual symptoms.

Date of exam _____

____ ____ 8. Does the patient have a SWOG performance status of 0-2?

____ ____ 9. Does the patient have a serum creatinine, SGOT, and bilirubin≤ 2 times the institutional upper limit of normal obtained within 28 days prior to this registration?

Serum Creatinine _____ ULN _____

SGOT _____ ULN _____

Bilirubin _____ ULN _____

Date Obtained _____

____ ____ 10. If the patient requires simultaneous administration of corticosteroids for cerebral edema, have they been receiving a stable dose for at least 4 weeks prior to this registration?

Note: Answer "N/A" if the patient does not require simultaneous administration of corticosteroids for cerebral edema.

____ ____ 11. If the patient has reproductive potential, has the patient agreed to use an effective local contraceptive method (such as condom, diaphragm, or IUD) or abstinence during and for three months after study therapy?

Criteria for Exclusion (All responses must be ***No***)

Yes ***No***

____ ____ 1. Has the patient received prior cytotoxic chemotherapy for meningioma?

____ ____ 2. Does the patient have meningiomatosis (diffuse meningeal infiltration resulting in only non-evaluable meningeal thickening)?

Note: Multiple measurable or evaluable meningioma tumor masses are allowed.

____ ____ 3. Does the patient have a malignant meningioma?

____ ____ 4. Has the patient had additive or ablative modulation of sex hormone or glucocorticoid pathways within the preceding 3 months (not including stable corticosteroid therapy for cerebral edema)?

____ ____ 5. Has the patient had prior mifepristone therapy for meningioma?

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Eligibility Checklist - Crossover
SWOG 9005 ECOG S9005

SWOG Patient No.	
Other Group Patient No.	

____ ____ 6. Does the patient have a serious intercurrent medical illness; that is, any illness that in the opinion of the investigator would prevent the patient from following the study regimen?

____ ____ 7. Does the patient have clinical adrenal insufficiency requiring exogenous corticosteroid replacement?

____ ____ 8. Does the patient have a known allergy to mifepristone?

____ ____ 9. Does the patient have another prior or concurrent malignancy within the preceding 5 years (except surgically treated squamous or basal cell skin cancer or cervical cancer in situ)?

____ ____ 10. If the patient is female, is she pregnant or lactating?

Note: If the patient is male, answer "N/A."

Additional Information (This information is required to register)

1. To order the patient's supply of drugs, the NCI investigator number is required. Please be prepared to supply this information at the time of registration.

   NCI Investigator number _____

   Investigator name _____

2. If you wish to use an express carrier to ship the drugs (at your expense), the following information is needed.

   Name of carrier _____

   Account number _____

SOUTHWEST ONCOLOGY GROUP

DOUBLE BLIND RANDOMIZED TRIAL OF THE ANTI-PROGESTATIONAL AGENT MIFEPRISTONE IN THE TREATMENT OF UNRESECTABLE MENINGIOMA, PHASE III

PARTICIPANTS: ALL SOUTHWEST ONCOLOGY GROUP, CCOP, AND AFFILIATE MEDICAL ONCOLOGISTS AND PATHOLOGISTS, M.D. ANDERSON CANCER CENTER, AND THE EASTERN COOPERATIVE ONCOLOGY GROUP

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Mifepristone (IND- 30091) (NSC-652104)

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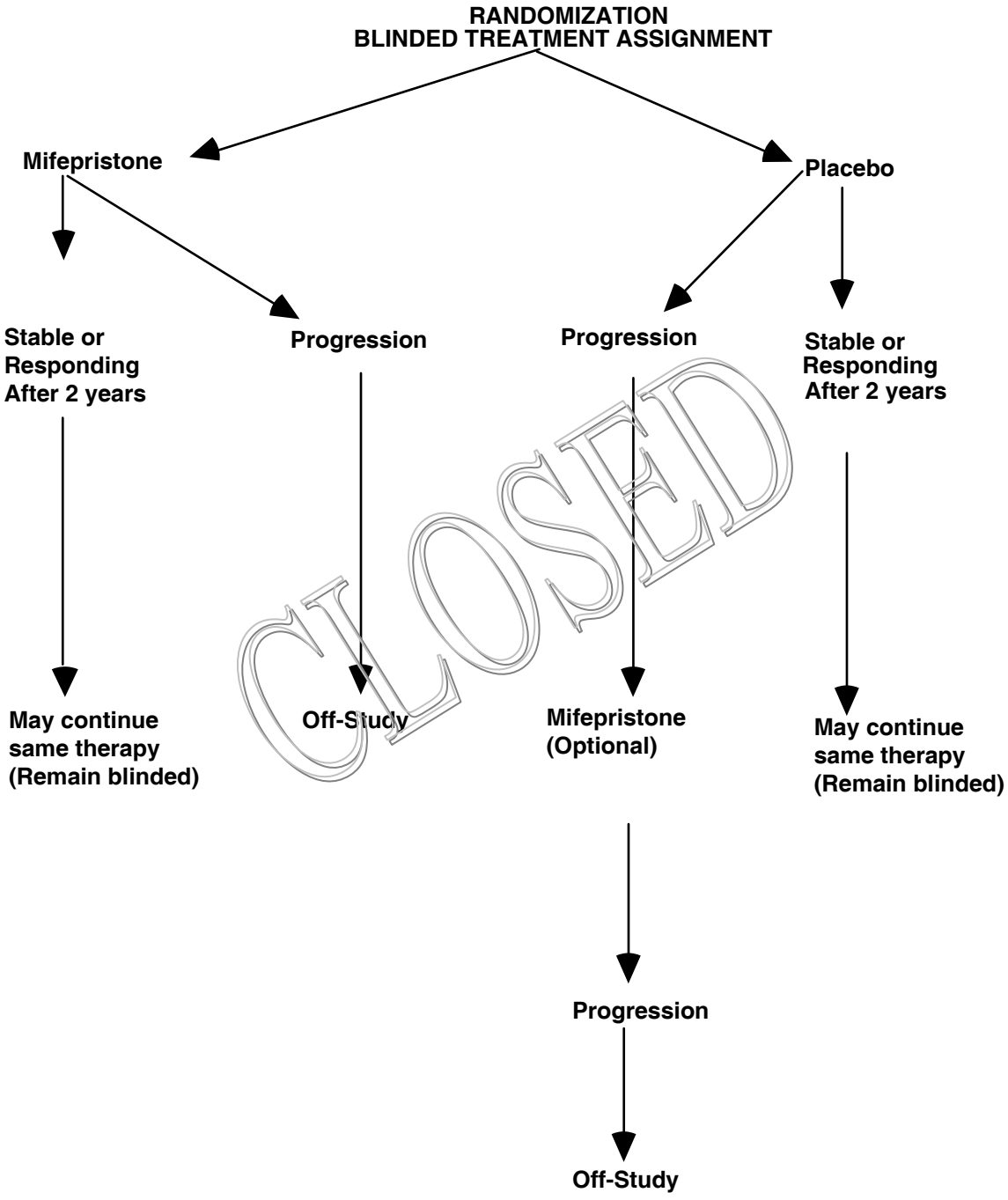
(Protocol Last changed 10/15/00)

SCHEMA



1.0 OBJECTIVES

1.1 To compare daily oral mifepristone vs placebo with respect to time to treatment failure in patients with unresectable meningioma.

1.2 To further evaluate the tolerance of long term oral mifepristone.

2.0 BACKGROUND

2.1 Meningioma is a relatively common intracranial neoplasm accounting for 15% to 18% of all CNS tumors. *(1)* The malignancy of these tumors has been questioned in view of the lack of tendency to metastasize. However in the closed space of the cranium even local symptoms may be devastating and the enlarging tumor may cause seizures, weakness, increased intracranial pressure, visual defects, or pain depending upon the location. Surgery remains the mainstay of therapy and multiple excisions are possible. However symptomatic recurrence is common, occurring in 16% of cases where microscopic total excision is performed and 39% of cases where limited resection is performed. (Average time to recurrence, 5 years). Location of the tumor may also make surgical excision technically hazardous or even impossible.

2.2 A number of factors suggest a hormonal relationship for meningiomas. These tumors occur twice as frequently in females as in males. *(2)* An association with breast cancer as well as the rapid appearance of meningiomas during pregnancy has also been noted. *(3,4)* Based on these observations several groups have assayed meningiomas for hormone receptors. Progesterone receptors, glucocorticoid receptors, estrogen receptors, and androgen receptors have been detected. However the progesterone receptor is both quantitatively and qualitatively the most common steroid hormone receptor in meningioma, having been detected in 70% of meningioma specimens, often in the absence of estrogen receptors. *(5)* Both in vitro and clinical studies have suggested that progestins can be modulators of meningioma growth. *(6-9)*

2.3 Mifepristone (RU 486) is a 19 norsteroid with anti-progesterone and anti glucocorticoid activity which competitively inhibits binding of the hormone to its receptor. *(10)* It also has weak anti-androgen activity. The anti-progestational activity is present at doses lower than the anti-glucocorticoid activity allowing specific use as an anti-progestational agent. Several in vitro studies have demonstrated that mifepristone can inhibit the growth of meningioma cell cultures. *(11, 12)* Treatment with mifepristone also led to complete inhibition of human meningioma xenografts in nude mice. *(13)*

2.4 As a result of these findings, a pilot study of the use of long term oral mifepristone in the treatment of unresectable meningioma has been performed at the University of Southern California Comprehensive Cancer Center. *(14,15)* Twenty-four patients (9 male/3 pre-menopausal female/12 post-menopausal female) have received daily oral doses of mifepristone (200 mg), for periods ranging from 2 to 36 months (12 months or more in 13 patients and 6 months or more in 20 patients). Six patients have shown suggestions of objective improvement (improved CT/MRI scan or improved visual field examination) accompanied in 4 patients by subjective improvement (improved extraocular muscle function or improved headache). Side effects of long term therapy have generally been mild and have included fatigue in 19 patients (severe in 2 patients), hot flashes in 9 patients, gynecomastia/breast tenderness in 5 patients, thinning of hair in 3 patients, and skin rash in 2 patients. Menses ceased in all 3 pre-menopausal patients (2 of these patients have discontinued mifepristone with return of normal menses). One patient who was exogenous steroid dependent at entry required an increase in baseline steroid dose during mifepristone treatment and one patient with adult onset diabetes required an increase in oral hypoglycemic treatment. These effects could be related to the anti-glucocorticoid properties of mifepristone. Elevation in thyroid stimulating hormone and decrease in thyroxine were noted but did not appear to be clinically significant.

2.5 Based on these encouraging preliminary results and the excellent tolerance of long term oral mifepristone, a randomized double-blind placebo controlled study will be performed to determine whether mifepristone can significantly prevent progression of unresectable meningioma.

3.0 DRUG INFORMATION

3.1 Mifepristone (RU 38486) (RU 486) Oral

a. Chemistry:

RU 486 is a 19-norsteroid chemically described as 17-beta-hydroxy-11-beta-(4-dimethylamino-phenyl)-17-alpha-(1-propynyl)-estra-4,9-dien-3-one.

b. Mechanism of action:

Mifepristone competitively binds to several steroid receptors, particularly progesterone and glucocorticoid receptors. It also has weak anti-androgenic activity.

c. Animal Toxicity:

In all animals studied, little or no toxicity was seen after a single dose of 1000 mg/kg. 1000 mg/kg in a oral micronised form was administered to mice which were then observed for 21 days. Changes included arched back, slowing of locomotion, and abdominal distension in males. Dogs treated with a similar regimen and observed for 14 days developed gastrointestinal symptoms with diarrhea and vomiting. In rats treated with 200 mg/kg daily for one month and 125 mg/kg daily for six months, there were the following changes noted: increased platelets and neutrophils, increased urea, lower glucose levels, decreased chloride and decreased alkaline phosphatase. Significant organ changes with respective hormonal effects were seen: atrophy of seminal vesicles and prostate, retardation of spermatogenesis, and thymic involution in males; decreased uterine endometrium, absence of ovarian corpora lutea, occasional ovarian cysts, and estrus condition of the vagina, in females. Other changes included, adrenal and anterior pituitary hyperplasia, stimulation of thyroid epithelium, changes in the kidneys including dilated tubules sometimes associated with glomerular sclerosis and interstitial fibrosis. In monkeys treated for six months at 45 mg/kg, there was weight loss with decrease in food consumption, vomiting, hypersalivation and amenorrhea. There was an increase in serum ACTH, cortisol and LH levels, a decrease in serum progesterone and cholesterol levels, and a decrease in urinary excretion of potassium and chloride. Pregnant rabbits treated with RU 486 developed total or partial interruption of pregnancy that was dose dependent. Some surviving fetuses showed anencephaly with malformation of the cranium including nonclosure of the cranium, hemorrhagic destruction of the upper part of the head and brain, missing spinal canal and non-closure of eyelids. Studies demonstrated non-mutagenicity of RU 486.

d. Human toxicity:

Twenty-four patients have been treated in a pilot study of long term treatment of unresectable meningioma with daily oral mifepristone at the University of Southern California Comprehensive Cancer Center. *(14,15)* Side effects have generally been mild and have included fatigue in 19 patients (severe in 2 patients), hot flashes in 9 patients, gynecomastia/breast tenderness in 5 patients, thinning of hair in 3 patients, and rash in 2 patients. One patient dependent upon

exogenous steroids required an increase in steroid dose and 1 patient with adult onset diabetes required an increase in oral hypoglycemic treatment, possibly due to anti-glucocorticoid effects of mifepristone. Cortisol levels increased from 13.12 ± 1.69 to 26.48 ± 3.84 µg/dl. TSH levels increased from 1.93 ± 0.60 to 4.37 ± 0.72 mIU/l and T_4 levels decreased from 5.77 ± 0.63 to 4.47 ± 0.69 µg/dl.

Seventy-five patients have been treated in 5 other studies of long term treatment with oral mifepristone for various indications (Cushing's syndrome, metastatic breast cancer, meningioma, endometriosis). Side effects noted in these studies include nausea in 19 patients, anorexia in 16 patients, asthenia in 12 patients, hot flashes in 10 patients, dizziness in 6 patients, somnolence in 4 patients, vomiting in 3 patients, transient elevation of liver function tests in 2 patients, and rash in 1 patient. *(16)*

Vaginal bleeding resembling menstruation may be seen shortly after mifepristone therapy is started. Cessation of menses is expected in pre-menopausal patients. However 2 pre-menopausal patients treated with long term oral mifepristone both had return of normal menses after discontinuation of mifepristone therapy.

For pre-menstrual women, continuous treatment with mifepristone initiated during the follicular phase of the menstrual cycle causes inhibition of ovulation with the persistence of moderate estrogen secretion uncompensated by progesterone secretion. Long term sequelae of unopposed estrogen can therefore not be ruled out. Approximately 50,000 women have received short term mifepristone and a prostaglandin analogue for pregnancy termination and approximately 90 patients have received long term mifepristone. Several cases of adenomatous hyperplasia of the endometrium in patients receiving long-term therapy have been reported. However, no case of endometrial or breast cancer has been reported. In a study performed in France with mifepristone followed by a prostaglandin analogue, 5 cases of phlebitis were seen among 10,000 pregnant women. One case of pulmonary embolism 2 months after pregnancy termination (during administration of an oral contraceptive) was reported from the United Kingdom. *(16)*

e. Pharmacology

RU 486 exerts its antiprogestational effect by binding to progesterone receptors with an affinity up to 5 times that of progesterone. It binds to glucocorticoid and androgen receptors but not to mineralocorticoid and estrogen receptors. There is potentiation of hexobarbital sleeping time, and anxiolytic effect in rats and mice.

f. Pharmacokinetics

Pharmacokinetics of RU 486 are not linear. After a single oral dose of 600 mg, metabolism occurs by successive demethylation and hydroxylation. The main route of elimination is biliary.

The T 1/2 of RU 486 is about 17 hours. The agent crosses the blood-brain barrier. It binds to alpha-1 acid glycoprotein in the plasma.

g. Pharmaceutical data:

Formulation: Mifepristone will be supplied as 200 mg tablets packaged in blister packs containing 35 tablets. Placebo will be formulated as tablets identical in appearance and packaged in the same manner as mifepristone.

Storage and stability: Mifepristone and placebo should be stored in a dry place at room temperature.

Supplier: Mifepristone and placebo tablets will be provided by Roussel-SANTE, and will be distributed by the NCI for this study, sponsored under Dr. Grunberg's IND (30091).

4.0 STAGING CRITERIA

Staging will not be done in this study.

5.0 ELIGIBILITY CRITERIA

5.1 Patients must have a histologically documented primary, recurrent or residual meningioma which is unresectable. Slides from all patients must be submitted for pathology review (see Section 12.1). Tissue blocks must be submitted (if available) for immunohistochemical staining (see Section 12.1e).

5.2 Patients must have active meningioma, which is defined to be one of the following:

a. Progressive disease within the past 2 years.

For patients with measurable disease, progressive disease is defined as an increase of over 25% in the cross sectional area of the meningioma on CT/MRI scan (using the same scan technique to document this increase) during this two year period.

For patients with evaluable disease, progressive disease is defined as disease that is not measurable, such that there has been a significant increase in the tumor mass, as judged by two independent observers, within the past two years.

b. Recurrent Disease, as defined by the reappearance of a previously completely resected meningioma, within the past two years.

c. New disease, defined as a diagnosis of meningioma within the previous two years

(5.2a, b or c must be documented on the initial Flow Sheet)."

5.3 Patients must have measurable or evaluable disease which is documented on CT or MRI scan. (See Sections 10.1.a. and 10.1.b.) These tests results must be obtained no more than 28 days prior to registration.

5.4 Patients should have already received radiotherapy unless radiotherapy is inappropriate due to tumor location(s) or unless radiotherapy, after discussion with the patient's physician, has been refused. If patients have received prior radiotherapy, this treatment must have been completed more than one year prior to study entry with documented progressive disease since completion of radiotherapy.

5.5 Patients must be 18 years or older, and must have a performance status 0-2 by Southwest Oncology Group criteria.

5.6 Patients must not have received prior cytotoxic chemotherapy for meningioma.

5.7 Patients must have serum creatinine, SGOT, and bilirubin ≤ 2 x IULN. These tests results must be obtained no more than 28 days prior to registration.

5.8 Patients requiring simultaneous administration of corticosteroids for cerebral edema must have been receiving a stable dose of corticosteroids for at least 4 weeks prior to study entry.

5.9 Patients receiving anti-epileptic medications are eligible. However barbiturates should be avoided if possible.

5.10 Patients with meningiomatosis (diffuse meningeal infiltration resulting in only nonevaluable meningeal thickening) are not eligible. However, patients with multiple measurable or evaluable meningioma tumor masses are eligible.

5.11 Patients with **malignant meningioma are not eligible**. Malignant meningioma is defined as meningioma that demonstrates hypercellularity, loss of architecture, nuclear pleomorphism, numerous mitoses, focal necrosis, and brain invasion. Slides must be submitted for pathology review (see Section 12.1)

5.12 Patients who have had additive or ablative modulation of sex hormone or glucocorticoid pathways within the preceding 3 months (not including stable corticosteroid therapy for cerebral edema) are not eligible. Such modulations include but are not limited to birth control pills, bilateral oophorectomy or orchiectomy, progestational inserts, oral or vaginal exogenous estrogens, androgens or antiandrogens, progestational agonists, tamoxifen, aminoglutethimide, o,p-DDD, ACTH, glucocorticoids not for cerebral edema, and leuprolides (or other LH-RH inhibitors). Patients must not have received prior mifepristone therapy for meningioma.

5.13 Patients must not have serious intercurrent medical illness; that is, any illness that in the opinion of the investigator would prevent following the study regimen.

5.14 Patients with clinical adrenal insufficiency requiring exogenous corticosteroid replacement are not eligible.

5.15 Patients with a known allergy to mifepristone are not eligible.

5.16 Patients with base of brain, cavernous sinus or optic nerve meningiomas or with visual symptoms must have a formal visual field examination to be completed within 28 days prior to registration.

5.17 Pregnant or lactating women may not participate. Pre-menopausal women and men of reproductive potential may not participate unless they have agreed to use an effective local contraceptive method (such as a condom, diaphragm, or IUD) or abstinence during and for 3 months after study therapy.

5.18 Patients with other prior or concurrent malignancy within the preceding 5 years, except surgically treated squamous or basal cell skin cancer or cervical cancer *in situ*, are not eligible.

5.19 Crossover Registration:

Patients who progress on placebo will be eligible to begin open-label mifepristone **provided** that all of the following criteria are met:

a. Patients must have been eligible for the initial registration;
b. Patients must satisfy the criteria in Sections 5.1, 5.3, and 5.5 - 5.18 at the time of re-registration. The CT or MRI scan for the crossover registration must be obtained within 60 days prior to registration.

c. There must be documentation of disease progression (per Section 10.1d.5); and

d. If placebo was discontinued prior to progression, discontinuation must have been due to unacceptable toxicity (eg., per Sections 8.3 - 8.4 or Section 16.0).

e. Patients treated with surgery following progression on placebo are eligible provided there is evidence of residual disease.

f. Patients treated with RT following progression on placebo are eligible. However, if the interim RT covered the entire tumor field, this treatment must have been completed more than one year prior to re-registration with documented progressive disease since completion of RT.

5.20 If day 28 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.

5.21 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.

5.22 At the time of patient registration, the date of institutional review board approval for this study must be provided to the Statistical Center.

6.0 STRATIFICATION/DESCRIPTIVE FACTORS

6.1 Stratification factors will include:

a. Male/pre-menopausal female/post-menopausal female. (Menopausal status is determined by the continuation or cessation of regular menstrual periods.)
b. Prior radiotherapy/no prior radiotherapy.
c. Documented progressive or recurrent disease/new diagnosis.

6.2 An additional descriptive factor will be:

a. Progesterone receptor status (< vs ≥ 5 f mol/mg protein vs unknown).

(If possible, assays for hormone receptors should be performed on fresh meningioma tissue or fresh meningioma tissue should be snap-frozen. However, hormone receptor data or samples are not required for study entry.)

7.0 TREATMENT PLAN

7.1 Pretreatment evaluations/measurements are to be completed as listed on the Study Calendar, Section 9.0. Eligible patients are randomized, with assignment blinded, to either mifepristone or placebo:

a. DRUG ORDERS AND SHIPMENT

1. Drug Orders will be placed by the individual institutions by completing a Clinical Drug Request Form, NIH Form 986. This form can be faxed to the Pharmaceutical Management Branch (PMB) at 301/480-4612 or mailed to the following address:

Pharmaceutical Management Branch
Drug Management and Authorization Section
Division of Cancer Treatment, NCI
Executive Plaza North, Room 707
9000 Rockville Pike
Bethesda, MD 20892-7422

If further clarification is needed, please contact the PMB directly by phone at 301/496-5725 or fax 301/402-4870.

The Clinical Drug Request Form must include the patient's TREATMENT PREPARATION IDENTIFICATION NUMBER which is provided to the institution by the Statistical Center at the time of registration. (See Section 13.4.) The form should contain orders for **SWOG-9005** only. The Pharmaceutical Management Branch (PMB) will ship a 3 month supply (3 packs) of drug or placebo directly to the Investigator's shipping address of record. All sites must maintain supplies of drug in a secure locked cabinet. Treatment should start within 2 working days of receipt of drug at the individual institution. All orders for crossover from placebo to "open label" active mifepristone (see Section 7.2.b.2) will also be placed by the individual institution using the Clinical Drug Request Form.

The institution should initiate replacement orders about 10 days before the previous supply will finish, to allow ample time for the drug to be sent. Reorders submitted by mail must be signed by the investigator or the investigator's designee of record, or the order will be returned.

If a commercial courier is used, please send order to the following address:

Drug Management and Authorization Section
Division of Cancer Treatment, NCI
Executive Plaza North, Room 707
6130 Executive Blvd.
Bethesda, MD 20852

3. DMAS will ship all orders by Federal Express (second day delivery) directly to the Investigator or the Investigator's designee. All shipments will contain a "Confirmation of Receipt" form which must be dated, signed and returned to the NCI Clinical Repository by FAX at (301) 762-1772. If a FAX is not available the form may be sent by express mail to:

NCI Clinical Repository
c/o ERC International
Attn: Mr. Robert Miller
627 Lofstrand Lane
Rockville, MD 20850

b. Initial Treatment Schedule

AGENT	DOSE	ROUTE	TX DURATION
Mifepristone	200 mg per day	P.O.	for 2 years
		OR	
Placebo	1 tablet daily	P.O.	for 2 years

c. If study medication (mifepristone or placebo) is stopped for any reason during the initial 2 year study period, therapy may be reinstituted if the discontinuance does not exceed 2 consecutive weeks or a total of 5 weeks (and the blind is not broken).

d. Once patients have been registered to the study, the Southwest Oncology Group Statistical Center will send the institution a patient warning card. It is the responsibility of the treating physician to make sure that the patient receives this card within a month of registration and that the patient is informed of the reasons for carrying this card. The warning card will alert medical personnel that the patient is being treated on a study that may include an investigational drug which partially blocks the glucocorticoid receptor, resulting in high serum cortisol levels. In case of an emergency, the card will advise physicians to treat the patient as if he/she has adrenal insufficiency as a concurrent problem.

7.2 Continuation of Therapy

a. Patients who are stable or responding to study therapy after 2 years have the option to continue with the same therapy. In these cases the randomization code will not be broken and therapy will continue to be blinded.

b. The randomization code will be broken if there is disease progression.

1. Patients who progress on mifepristone will be taken off study.
2. Patients who progress on placebo have the option to begin open-label mifepristone, 200 mg, P.O., daily on the crossover registration.
3. All inquiries relating to breaking the randomization code will be directed to the Southwest Oncology Group Statistical Center.

c. Follow-up of patients on extended therapy:

1. Patients who continue their original therapy past 2 years will continue to follow the schedule of clinic visits and studies established for the second year of protocol therapy.

2. Patients who begin mifepristone due to progression on placebo will have monthly clinic visits for 3 months and then follow the schedule of clinic visits and studies established for the second year of protocol therapy.

3. If therapy is stopped for any reason, therapy may be reinstituted if the discontinuance does not exceed 2 consecutive weeks or a total of 5 weeks in any one year.

7.3 **Criteria For Removal From Protocol Treatment on Initial Registration:**

a. Progression of disease.
b. Unacceptable Toxicity.
c. Administration of Conflicting Therapy

1. Administration of other antitumor treatment, including but not limited to surgery, radiotherapy or chemotherapy.

2. Administration or performance of other hormone modulating medications or procedures including but not limited to LHRH analogues, somatostatin analogues, bromocriptine, estrogens, progestins, androgens, antiestrogens, oophorectomy, adrenalectomy, or hypophysectomy.

However, patients receiving corticosteroids or thyroid hormone supplementation at study initiation may have the corticosteroid or thyroid dose modified as clinically indicated. Corticosteroids should not be decreased or stopped at time of study initiation and may need to be transiently increased due to the antiglucocorticoid properties of mifepristone if severe asthenia (weakness) develops. Any change in corticosteroid or thyroid dose must be indicated on the flow sheet. In addition corticosteroids or thyroid supplementation may be initiated during the study as indicated in Section 8.3 and 8.4.

d. Interruption of therapy exceeding the limits set in Sections 7.1c or 7.2.c.3.

e. When the final analysis is completed (see Section 11.2) the randomization code will be broken for all patients still on study. If mifepristone is found to significantly improve time to treatment failure or 2 year freedom from progression, then patients on mifepristone may continue mifepristone, and patients on placebo will have therapy stopped. If no significant advantage for mifepristone has been demonstrated, all patients will stop therapy.
f. The patient may withdraw from the study at any time for any reason.

g. The randomization code has been broken because of toxicity (e.g. see Sections 8.3 and 8.4).

7.4 **Criteria For Removal From Protocol Treatment For Patients Who Have Crossed Over To Mifepristone Therapy (Second Registration):** criteria are the same as those set forth in sections 7.3a-f. Additionally, patients will be removed from protocol treatment for adrenal insufficiency and severe hypothyroidism as discussed in Sections 8.3 and 8.4.

7.5 All reasons for discontinuation of treatment must be documented in the Flow Sheets.

7.6 The patient will return drug packets for tablet counts at each clinic visit. The number of tablets returned must be documented on the flow sheets, and unused tablets will be returned to the DMAS for accountability documentation. Remaining tablets and packets can be stored at the institution's research pharmacy and returned in batches to the NCI when convenient. (Drug returns should be sent to the address listed in Section 7.1.a.3). As with all investigational agents, accurate accountability records must be maintained on site and available for audit.

7.7 All patients will be followed until death.

8.0 TOXICITIES TO BE MONITORED AND DOSAGE MODIFICATIONS

8.1 There will be no dosage modifications in this protocol.

8.2 Clinical Tolerance

a. At every clinic visit, all patients, regardless of sex or menopausal status will be specifically questioned concerning:

1. Fatigue
2. Hot flashes
3. Gynecomastia
4. Hair loss
5. Cessation/change in menses (female patients only). If any uterine bleeding occurs, the date, amount and duration should be noted.
6. Phlebitis
7. Rash
8. Dizziness
9. Nausea
10. Somnolence

b. In addition, patients will be evaluated for any other potential toxicity not listed above.

8.3 If severe adrenal insufficiency is suspected (severe asthenia/SWOG Grade 3-4 weakness), the Study Coordinator should be notified. A blood sample for cortisol (preferably AM cortisol) will be immediately collected and assayed. Treatment with hydrocortisone, 25 mg, P.O., three times a day will be initiated without breaking the randomization code. If symptoms do not rapidly improve and if no other cause for asthenia can be found, the treatment code may be broken. In this case, protocol treatment will be discontinued.

8.4 If severe hypothyroidism is suspected, the Study Coordinator should be notified. A blood sample for thyroid function tests will be immediately collected and assayed. Treatment with synthroid, 0.1 mg, P.O. daily, will be initiated without breaking the randomization code. If symptoms do not improve, the treatment code may be broken. In this case, protocol treatment will be discontinued.

8.5 For treatment related questions, please contact Dr. Steven Grunberg at 802/656-3827 or Dr. Christy Russell at 213/764-3903.

8.6 Unexpected, severe 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. The Operations Office will also notify Roussel-SANTE.

9.0 STUDY CALENDAR

REQUIRED STUDIES	PRE	Mo. 1	Mo. 2	Mo. 3	Mo. 4	Mo. 5	Mo. 6	Mo. 7	Mo. 8	Mo. 9	Mo. 10	Mo. 11	Mo. 12	Mo. 13	Mo. 14	Mo. 15	Mo. 16	Mo. 17	Mo. 18	Mo. 19	Mo. 20	Mo. 21	Mo. 22	Mo. 23	Mo. 24	Mo. 25	Follow Up Δ
PHYSICAL	STUDY																										
History	X																										
Physical Examination √	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X			X			X			X	X	X
Neurologic Examination	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X			X			X			X	X	X
Gynecologic Exam (PAP) Ω	X													X												X	X	X
Toxicity Notation	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
LABORATORY																												
CBC / Differential / Platelets	X				X			X			X			X			X			X			X			X	X	X
Cl-/PO4	X				X			X			X			X			X			X			X			X	X	X
Na+/K+	X				X			X			X			X			X			X			X			X	X	X
Creatinine	X				X			X			X			X			X			X			X			X	X	X
Alkaline Phosphatase	X				X			X			X			X			X			X			X			X	X	X
BUN	X				X			X			X			X			X			X			X			X	X	X
Bilrubin	X				X			X			X			X			X			X			X			X	X	X
SGOT	X				X			X			X			X			X			X			X			X	X	X
Fasting Blood Glucose	X				X			X			X			X			X			X			X			X	X	X
AM Cortisol #	X		X					X						X						X						X	X	X
T4, T3, TSH #	X		X					X						X						X						X	X	X
T3 resin uptake #	X		X					X						X						X						X	X	X
Urine Pregnancy Test ©	X																											
Patient Warning Cards £		X																										
X-RAYS AND SCANS																												
CT/MRI	X							X						X						X						X	X	X
Formal Visual Fields *	X							X*						X*						X*						X*	X*	X*
Mammogram Ω	X													X												X	X	X
Other scans	X							X†						X†						X†						X†	X†	X†
TREATMENT																												
Mifepristone or		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™
Placebo		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™
Pill Count		X	X	X	X	X	X	X	X	X	X	X	X	X			X			X			X			X	X≠	X≠

Note: All forms used in this study are listed in Section 18.0 The schedule for submission of these forms is listed in Section 14.0.

√ Including blood pressure.

Ω In women only. Prestudy tests should be performed within 1 year prior to registration.

Serum samples will be collected at baseline, one month after initiation of therapy, every 6 months while receiving therapy and one month after discontinuation of therapy. Samples will be centrifuged and serum frozen for assay at the time the randomization code is broken (see Section 15.0) except as indicated in Section 8.3 and 8.4. These studies are NOT to be run during blinded treatment.

© Pre-menopausal women only.

≠ Pills must be returned at every office visit and pill counts recorded on flow sheets.

† If abnormal at baseline.

™ As indicated in Section 7.2.

£ Distributed within a month of registration. See Section 7.1d.

* All patients with a base of brain cavernous sinus or optic nerve meningiomas or with visual symptoms should have baseline visual field exams. Serial exams should be performed in patients who were abnormal at baseline. Subsequent exams should be done as clinically indicated in patients who were normal at baseline.

Δ Patients who continue therapy past 2 years will continue to follow the schedule of clinic visits and studies established for the second year of therapy. CT/MRI and Formal Visual Fields, however, may be done annually.

10.0 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS

10.1 Definitions

a. **Measurable Disease:** Bidimensionally measurable lesion with clearly defined margins by CT or MRI scan, with at least one diameter greater than .5 cm.

b. **Evaluable Disease:** Unidimensionally measurable lesions, masses with margins not clearly defined; any lesion with both diameters less than .5 cm.

c. **Non-Evaluable Disease:** Pleural effusions; ascites.

d. **Objective Status, To Be Recorded at Each Evaluation:** If an organ has too many measurable lesions to measure at each evaluation, choose three to be followed before the patient is entered on study. The remaining measurable lesions in that organ will be considered evaluable for the purpose of objective status determination. Unless progression is observed, objective status can only be determined when ALL measurable and evaluable sites and lesions are assessed.

1. **Complete Response (CR):** Complete disappearance of all measurable and evaluable disease. No new lesions. No disease related symptoms. No evidence of non-evaluable disease. All measurable, evaluable and non-evaluable lesions and sites must be assessed. Refers to clinical CR--when restaging surgery is required, a separate pathologic response variable is coded.

2. **Partial Response (PR):** Applies only to patients with at least one measurable lesion: Greater than or equal to 50% decrease under baseline in the sum of products of perpendicular diameters of all measurable lesions. No progression of evaluable disease. No new lesions. All measurable and evaluable lesions and sites must be assessed.

3. **Partial Response, Non-Measurable (PRNM):** Significant response of evaluable or non-evaluable disease confirmed by two independent observers.

4. **Stable/No Response:** Does not qualify for CR, PR, or progression. All measurable and evaluable sites and lesions must be assessed.

5. **Progression:** 25% increase or an increase of 10 sq. cm (whichever is smaller) in the sum of products of perpendicular diameters of measurable lesions over smallest sum observed (over baseline if no decrease), OR reappearance of any lesion which had disappeared, OR clear worsening of any evaluable disease, OR appearance of any new lesion/site, OR failure to return for evaluation due to deteriorating condition (unless deterioration is clearly unrelated to this cancer) or significant neurologic deterioration (see Section 10.5). Worsening of existing non-evaluable disease does not constitute progression.

Exceptions: (1) In cases for which initial flare reaction is possible (hypercalcemia, increased bone pain, erythema of skin lesions), either symptoms must persist beyond four weeks or there must be additional evidence of progression. (2) Lesions which appear to increase in size due to presence of necrotic tissue will not be considered to have progressed.

6. **Unknown:** Progression has not been documented and one or more measurable or evaluable lesions or sites have not been assessed.

10.2 **Note that non-evaluable disease** does not affect objective status except in determination of CR (must be absent), and in determination of progression (if NEW sites of non-evaluable disease develop).

10.3 **Best Response:** This will be calculated from the sequence of objective statuses.

For patients with all disease sites assessed every three to six weeks, two objective statuses of CR are required for a best response of CR; two of PR or better, but not qualifying for CR, are required for PR; two of stable/no response or better, but not qualifying as PR or CR, are required for stable/no response; patients with objective status of progression on or before the second evaluation (second AFTER the prestudy evaluation) will have a best response of increasing disease.

For patients with disease scheduled to be assessed only at greater than six week intervals, only one assessment of stable/no response or better before progression, but not qualifying for a CR or PR is required for a best response of stable/no response. For CR or PR response must be confirmed; a second assessment should be scheduled for four weeks after the first documentation of response. Patients with objective status of progression at the first evaluation will have a best response of increasing disease. Best response is unknown if the patient does not qualify for best response of increasing disease and all objective status determinations before progression are unknown.

10.4 CT/MRI scan will be used to demonstrate meningioma. The type of scan used at baseline will be continued throughout the study and will be performed according to the following criteria:

a. The reference plane will be the orbito meatal plane. This will be visualized by a radiological mode. If this is not possible, anatomical reference points (Canthus Traggus) will be used. Imaging studies must be repeated using the same plane of section and slice thickness throughout the study for accurate correlation. All cross sections will have the same thickness (5 mm).

b. The greatest diameter and its largest perpendicular diameter expressed in mm will be measured at the keyboard and will be indicated on each film. The number of cross sections on which the meningioma can be seen will be noted. The presence of calcifications, or mass effect will be noted and peritumoral edema will be quantified.

c. The area of the meningioma will be obtained by multiplying the greatest diameter by its largest perpendicular diameter.

10.5 **Criteria for Neurologic Evaluation:**

Progression of disease will be defined as an increase by 2 SWOG toxicity grades of any neurologic symptom or sign or clear worsening of the visual field examination.

10.6 **Performance Status:** Patients will be graded according to the current Southwest Oncology Group grading scale:

GRADE	SCALE
0	Fully active; able to carry on all predisease activities without restriction. (Karnofsky 90-100)

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. (Karnofsky 70-80)
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. (Karnofsky 50-60)
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours. (Karnofsky 30-40)
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. (Karnofsky 10-20)
5	Dead

10.7 **Time to Treatment Failure:** From date of registration to first date of documentation of one of the following:

a. Progression as defined in 10.1.d.5 (clear worsening of evaluable disease must be confirmed by 2 investigators).
b. Significant deterioration of at least one neurologic symptom as defined in Section 10.5.
c. Discontinuation of treatment for any reason.
d. Death from any cause.

10.8 **Time to Death:** From date of registration to date of death.

11.0 STATISTICAL CONSIDERATIONS

11.1 With participation of other cooperative groups, it is anticipated that 50 eligible patients per year will be accrued to this study for a total of 200 patients. Patients will be stratified according to disease status, sex/menopausal status and prior RT and randomized to receive either RU-486 or placebo according to a dynamic allocation scheme. Treatment will remain double blinded as much as possible. (It is recognized that certain symptoms, such as a cessation of menses in a premenopausal female, may suggest a specific treatment arm).

11.2 The primary endpoint to be compared on the two arms is time to treatment failure. Patients will be accrued for four years and the final analysis will be done after two additional years of follow-up. In addition to the usual study monitoring, one formal interim analysis is planned after 75% of accrual is complete. If RU-486 is superior to placebo at the .01 level at this time, consideration will be given to stopping the trial early and concluding RU-486 is effective. The final analysis will be performed at the .045 level in order to have an overall .05 level for the study. Assuming time to failure on the placebo arm is exponentially distributed with one year median, the one-sided test of equality of time to treatment failure will have power at least .83 to detect a 50% improvement due to mifepristone. Survival will also be compared although additional follow-up will be required for adequate power.

11.3 Subsequent breast or endometrial cancer is a potential sequela of unopposed estrogen but has never been observed with short or long term mifepristone therapy. The probability of observing very rare potential toxicities on mifepristone such as endometrial cancer, breast cancer, or thrombophlebitis in a study of this size will be low. Toxicities must occur with probability at least .02 to be likely to be observed at least once (87% chance).

12.0 DISCIPLINE REVIEW

12.1 Pathology Review

a. Pathology review will be performed on all patients registered to this study. The purpose of the stained slide review is to verify the histologic diagnosis of primary, recurrent or residual meningioma which is not malignant. The purpose of the tissue analysis is to confirm or determine (if unknown) hormone receptor status by immunohistochemical techniques. Submission of tissue blocks from all cases is mandatory (if available). Slides from all cases must be forwarded within 30 days to:

Peter C. Burger, M.D.
Professor of Pathology
The Johns Hopkins Hospital
Carnegie Bldg., Room 422
Baltimore, MD 21287

Blocks from all cases (if available) must be forwarded within 30 days to:

Andy E. Sherrod, M.D.
Department of Pathology
University of Southern California
1441 Eastlake Avenue, Room 244
Los Angeles, CA 90033

A copy of the Protocol Specific Pathology Submission Form must be submitted to the Statistical Center when submissions are made to Drs. Burger and Sherrod.

The materials must be identified with a "SWOG Pathology Materials" label on the outside of each package. If this label is missing, the materials will not be reviewed, rendering the patient ineligible. These labels will be provided by the Statistical Center. To obtain additional labels, please call 206/667-4623 and ask for the Data Operations Technical Manager.

b. ECOG Institutions:

Materials required for pathology review and tissue blocks (if available) must be sent to:

Pathology Coordinating Office
ECOG Coordinating Center
303 Boylston Street
Brookline, MA 02146-7648
Phone: 617/632-3610

The ECOG Pathology Coordinating Office will forward the materials directly to the pathology reviewers.

c. Materials required for stained slide review:

1. One to two representative H & E stained slides demonstrating lesion.

2. A copy of the pathology report and operative report.

3. Protocol Specific Pathology Submission Form

d. Materials required for tissue analysis:

1. Tissue blocks

2. Protocol Specific Pathology submission form (in addition to 12.1.d.3 requirement)

e. Each investigator will be reimbursed a flat fee for the shipment of tissue blocks. It is the investigator's responsibility to request reimbursement for the shipment directly from the Southwest Oncology Group Operations office by completing and sending the **SWOG-9005** Sample Submission Reimbursement Form to the attention of:

Marjorie Godfrey
Southwest Oncology Group Operations Office
14980 Omicron Drive
San Antonio, Texas 78245-3217
Phone: 210/677-8308

12.2 Radiology Review

a. Scans and formal visual field examinations at baseline, progression, and at two years (unless patient has already progressed) are to be submitted for review. Copies of these CT or MRI scans and formal visual field examinations should be submitted within 30 days for review directly to:

Jamshid Ahmadi, M.D.
Department of Radiology
Division of Neuroradiology, Suite 5139
Los Angeles, CA 90033
Phone: 213/226-7425

b. ECOG institutions will submit the required radiology materials directly to the Southwest Oncology Group Statistitical Center.

c. All required radiology materials will be logged into the Group Radiology Records and will then be forwarded to the reference radiologist Dr. Jamshid Ahmadi for review.

13.0 REGISTRATION GUIDELINES

13.1 Instructions for Southwest Oncology Group Institutions

All patients must be registered with the Southwest Oncology Group Statistical Center by telephoning 206/667-4623, 6:30 a.m. to 5:00 p.m. Pacific time, Monday through Friday, excluding holidays. Patients should start treatment within 2 working days of receipt of drug at the individual institution. Patients who progress on placebo and are eligible to begin open-label treatment with mifepristone must have a second registration prior to beginning cross-over therapy.

13.2 Instructions for ECOG Institutions:

Randomization procedures apply to both initial and cross-over registrations. To register a patient, the investigator will telephone the Central Randomization Desk at the ECOG Statistical Center Data Management Office at 617/632-2022 between 9:30 a.m. to 5:30 p.m. ET Monday - Friday. ECOG members should not call the Southwest Oncology Group directly. A signed HHS 596 form for this protocol must be on file at the ECOG Operations Office before any ECOG institution may enter a patient.

Upon confirming eligibility, the ECOG Randomization Desk will call the Southwest Oncology Group Statistical Center at 206/667-4623 between 6:30 a.m. and 2:00 p.m. PT Monday - Friday for registration. Upon registration with the Southwest Oncology Group, ECOG will receive an intergroup case number and the specific treatment arm to which the patient was assigned. This information will then be relayed to the ECOG investigator. The Southwest Oncology Group Statistical Center will forward a confirmation of treatment assignment to the ECOG Statistical Center Data Management Office (303 Boylston Street, Brookline, MA 02146-7215) for routing to the participating institution.

13.3 Following the registration, it is the institution's responsibility to place an order for the patient's blinded drug with the Pharmaceutical Management Branch. For this purpose, the patient's treatment preparation identification number is provided to the caller at the time of registration. THE TREATMENT PREPARATION IDENTIFICATION NUMBER MUST BE RECORDED ON THE CLINICAL DRUG REQUEST FORM.

13.4 At the time of registration, the caller must be prepared to answer every question on the eligibility checklist, provide stratification/descriptive factors, and provide NCI and Southwest Oncology Group investigator numbers.

13.5 The caller must also be prepared to provide the date of institutional review board approval for this study. Patients will not be registered if the IRB approval date is not provided or is > 1 year prior to the date of registration.

13.6 Exceptions to the current registration policies will not be permitted. Therefore, late registrations (after initiation of treatment), exceptions to eligibility requirements, participation by an institution/member not identified as eligible **AND/OR** cancellations will not be allowed.

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 model consent form) must be photocopied for data submission to the Statistical Center.

14.3 Instructions for Southwest Oncology Group Institutions

a. Group members and CCOPs must submit two copies of all data forms directly to the Statistical Center in Seattle. CGOP's must submit (number of copies to be determined by Group member) copies of all forms to their group member institution for forwarding to the Statistical Center.

b. WITHIN 14 DAYS OF INITIAL REGISTRATION:

Submit the following:

Eligibility Checklist
Meningioma Prestudy Form
Pathology Report
Study Specific Solid Tumor Flow Sheet (Section 18.0) documenting history and physical, prestudy tests/exam results, the first seven days of protocol treatment, dose calculations and toxicity notations.

c. WITHIN 14 DAYS OF CROSSOVER REGISTRATION:

Submit the following:

Eligibility Checklist for Crossover Registration

Meningioma Prestudy Form

Study Specific Solid Tumor Flow Sheet (Section 18.0) documenting history and physical, prestudy tests/exam results, the first seven days of protocol treatment, dose calculations and toxicity notations.

d. WITHIN 30 DAYS OF REGISTRATION:

Pathology materials are to be submitted as described in Section 12.0.

e. MONTHLY DURING THE FIRST YEAR, EVERY 3 MONTHS WHILE ON PROTOCOL TREATMENT AND EVERY 6 MONTHS THEREAFTER:

Submit the Study Specific Solid Tumor Flow Sheet documenting required parameters as specified on the Study Calendar.

f. WITHIN 30 DAYS OF REGISTRATION, PROGRESSION, AND AT 2 YEARS (UNLESS PATIENT HAS ALREADY PROGRESSED):

Submit copies of CT or MRI scans and copies of formal visual field examinations as described in Section 12.2.

g. WITHIN 14 DAYS OF GOING OFF TREATMENT:

Submit the Off Treatment Notice.

h. WITHIN 14 DAYS OF TREATMENT FAILURE:

Submit the Study Specific flow sheet documenting the date and type of first failure (even if this occurs after the patient is off protocol treatment).

i. WITHIN 4 WEEKS OF KNOWLEDGE OF DEATH:

Submit the Notice of Death and final Flow Sheet documenting death information to the Statistical Center.

14.4 INSTRUCTIONS FOR ECOG INSTITUTIONS

ECOG participants are to submit originals of completed forms to the ECOG Statistical Center Data Management Office. The ECOG Statistical Center Data Management Office will forward the required number of copies to the Southwest Oncology Group Statistical Center. Do not submit forms directly to the Southwest Oncology Group.

15.0 SPECIAL INSTRUCTIONS

Serum samples for cortisol and thyroid function tests are to be centrifuged, frozen in a -20 ° C freezer, and stored at the individual institutions. Assays for an individual patient should be performed in a single batch at the time the randomization code is broken. For patients suspected of developing severe adrenal or thyroid insufficiency during the study, serum samples should be assayed as directed in Section 8.3 and 8.4.

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). 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).

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 inspection at any time.

Adverse Experiences

Any adverse experience, if deemed drug related, must be reported to the Operations Office Adverse Drug Reaction (ADR) representative (210/677-8808), who will obtain information on the ADR. Adverse drug reactions for ECOG patients will be first reported to the ECOG Statistical Center Data Management Office. All ADR forms should be submitted to the ECOG Statistical Center Data Management Office, who will route forms to the Southwest Oncology Group. Depending on the nature of the reaction and whether it was caused by an investigational or commercial agent, the ADR representative will advise whether the report to the Study Coordinator, Dr. Grunberg, should be phoned in, written in, or both. See guidelines below. On Phase II and III studies, all deaths considered drug-related must be reported immediately to the ADR representative. On double-blinded studies, if the investigator must know what treatment the subject received to make therapeutic decisions, the code for that particular subject can be broken by telephoning the Statistical Center.

All adverse experiences must also be reported to the Institutional Review Board within 10 days and documentation of this report sent to the Operations Office.

All adverse experiences must also be recorded in the appropriate section of the case report form. The report should include, whenever possible, the investigator's written medical judgment as to relationship of the adverse experience to study medication(s) (i.e., "probable", "possible" or "unrelated").

GUIDELINES FOR REPORTING OF ADVERSE DRUG REACTIONS (ADRs)
OCCURRING WITH **INVESTIGATIONAL** AGENTS
ON PHASE II AND III STUDIES

WITHIN 24 HOUR OF THE REACTION

CALL THE OPERATIONS OFFICE AT 210/677-8808

WITHIN 10 DAYS, SEND TO THE OPERATIONS OFFICE

1) **A COPY OF THE ADR REPORTING FORM**
2) **IRB NOTIFICATION DOCUMENTATION**
3) **COPIES OF ALL DATA RECORDS**

IN ADDITION, FOLLOW THE NCI GUIDELINES BELOW

UNKNOWN REACTION[4,5]		KNOWN REACTION[4,5]	
Grades 2-3[2]	Grades 4-5	Grades 1-3	Grades 4-5
Written report to Dr. Grunberg within 10 working days.[3]	Report by phone to Dr. Grunberg within 24 hours.[1] Written report to follow within 10 working days.	Not to be reported as ADRs. These toxicities should be submitted as part of study summary.	Written report to Dr. Grunberg within 10 working days. Grade 4 myelo-suppression not to be reported, but should be submitted as part of study results. Grade 5 aplasia in leukemia patients-- written report within 10 working days.

1. For grading reaction, see Southwest Oncology Group Toxicity Criteria, Section 19.0.
2. Dr. Grunberg's telephone number available 24 hours daily: 802/656-4414.
3. Send reports to:

ATTN: ADR Program
Southwest Oncology Group
14980 Omicron
San Antonio, Texas 78245-3215

and

Steven M. Grunberg, M.D.
Medical Center Hospital of Vermont
Section of Hematology/Oncology
One South Prospect Street
Burlington, Vermont 05401
Fax: 802/656-5946

4. A list of all known toxicities can be found in either the Drug Information, Background or Informed Consent Form of the protocol.
5. Reactions judged definitely not to be treatment related should not be reported. **However, a report shall be submitted if there is only a reasonable suspicion of drug effect.**
6. For reporting cases of secondary AML or MDS, please use the "NCI/CTEP Secondary AML/MDS Report Form" in lieu of the ADR Reporting Form. Copies of the "NCI/CTEP Secondary Leukemia Report Form" will be forwarded from the Operations Office to the Statistical Center within one working day.

17.0 BIBLIOGRAPHY

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8. Waelti ER, Markwalder T-M: Endocrine manipulation of meningiomas with medroxyprogesterone acetate. Effect of MPA on growth of primary meningioma cells in monolayer tissue culture. Surg Neurol 31:96-100, 1989.

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10. Baulieu E-E: Contragestion and other clinical applications of RU486, an antiprogesterone at the receptor. Science 245:1351-1357, 1989.

11. Olson JJ, Beck DW, Schlechte J, et al: Hormonal manipulation of meningiomas in vitro. J Neurosurg 65:99-107, 1986.

12. Blankenstein MA, van't Verlaat JW, Croughs RJM: Hormone dependency of meningiomas. Lancet 1:1381, 1989 (letter)

13. Olson JJ, Beck SW, Schlechte JA, et al: Effect of the antiprogesterone RU-38486 on meningioma implanted into nude mice. J Neurosurg 66:584-587, 1987.

14. Grunberg SM, Weiss MH, Spitz IM et al: Treatment of unresectable meningiomas with the anti-progestational agent mifepristone. J Neurosurg 74:861-866, 1991.

15. Grunberg SM, Weiss MH, Sptiz IM et al: Treatment of meningioma with the oral anti-progestational agent mifepristone (RU486). Proc ASCO 10:126, 1991 (abstract)

16. Silvestre L: Personal Communication

18.0 MASTER FORMS SET

18.1 Attached are copies of all data forms which must be completed for this study. The model informed consent form is also included in this packet which must be reviewed and approved by the institutional review board prior to registration and treatment of patients on this study.

18.2 Forms to be used for patients treated on this study include:

a. Meningioma Prestudy Form

b. Flow Sheet

c. Protocol Specific Pathology Submission Forms

d. Off Treatment Notice

e. Notice of Death

CONSENT FORM
AND
INFORMATION ABOUT

SWOG-9005, "Double Blind Randomized Trial of the Anti-Progestational Agent Mifepristone in the Treatment of Unresectable Meningioma"

TO BE CONDUCTED AT

_____

_____

I. You are invited to take part in this research study because you have a meningioma of your brain or spinal cord which has been growing steadily or has just appeared and cannot be completely removed and cured by surgery. Although meningioma is not a malignant cancer, its slow and steady growth near the brain or spinal cord can cause problems including changes in vision, weakness, paralysis, or seizures depending upon the location. We want to find out whether patients will respond and how long their response lasts if treated with the experimental anti-progestational agent mifepristone. Progesterone is a normal sex hormone that may affect the growth of some meningiomas and mifepristone is an agent that blocks the action of progesterone.

We also want to find out what kind of side effects mifepristone causes and how often they occur.

We cannot and do not guarantee you will benefit if you take part in this study. The treatment you receive may even be harmful.

II. If you decide to take part in this study you will be assigned to one of two types of treatment by a process called randomization, similar to flipping a coin. Neither you nor your doctor will know which treatment you are getting while you are receiving it (this is called double-blind).

You may receive mifepristone or you may receive an identical pill with no active ingredients (a placebo).

In either case you will be given pills which will come in a blister pack when you come to clinic and will be instructed to take 1 tablet per day. Therapy will continue for 2 years. You will be seen by your doctor at least once a month during the first year and once every 3 months during the second year. At these visits you will be asked about the symptoms of your meningioma and you will be asked about possible side effects. You must bring your medication with you at each clinic visit so that the remaining pills can be counted. Blood tests will be drawn every 3 months to see how your body is tolerating treatment. CT scans or MRI scans (and eye examinations if your vision is abnormal due to your meningioma) will be performed every 6 months to see if the tumor is changing size.

Mifepristone can interfere with the body's ability to use its own steroid (hormones that are necessary in high amounts in emergency situations). Since you or your doctor will not know whether you are taking mifepristone or not, you will be given a card to carry in your wallet that says you might have "adrenal insufficiency" (not enough steroids). That way, in an emergency situation, physicians may be able to prevent any possible problems. You should receive this card within a month after starting treatment.

At the end of two years, if your meningioma has stayed the same size or has shrunk, you will have the choice of continuing the same therapy. If your meningioma starts growing during treatment, you and your doctor will immediately be told what kind of treatment you have been receiving. If your meningioma has grown while receiving placebo, you will have the choice of starting mifepristone immediately. Before you begin mifepristone treatment, you must repeat the scans and lab tests that were required at the beginning of the study. If your meningioma has grown while receiving mifepristone, then other types of treatment will have to be considered.

The drug manufacturer for mifepristone Roussel SANTE through the Division of Cancer Treatment, National Cancer Institute will provide you with the investigational agent mifepristone or the placebo free of charge for this study. Should this agent become commercially available during the course of the study, however, you may be asked to purchase subsequent doses of the medicine.

III. Some of the side effects some people have had from mifepristone are outlined below.

Mifepristone

The most common side effect is tiredness which is usually mild but may be severe. Other possible side effects include hot flashes, breast tenderness, slight thinning of the hair, rash, dizziness, sleepiness, poor appetite, nausea, vomiting, and a rare risk of increased formation of blood clots (phlebitis or embolism). Women who are having their menstrual periods should expect to have one further menstrual period soon after starting mifepristone and then no further menstrual periods while on treatment.

Mifepristone does cause a hormonal imbalance in the body by blocking progesterone. Several cases of adenomatous hyperplasia of the endometrium (overgrowth of the lining of the uterus), probably resulting from hormonal imbalance, have been seen. Some types of hormonal imbalance can increase the risk of breast cancer or uterine cancer in women. Although this has never been reported with mifepristone, all women will have a mammogram (breast x-ray) and a PAP smear once a year while on treatment.

A placebo is a pill with no active ingredients. There should therefore be no side effects of receiving a placebo. However if you are receiving a placebo you will be receiving no active ingredients against your meningioma.

IV. There may be other treatments for your meningioma, including standard treatments such as surgery and radiotherapy, or possibly other chemotherapy drugs. However, your doctors feel that your treatment on this study is a reasonable alternative at this time.

V. If you are pregnant, you cannot take part in this study. You will take a urine test to see if you are pregnant before you start treatment. If you are sexually active, you must take precautions to avoid the possibility of becoming pregnant during or for 3 months after treatment because we do not know how this drug could affect an unborn child. You may not, however, take birth control pills while on this study. Abnormal offspring were noted in rabbits that received RU 486 during pregnancy.

VI. If you experience illness as a result of treatment on this study, you will (will not) receive free emergency medical treatment. We cannot give you free continuing medical care and/or hospitalization, nor can we pay you to take part in this study.

VII. We will keep any information we learn from this study confidential and disclose it only with your permission. By signing this form, however, you allow us to make your records available to the National Cancer Institute, the Food and Drug Administration, a qualified representative of the drug manufacturer, and the Southwest Oncology Group. If we publish the information we learn from this study in a medical journal, you will not be identified by name.

VIII. Whether or not you take part in this study will not affect your future relations with your doctors or _____ (hospital name). If you decide to take part, you are free to stop whenever you want.

IX. The doctor(s) involved with your care can answer <u>any</u> questions you may have about the drug program. In case of a problem or emergency, you can call the doctors listed below day or night.

	Office	Home
Dr.		
Dr.		
Dr.		

You can also call the Institutional Review Board (#_____) if you have any questions, comments or concerns about the study or your rights as a research subject.

X. We will give you a copy of this form to keep.

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

_____ _____
Date Signature of Subject

_____ _____
Signature of Witness Signature of Investigator

_____
Time

MENINGIOMA PRESTUDY

SWOG Study No. ☐☐☐☐ Protocol Step ☐

SWOG Patient No. ☐☐☐☐☐☐ Patient's Name _____ (L) (F) (M)

Institution / Member _____ S.S. No. ☐☐☐-☐☐-☐☐☐☐

Physician _____ Hospital No. _____

Groups other than SWOG: Name/Study No./Pt No. _____ / _____ / _____

Amended data: ☐ Yes, mark amended items in red.

Instructions: All dates are MONTH, DAY, YEAR. Indicate an unknown part of a date with a horizontal line drawn across the appropriate boxes.

PATIENT CHARACTERISTICS

Date of birth ☐☐-☐☐-☐☐

Sex ☐ Male ☐ Female

Race ☐ White ☐ Black ☐ Other ☐ Unknown

Weight ☐☐☐.☐ kg

Height ☐☐☐ cm

BSA ☐.☐☐ m^2

Performance status

- ☐ 0-Fully active
- ☐ 1-Symptoms but ambulatory and able to do light work
- ☐ 2-No work but self care and active > 50% of waking hours
- ☐ 3-Limited self care, confined to bed or chair > 50% of waking hours
- ☐ 4-Completely disabled

DISEASE DESCRIPTION

DIAGNOSIS

Date of First Pathologic Diagnosis ☐☐-☐☐-☐☐

Histology

- 1- ☐ Fibrous
- 2- ☐ Meningiothelial/cellular
- 3- ☐ Anaplastic
- 4- ☐ Other, specify: _____

CURRENT LOCATION OF TUMOR (most involved area)

- 1- ☐ Cerebral cortex
- 2- ☐ Cavernous sinus
- 3- ☐ Base of brain
- 4- ☐ Spinal cord
- 5- ☐ Other, specify: _____

TUMOR STATUS AT REGISTRATION

- 1- ☐ Progressive
- 2- ☐ Recurrent
- 3- ☐ Residual

CURRENT SYMPTOMS

Symptoms:	Grade
Disorientation	☐
Somnolence/Agitation	☐
Personality change	☐
Convulsions	☐
Malaise/Fatigue/Lethargy	☐
Anxiety/Depression	☐
Weakness	☐
Incoordination/Ataxia	☐
Speech Impairment	☐
Numbness	☐
Hearing	☐
Vision	☐
Taste	☐
Headache	☐
Dizziness/Vertigo	☐
Insomnia	☐
Other, specify: _____	☐
Other, specify: _____	☐
Other, specify: _____	☐

Grade Codes*
0=None or normal
1=Mild
2=Moderate
3=Severe
4=Life threat
9-Unknown

* Refer to Southwest Oncology Group Toxicity Criteria for definition of mild, moderate, severe, and life threatening.

Notes:

MENINGIOMA PRESTUDY

SWOG Study No. ☐☐☐☐ Protocol Step ☐

SWOG Pt. No. ☐☐☐☐☐☐ Patient's Name _____ (L) (F) (M)

Amended data: ☐ Yes, mark amended items in red.

INSTRUCTIONS: All dates are MONTH, DAY, YEAR. Indicate an unknown part of a date with a horizontal line drawn across the appropriate boxes.

PRIOR TREATMENT

Prior SURGERY ☐ No (skip to next section) ☐ Yes

Code No if incisional or needle biopsy is the only prior surgery

Surgical Procedure Description (Record one procedure per line)	# Surgery Code	Date
		☐☐-☐☐-☐☐
		☐☐-☐☐-☐☐
		☐☐-☐☐-☐☐

Prior RADIATION THERAPY ☐ No (skip to next section) ☐ Yes

Site	Start Date	Stop Date	* Best Response
	☐☐-☐☐-☐☐	☐☐-☐☐-☐☐	
	☐☐-☐☐-☐☐	☐☐-☐☐-☐☐	
	☐☐-☐☐-☐☐	☐☐-☐☐-☐☐	

Prior SYSTEMIC THERAPY ☐ No ☐ Yes

Treatment Description (Do not list agents in a combination separately)	+ Type Therapy	Start Date	Stop Date	* Best Response
		☐☐-☐☐-☐☐	☐☐-☐☐-☐☐	
		☐☐-☐☐-☐☐	☐☐-☐☐-☐☐	
		☐☐-☐☐-☐☐	☐☐-☐☐-☐☐	
		☐☐-☐☐-☐☐	☐☐-☐☐-☐☐	

Surgery codes: 0=Biopsy, 1=Partial resection, 2=Complete resection, 3=Other, 9=Unknown

+ Therapy codes: 1=Chemotherapy, 2=Immunotherapy, 3=Hormonal therapy, 4=Other, 9=Unknown

* Best Response: 1=CR, 2=PR, 3=Response, NOS, 4=Stable, 5=Progressive disease, 6=Not applicable, 9=Unknown

Notes:

BY: _____ **DATE:** _____

GUIDELINES

MENINGIOMA PRESTUDY GUIDELINES

THIS DOCUMENT IS NOT AVAILABLE IN ELECTRONIC FORM. PLEASE CONSULT A PRINTED/MAILED COPY OF THE PROTOCOL OR YOUR SOUTHWEST ONCOLOGY GROUP CLINICAL RESEARCH ASSOCIATES MANUAL FOR A PRINTED COPY

BRAIN TUMOR FLOW SHEET **SWOG-9005**

PT. # REG DATE

UNIT # PAGE

PATIENT

INVESTIG.

INSTITUTION

STUDY # 9005 RX. #

DISEASE CAT

PROGRESS NOTES (DATE EACH)

DATE 19 Mo./Day					
DAY ON STUDY					
TREATMENT					
Medication					
# of packs dispensed					
Pill Count Returned					
Steroid					
Antibiotics					
Thyroid hormone supplementation					
PHYSICAL					
Temperature (C) (F)					
Height (cm) (in)					
Weight (kg) (lb)					
Performance Status (0-5)					
Blood pressure					
BLOOD					
*Hgb gm% (LLN=)					
HCT gm%					
*Platelets 1,000/µl (LLN=)					
WBC 1,000/µl					
Neutrophils %					
Eosinophils %					
Basophils %					
Lymphocytes %					
Monocytes %					
RBC					
LABORATORY					
*Creatinine (ULN=)					
*Alkaline Phosphatase (ULN=)					
BUN					
*Bilirubin (ULN=)					
*SGOT (ULN=)					
Fasting Blood Glucose					
AM Cortisol √					
T3 / T4 √					
TSH / T3 Resin uptake √					
Cl / PO4	/	/	/	/	/
Na+ / K+	/	/	/	/	/
Pregnancy Test					
PAP					
RADIOLOGY					
CT/MRI (Specify)					
with contrast					
without contrast					
Tumor Measurement (diameter cm)					
Mammogram					
Visual Field Exam					
TYPE OF FAILURE					
Objective progression of					
measurable disease					
Clear worsening of evaluable disease					
(confirmed by 2 investigators)					
Significant deterioration of at least					
one neurologic symptom					
Death					
RESPONSE					
Objective - Tumor size					
Subjective - (N-I-D)					

* Please list institutional lower limits of normal for HGB and platelets and upper limits of normal for laboratory tests as indicated.

√ See Section 15.0. Serum samples are to be collected and frozen. These studies are NOT to be run during blinded treatment.

Amended 12/1/92

BRAIN TUMOR FLOW SHEET **SWOG-9005**

PT. # REG DATE

UNIT # PAGE

PATIENT

INVESTIG.

INSTITUTION

STUDY # 9005 RX. #

DISEASE CAT

PROGRESS NOTES (DATE EACH)

DATE 19 Mo./Day					
DAY ON STUDY					
NEURO SYMPTOMS / EXAM					
Conscious State	N A	N A	N A	N A	N A
Personality	N A	N A	N A	N A	N A
Gait	N A	N A	N A	N A	N A
Headache	P A	P A	P A	P A	P A
Seizures	P A	P A	P A	P A	P A
Double/Blurred Vision	P A	P A	P A	P A	P A
Dizziness/Vertigo	P A	P A	P A	P A	P A
Higher Cognitive Function	N A	N A	N A	N A	N A
CN III, IV & VI	N A	N A	N A	N A	N A
Visual Fields	N A	N A	N A	N A	N A
CN Other (CN V,VII, VIII, IX-XII)	N A	N A	N A	N A	N A
Motor	N A	N A	N A	N A	N A
Sensory	N A	N A	N A	N A	N A
Cerebellar (Ataxia)	N A	N A	N A	N A	N A
Bladder/Bowel Function	N A	N A	N A	N A	N A
TOXICITY (GRADE 0-4)					
Alopecia					
Anxiety					
Breast Tenderness					
CNS-other (specify)					
Convulsions					
Disorientation					
Dizziness					
Fatigue					
Gynecomastia					
Headache					
Hearing					
Hot Flashes					
Incoordination / Ataxia					
Insomnia					
Lethargy					
Malaise					
Menses					
Nausea					
Neurocortical-other (specify)					
Neuromotor-other (specify)					
Neurosensory-other (specify)					
Neuro-other (specify)					
Numbness / Other PNS	/	/	/	/	/
Personality Change					
Phlebitis / Embolism	/	/	/	/	/
Rash					
Somnolence					
Speech impairment					
Taste					
Uterine Bleeding-describe					
Vision					
Vomiting					
Weakness					
Other- (specify)					

Complete the form by recording values in empty boxes or circling the appropriate response:

N or A - Normal or Abnormal

P or A - Present or Absent

Additional comments (change in neuro status, alterations in therapy, or removal from study) should be recorded in "Progress Notes".

SOUTHWEST ONCOLOGY GROUP

PATHOLOGY SUBMISSION FORM

SWOG Study No. | S | 9 | 0 | 0 | 5 | **Protocol Step** | 1 |

Instructions: Submit copy of this form to SWOG Statistical Center. Mail required materials and this form to the following pathologist.

Peter C. Burger, M.D.
Professor of Pathology
The Johns Hopkins Hosp.
Carnegie Bldg., Rm. 422
Baltimore, MD 21287

Required Materials:

1-2 Representative H&E Stained Slides
Copy of Pathology Report
Copy of Operative Report

TO BE COMPLETED BY SUBMITTING INSTITUTION

SWOG Pt.No.: | | | | | | | **Patient'sName:** _____ **(L,F,M)**

Institution/Member: _____ **Physician:** _____

Groups Other than SWOG: Name/Study No./Pt.No.: _____

Reason for Submission circle: **Pre-registration Biopsy**

No. of Slides: | | **No. of Blocks:** | | **Date Sample Obtained:** | | | - | | | - | | | **(M,D,Y)**

Required Materials:	**Enclosed (circle)**	**Specimen #**
1-2 Representative H&E Stained Slides	**yes no (explain in NOTES)**	_____
Copy of Pathology Report	**yes no (explain in NOTES)**	
Copy of Operative Report	**yes no (explain in NOTES)**	

NOTES:

TO BE COMPLETED BY SWOG PATHOLOGIST'S OFFICE

SWOG Pathologist Name: _____

Required Materials:	**Adequate as Received (circle)**	
1-2 Representative H&E Stained Slides	**yes**	**no (explain in NOTES)**
Copy of Pathology Report	**yes**	**no (explain in NOTES)**
Copy of Operative Report	**yes**	**no (explain in NOTES)**

NOTES:

SOUTHWEST ONCOLOGY GROUP

PATHOLOGY SUBMISSION FORM

SWOG Study No. | S | 9 | 0 | 0 | 5 | **Protocol Step** | 1 |

Instructions: Submit copy of this form to SWOG Statistical Center. Mail required materials and this form to the following pathologist.

Required Materials:

Tissue Blocks

Andy E. Sherrod, M.D.
Department of Pathology
University of Southern California
1441 Eastlake Ave., Rm. 244
Los Angeles, CA 90033

TO BE COMPLETED BY SUBMITTING INSTITUTION

SWOG Pt.No.: | | | | | | | **Patient'sName:** _____ **(L,F,M)**

Institution/Member: _____ **Physician:** _____

Groups Other than SWOG: Name/Study No./Pt.No.: _____

Reason for Submission circle: **Pre-registration Biopsy**

No. of Slides: | | **No. of Blocks:** | | **Date Sample Obtained:** | | | - | | | - | | | **(M,D,Y)**

Required Materials:	**Enclosed (circle)**	**Specimen #**
Tissue Blocks	**yes no (explain in NOTES)**	_____

NOTES:

TO BE COMPLETED BY SWOG PATHOLOGIST'S OFFICE

SWOG Pathologist Name: _____

Required Materials:	**Adequate as Received (circle)**
Tissue Blocks	**yes no (explain in NOTES)**

NOTES:

OFF TREATMENT NOTICE

Amended data: ☐ Yes, mark amended items in red.

NABTC Study No. ☐☐☐☐ Protocol Step ☐

NABTC Pt. No. ☐☐☐☐☐☐ Patient's Name _____ (L,F,M)

Institution / Member _____ Physician _____

INSTRUCTIONS: For each protocol step, submit this form within 2 weeks after completion (or discontinuation) of treament. List protocol-directed treatments that the patient received.

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

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

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

Indicate an unknown part of a date with a horizontal line drawn across the appropriate boxes.

Start Date (M,D,Y)	Stop Date (M,D,Y)	REGIMEN or PROCEDURE or SITE(S)
☐☐-☐☐-☐☐	☐☐-☐☐-☐☐	
☐☐-☐☐-☐☐	☐☐-☐☐-☐☐	
☐☐-☐☐-☐☐	☐☐-☐☐-☐☐	
☐☐-☐☐-☐☐	☐☐-☐☐-☐☐	
☐☐-☐☐-☐☐	☐☐-☐☐-☐☐	

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

Reason OFF TREATMENT (Check one)

1-☐ Treatment completed per protocol
2-☐ Toxicity, medically required, specify: _____
3-☐ Patient refused, due to toxicity, specify: _____
4-☐ Patient refused, other than toxicity, specify: _____
5-☐ Progression or relapse. Sites: _____
6-☐ Death (attach **Notice of Death** form)
7-☐ Other, specify: _____

Date OFF TREATMENT

Date of completion, progression, death or decision to discontinue therapy ☐☐-☐☐-☐☐ (M,D,Y)

Will patient receive **Further Treatment**?

☐ No ☐ Yes, specify: _____ ☐ Unknown

Date of **Last Contact** (or **death**): ☐☐-☐☐-☐☐ (M,D,Y)

VITAL STATUS: ☐ Alive ☐ Dead (attach **Notice of Death** form)

Notes:

By: _____ **Date:** _____

NOTICE OF DEATH

Amended data: ☐ Yes, mark amended items in red.

Most Recent NABTC Study No. ☐☐☐☐

NABTC Patient No. ☐☐☐☐☐☐ Patient Name _____ (L) (F) (M)

Institution _____ Physician _____

INSTRUCTIONS: Submit within 4 weeks of knowledge of death.

Date of death ☐☐ - ☐☐ - ☐☐ **(M,D,Y)**

Causes of Death

Any cancer (check one)

1-☐ No 2-☐ Primary cause 3-☐ Contributory 4-☐ Possible 5-☐ Unknown

If patient has had multiple tumor types, specify those which were causes of death:

_____

_____

Toxicity from disease related treatment (check one)

1-☐ No 2-☐ Primary cause 3-☐ Contributory 4-☐ Possible 5-☐ Unknown

If 2, 3, or 4, specify treatment and toxicity _____

_____

Non-cancer and non-treatment related causes (check one)

1-☐ No 2-☐ Primary cause 3-☐ Contributory 4-☐ Possible 5-☐ Unknown

If 2, 3, or 4, specify _____

_____

Autopsy done? ☐ **No** ☐ **Yes** ☐ **Unknown**

Death information obtained from (check all that apply):

☐ **Autopsy report**

☐ **Medical record / death certificate**

☐ **Physician**

☐ **Relative or friend**

☐ **Other, specify** _____

Notes:

BY: _____ **DATE:** _____

19.0 APPENDIX

19.1 This section includes Southwest Oncology Group Toxicity Criteria.

SOUTHWEST ONCOLOGY GROUP TOXICITY CRITERIA

1. Toxicity grade should reflect the most severe degree occurring during the evaluated period.
2. Toxicity grade = 5 if that toxicity caused or contributed to the death of the patient.
3. Do not code if the symptoms are certainly or most likely due to disease or other non-treatment cause.
4. If patient at baseline has Grade 1 or greater, do not code unless patient worsens due to toxicity. If there is worsening, code the level the patient increases to -- do NOT adjust for baseline.
5. Code all toxicities that apply, e.g., for a patient with pneumonitis, code pneumonitis as well as any pulmonary function codes which apply.
6. NCI codes for infection, pulmonary, neuro-sensory, neuro-cortical, neuro-cerebellar, neuro-constipation and skin will be calculated at the Statistical Center from the Southwest Oncology Group codes.
7. Note that for some toxicities certain grades are not defined and may not be coded.
8. Granulocytes/Bands refers to segmented neutrophils plus bands.

		GRADE				
Codes	Toxicity	0	1	2	3	4
	HEMATOLOGIC					
HE0	WBC	≥ 4.0	3.0 - 3.9	2.0 - 2.9	1.0 - 1.9	< 1.0
HE1	PLT	≥ LLN	75.0 - < LLN	50.0 - 74.9	25.0 - 49.9	< 25.0
HE2	Hgb	≥ LLN	10.0 - < LLN	8.0 - 9.9	6.5 - 7.9	< 6.5
HE3	Granulocytes/ Bands	≥ 2.0	1.5 - 1.9	1.0 - 1.4	0.5 - 0.9	< 0.5
HE4	Lymphocytes	≥ 2.0	1.5 - 1.9	1.0 - 1.4	0.5 - 0.9	< 0.5
HE9	Hematologic- Other (specify)		mild	moderate	severe	life-threatening
	CARDIAC					
CA0	Cardiac- Dysrhythmia	none	asymptomatic, transient requiring no therapy	recurrent or persistent, no therapy required	requires treatment	requires monitoring; or hypotension or ventricular tachycardia, or fibrillation
CA1	Cardiac- EF/CHF	none	asymptomatic, decline of resting ejection fraction by ≤ 20% of baseline value	asymptomatic, decline of resting ejection fraction by > 20% of baseline value	mild CHF, responsive to therapy	severe or refractory CHF
CA2	Cardiac- Ischemia	none	non-specific T-wave flattening	asymptomatic, ST and T wave changes suggesting ischemia	angina without evidence for infarction	acute myocardial infarction
CA3	Cardiac- Pericardial	none	asymptomatic effusion, no intervention required	pericarditis (rub, chest pain, ECG changes)	symptomatic effusion; drainage required	tamponade; drainage urgently required
CA9	Cardiac- Other (specify)		mild	moderate	severe	life-threatening
	CIRCULATORY					
CI0	Hypertension	none or no change	asymptomatic, transient increase by > 20mm Hg (D) or to > 150/100 if previously WNL. No treatment required	recurrent or persistent increase by > 20mm Hg (D) or to > 150/100 if previously WNL. No treatment required	requires therapy	hypertensive crisis
CI1	Hypotension	none or no change	changes requiring no therapy (including transient orthostatic hypotension)	requires fluid replacement or other therapy but not hospitalization; or syncope	requires therapy and hospitalization; resolves within 48 hrs of stopping the agent	requires therapy and hospitalization for > 48 hrs after stopping the agent, or shock

Codes	Toxicity	GRADE 0	1	2	3	4
CI2	Phlebitis/ Thrombosis/ Embolism	none		superficial phlebitis (not local)	Deep vein thrombosis	major event (cerebral, hepatic, pulmonary, other infarction) or pulmonary embolism
CI3	Edema	none	1+ or dependent in evening only	2+ or dependent throughout day	3+	4+, generalized anasarca
CI4	Veno-Occlusive Disease	none			yes	
CI9	Circulatory Other (specify)		mild	moderate	severe	life-threatening
	CLOTTING					
CL0	Fibrinogen	≥ LLN	0.99 - 0.75 x LLN	0.74 - 0.50 x LLN	0.49 - 0.25 x LLN	≤ 0.24 x LLN
CL1	Prothrombin Time	≤ ULN	1.01 - 1.25 x ULN	1.26 - 1.50 x ULN	1.51 - 2.00 x ULN	> 2.00 x ULN
CL2	Partial Thromboplastin Time	≤ ULN	1.01 - 1.66 x ULN	1.67 - 2.33 x ULN	2.34 - 3.00 x ULN	> 3.00 x ULN
CL9	Clotting - Other (specify)		mild	moderate	severe	life-threatening
	DERMATOLOGIC					
SK0	Local	none	pain, erythema or itching	pain and swelling, with inflammation or phlebitis	ulceration or necrosis	plastic surgery indicated
SK1	Skin Rash/Urticaria	none	asymptomatic scattered macular or papular eruption (also code Skin Ulceration or Skin Necrosis if applicable)	scattered eruption with pruritus or other symptoms	generalized symptomatic eruption	exfoliative dermatitis
DE6	Pruritus	none	mild and localized; relieved spontaneously or by local measures	intense or widespread; relieved spontaneously or by systemic measures	intense or widespread; incompletely relieved any measure	
SK2	Blistering	none	asymptomatic eruption	limited eruption, symptomatic (also code Desquamation, Skin Ulceration or Skin Necrosis if applicable)	generalized symptomatic eruption	
SK3	Erythema	none	asymptomatic	erythema with pruritus or tenderness		
SK4	Erythema in RT Field	(same definition as Erythema)				
SK5	Desquamation	normal	peeling, dry desquamation	patchy moist desquamation (also code Skin Ulceration or Skin Necrosis if applicable)	confluent moist desquamation other than skin folds	
SK6	Desquamation in RT Field	(same definition as Desquamation)				
SK7	Skin Necrosis (non-local)	none				yes
SK8	Skin Ulceration (non-local)	none				yes but ≤ 2 weeks
SK9	Chronic Skin Change	none		telangiectatic changes or atrophy	fibrosis, contractures or scarring	non-healing ulcers > 2 weeks
DE0	Pigmentation Changes	none	mild	pronounced		
DE1	Photosensitivity	normal		yes (also code Erythema, Blistering or Desquamation if applicable)		
DE2	Dry Skin	normal	controlled with emollients	not controlled with emollients		
DE3	Hand-foot Syndrome	no	-	yes (also grade appropriate dermatologic phenomena)		
DE4	Granuloma	no	-	yes (also grade Pain if it applies)		

Codes	Toxicity	GRADE 0	1	2	3	4
DE5	Skin Yellowing	none	present on close exam	prominent (seen at a distance)		
DE9	Dermatologic- Other (specify)		mild	moderate	severe	life-threatening
	ENDOCRINE					
EN0	Impotence/ Libido	normal	decrease in normal function		absence of function	
EN1	Sterility				yes	
EN2	Gynecomastia	normal	mild	pronounced or painful		
EN3	Hot flashes	none	mild or < 1/day	moderate and ≥ 1/day	frequent and interferes with normal function	
EN4	Menses: At time off study, did pt. experience -	normal menses throughout	occasionally irregular or lengthened interval, but continuing	very irregular, but continuing	amenorrhea, no menses for at least 6 mo	
EN5	Cushingoid	normal	mild	pronounced		
EN6	Erectile Impotence	nothing wrong	mild (erections impaired but satisfactory)	moderate (erections impaired, unsatisfactory for intercourse)	severe (no erections)	
EN9	Endocrine- Other (specify)		mild	moderate	severe	life-threatening
	EYE					
EY0	Conjunc-tivitis/ Keratitis	none	erythema or chemosis not requiring steroids or antibiotics	requires treatment with steroids or antibiotics (also code Vision if applicable)	corneal ulceration or visible opacification	
EY1	Dry eye	normal		requires artificial tears		requires enucleation
EY2	Glaucoma	no change			yes	
EY9	Eye- Other (specify)		mild	moderate	severe	life-threatening
	FLU-LIKE SYMPTOMS					
FL0	Fever in Absence of Infection	none	37.1 - 38.0°C 98.7 - 100.4°F	38.1 - 40.0°C 100.5 - 104.0°F	> 40.0°C > 104.0°F for less than 24 hours	> 40.0° C (104.0°F) for more than 24 hours or fever accompanied by hypotension
FL1	Chills	none	mild or brief	pronounced and prolonged		
FL2	Myalgia/ Arthralgia	normal	mild	decrease in ability to move	disabled	
FL3	Sweats	normal	mild and occasional	frequent or drenching		
FL4	Facial Flushing	normal	yes			
FL9	Other Flu-Like Symptoms (specify)		mild	moderate	severe	life-threatening
	GASTROINTESTINAL					
GI0	Nausea	none	able to eat reasonable intake	intake significantly decreased but can eat	no significant intake	
GI1	Vomiting	none	1 episode in 24 hrs	2 - 5 episodes in 24 hrs	6 - 10 episodes in 24 hrs	> 10 episodes in 24 hrs or re-quiring parent-eral support
GI2	Diarrhea	none	increase of 2 - 3 stools/day over pretreatment	increase of 4 - 6 stools/day, or nocturnal stools or mod-erate cramping	increase of 7 - 9 stools/ day, or incon-tinence, or severe cramping	increase of ≥ 10 stools/ day, grossly bloody diarrhea or need for parenteral support

		GRADE				
Codes	Toxicity	0	1	2	3	4
GI3	Constipation	none	stool softener required	laxatives required	obstipation with enema, manual or surgical evacuation required	
GI4	Ileus	no			yes, < 96 hrs	yes, ≥ 96 hrs
GI8	Anal Incontinence	no	resolves without treatment (< 1 wk); self-limited illness	controlled by diet or generic antidiarrheal	medically uncontrollable or controlled by surgery	
GI5	Gastritis/ Ulcer	no	antacid	requires vigorous medical management or non-surgical treatment	uncontrolled by medical management; requires surgery for GI ulceration	perforation or bleeding
GA0	Pancreatitis	no			inflammatory response confined to pancreas; self-limited illness	shock; pancreatic hemorrhage or necrosis; chronic illness
GI6	Small Bowel Obstruction	no		intermittent, no intervention	requires intervention	requires operation
GI7	Intestinal Fistula	no			yes	
GI9	GI - Other (specify)		mild	moderate	severe	life-threatening
	HEMORRHAGE					
HM0	Hemorrhage (clinical)	none	mild, no transfusion	gross, 1-2 units transfusion per episode	gross, 3-4 units transfusion per episode	massive, > 4 units transfusion per episode
HM2	Epistaxis	none	self-limited, controlled by conservative measures		cauterization, artery ligation or packing of posterior nasal cavity; requires hospitalization	
HM1	Rectal Bleeding	none		intermittent, no steroids	requires steroids	requires transfusion (code hemorrhage also)
HM3	Vaginal bleeding	normal	prolonged, increased frequency or profuse but self-limited; no or minimal local tx required	medical therapy required	uterine curettage	requires transfusion (code hemorrhage also)
	IMMUNOLOGICAL					
IM0	Allergy (also code rash if it applies)	none	transient rash, drug fever < 38° C, 100.4°F	urticaria, drug fever ≥ 38° C, 100.4°F, mild bronchospasm	serum sickness, bronchospasm, requires parenteral meds	anaphylaxis
IM1	Immunosensitivity Reaction	none	(definitions will be agent specific)			
IM2	Acute GVHD	none	I	II	III	IV
IM9	Immuno - Other (specify)		mild	moderate	severe	life-threatening
	INFECTION					
IN0	Other Infection (specify site)	none	no active treatment (e.g., viral syndromes)	PO antibiotics	IV antibiotic or antifungal or hospitalization	life-threatening e.g., septic shock
IN1	Respiratory Infection	(Same definitions as Other Infection)				
IN2	Urinary tract Infection	(Same definitions as Other Infection)				

Codes	Toxicity	GRADE 0	1	2	3	4
IN3	Wound Infection	no		PO antibiotics	IV antibiotic or antifungal or surgical intervention	life-threatening e.g., septic shock
IN5	Infection at Catheter Site	no		Local care and PO antibiotics; local infection	Febrile illness; IV antibiotic or antifungal or surgical intervention	life-threatening e.g., septic shock
IN4	Abscess	no		yes		
		(also code Infection if it applies)				
	LIVER					
LI0	Bilirubin	≤ ULN		< 1.5 x ULN	1.5 - 3.0 x ULN	> 3.0 x ULN
LI1	Transaminase (SGOT,SGPT)	≤ ULN	≤2.5 x ULN	2.6 - 5.0 x ULN	5.1 - 20.0 x ULN	> 20.0 x ULN
LI2	Alk Phos or 5' nucleotidase	≤ ULN	≤ 2.5 x ULN	2.6 - 5.0 x ULN	5.1 - 20.0 x ULN	> 20.0 x ULN
LI3	Liver - Clinical	no change from baseline			precoma	hepatic coma
LI9	Liver - Other (specify)		mild	moderate	severe	life-threatening
	LUNG					
LU0	Dyspnea	no change		SOB on significant exertion	dyspnea at normal level of activity	dyspnea at rest
LU1	p02/pCO2	no change or p02 > 85 and pCO2 ≤ 40	p02 > 70 and pC02 ≤ 50, but not Grade 0	p02 > 60 and pCO2 ≤ 60, but not Grade 0-1	p02 > 50 and pCO2 ≤ 70, but not Grade 0 - 2	p02 ≤ 50 or pCO2 > 70
LU2	CO Diffusion Capacity	> 90% of pretreatment value	decrease to 76 - 90% of pretreatment	decrease to 51 - 75% of pretreatment	decrease to 26 - 50% of pretreatment	decrease to ≤ 25% of pretreatment
LU3	Pulmonary Fibrosis	normal	radiographic changes, no symptoms		changes with symptoms (also code symptoms)	
LU4	Pulmonary Edema	none			radiographic changes and diuretics required	requires intubation
LU5	Pneumonitis (non-infectious)/ Pulmonary Effusions/ Infiltrates	normal	radiographic changes, symptoms do not require steroids	steroids required or tap of effusion	oxygen required	requires assisted ventilation
LU6	Cough	no change	mild, relieved by OTC meds	requires narcotic antitussive	uncontrolled coughing spasms	
LU9	Lung -Other (specify)		mild	moderate	severe	life-threatening
	METABOLIC					
ME0	Hyponatremia	no change or > 135	131-135	126-130	121-125 (also code any CNS toxicities which apply)	≤ 120
ME1	Hypokalemia	no change or > 3.5	3.1-3.5	2.6-3.0	2.1-2.5 (also code Cardiac if applicable)	≤ 2.0
ME2	Hyperglycemia	< 116	116-160	161-250	251-500	> 500 or ketoacidosis
ME3	Hypoglycemia	> 64	55-64	40-54	30-39	< 30
ME4	Amylase	≤ ULN	< 1.5 x ULN	1.5-2.0 x ULN	2.1-5.0 x ULN	> 5.0 x ULN
ME5	Hypercalcemia	< 10.6	10.6-11.5	11.6-12.5	12.6-13.5	> 13.5
ME6	Hypocalcemia	> 8.4	8.4-7.8	7.7-7.0	6.9-6.1	≤ 6.0
ME7	Hypomagnesemia	> 1.4	1.4-1.2	1.1-0.9	0.8-0.6	≤ 0.5
ME8	Hypothyroidism	no	TSH elevated, asymptomatic, no therapy given	Symptomatic; thyroid hormone replacement therapy given	Patient hospitalized for manifestations of hypothyroidism	Myxedema coma
ME9	Metabolic- Other (Specify)		mild	moderate	severe	life-threatening

Codes	Toxicity	GRADE 0	1	2	3	4
	MUCOSAL					
MU0	Stomatitis	none	painless ulcers, erythema or mild soreness	painful erythema, edema, or ulcers, but can eat solids	painful erythema edema, or ulcers and cannot eat solids	requires parenteral or enteral support
MU1	Pharynx/ Esophagitis	none	painless ulcers, erythema, mild soreness or mild dysphagia	painful erythema, edema, or ulcers or moderate dysphagia but can eat solids	cannot eat solids	requires parenteral or enteral support or complete obstruction or perforation
MU2	Vaginitis	none	(same definition as Other Mucositis)			
MU3	Pseudomembranes	none			yes	
MU9	Other Mucositis (specify site)	none	erythema, or mild pain not requiring treatment	patchy & produces serosanguinous discharge or requires non-narcotic for pain	confluent fibrinous mucositis or requires narcotic for pain or ulceration	necrosis
	NEUROLOGIC/NEUROCENTRAL					
NC0	Disorientation	normal	confusion or disorientation, easily reoriented, some change in activity	confusion or disorientation requiring supervision	confusion or disorientation requiring institutionalization; or hallucinations	
NC1	Somnolence/ Agitation	normal	somnolence or agitation, non-disabling change in activity	somnolence or agitation, requires care-giver	somnolence or agitation, requires institutionalization	coma
NC2	Personality Change	no change	change, not disruptive to pt or family	disruptive to pt or family	harmful to others or self	psychosis
NC3	Convulsions	normal	focal seizure without impairment of consciousness	focal seizure with impairment of consciousness	generalized seizure, tonic-clonic or absence attack	seizure with loss of consciousness > 10 min
NC4	Malaise/ Fatigue/Lethargy	none	mild, able to continue normal activities	change in normal daily activity	in bed or chair > 50% of waking hrs	
NC5	Anxiety/ Depression	normal	mild, able to continue normal activities	change in normal activity	unable to function	suicidal
NC6	Cerebral Necrosis	none				present
NC8	Neurocortical - Other (specify)		mild	moderate	severe	life-threatening
NC9	CNS - Other (specify)		mild	moderate	severe	life-threatening
	NEUROMOTOR					
NM0	Weakness	none or no change	subjective weakness; no objective findings	mild objective weakness without significant impairment of function	objective weakness with impairment of function	paralysis
NM1	Incoordination/ Ataxia	normal	slight incoordination, dysdiadokinesis	intention tremor, dysmetria, nystagmus	locomotor ataxia	
NM2	Speech Impairment	normal		slurred speech	expressive aphasia or severe difficulty communicating	mute
NM3	Cerebellar Necrosis	no				present
NM8	Neurocerebellar - Other (specify)		mild	moderate	severe	life-threatening
NM9	Neuromotor Other (specify)		mild	moderate	severe	life-threatening

Codes	Toxicity	GRADE 0	1	2	3	4
	NEUROSENSORY					
NS0	Paresthesia	normal	mild paresthesia	moderate paresthesia, non-disabling	disabling paresthesia (interferes with function)	
NS1	Numbness/ Other PNS	normal		non-disabling objective sensory loss	disabling objective sensory loss	
NS2	Reflexes	normal	diminished reflexes	loss of deep tendon reflexes		
NS3	Hearing	none or no change	asymptomatic, hearing loss on audiometry only	tinnitus	hearing loss interfering with function but correctable with hearing aid	deafness not correct-able
NS4	Vision	none or no change		nyctalopia with normal vision in normal light	symptomatic subtotal loss of vision or blurred vision in normal light	blindness
NS5	Taste	normal	slightly altered taste metallic taste	markedly altered taste		
NS9	Neurosensory - Other (specify)		mild	moderate	severe	life-threatening
	NEURO - OTHER					
NR0	Headache	none	mild	moderate, or severe but transient	unrelenting and severe	
NR1	Dizziness/Vertigo	none	non-disabling		disabling	
NR2	Insomnia	normal	occasional difficulty sleeping, may require sleeping pills		difficulty sleeping despite medication	
NR3	Restlessness	normal		requires sedation		
NR4	Arachnoiditis	no			yes (also code symptoms)	
NR9	Neuro - Other (specify)		mild	moderate	severe	life-threatening
	PAIN					
PA0	Other Pain (specify site)	normal	non-narcotics	oral narcotics	parenteral narcotics	uncontroll-able
PA1	Bone Pain		(Same definitions as Other Pain)			
PA2	Tumor Flare (also code Hypercalcemia if it applies)	none	pain requiring non-narcotic or redness or increase in tumor size	(Grade 2 - 5 same definitions as Other Pain)		
PA3	Abdominal Pain		(Same definitions as Other Pain)			
	RENAL/BLADDER					
BL0	Incontinence	normal	with coughing, sneezing, etc.	spontaneous, some control	no control	
BL1	Dysuria	none	mild pain	painful or burning urination, controlled by pyridium	not controlled by pyridium	
BL2	Urinary Retention	none	urinary residual > 100cc or occa-sionally requires catheter or diffi-culty initiating urinary stream	self catheterization always required for voiding	surgical procedure required (TUR or dilatation)	
BL3	Increased Frequency/ Urgency	no change	increase in frequ-ency or nocturia up to 2x normal	increase > 2x normal, but < hourly	with urgency and hourly or more, or requires catheter	
BL4	Hemorrhagic Cystitis	none	blood on microscopic exam	frank blood, no treatment required	bladder irrigation required	requires cystec-tomy or transfu-sion (also code hemorrhage)

Codes	Toxicity	GRADE 0	1	2	3	4
BL5	Bladder Cramps	none		yes (Code pain if applicable)		
BL9	Bladder - Other (specify)		mild	moderate	severe	life-threatening
RE0	Creatinine	≤ ULN	< 1.5 x ULN	1.5 - 3.0 x ULN	3.1 - 6.0 x ULN	> 6.0 x ULN
RE1	Proteinuria	no change	1+ or < 0.3 g% or < 3 g/l	2 - 3+ or 0.3 - 1.0 g% or 3 - 10 g/l	4+ or > 1.0 g% or > 10 g/l	nephrotic syndrome
RE2	Hematuria	neg	micro only	gross, no clots	gross + clots	requires transfusion (also code hemorrhage)
RE3	Renal failure					dialysis required
RE9	Renal - Other (specify)		mild	moderate	severe	life-threatening
GU0	Ureteral Obstruction	none	unilateral, no surgery required	bilateral, no surgery required	not complete bilateral, but stints, nephrostomy tubes or surgery required	complete bilateral obstruc-tion
GU1	GU Fistula	none			yes	
GU9	GU - Other (specify)		mild	moderate	severe	life-threatening
	MISCELLANEOUS					
M00	Alopecia	no loss	mild hair loss	pronounced or total hair loss		
M01	Weight Gain	< 5.0%	5.0-9.9%	10.0-19.9%	≥ 20.0%	
M02	Weight Loss	< 5.0%	5.0-9.9%	10.0-19.9%	≥ 20.0%	
M03	Laryngitis	normal	mild or intermittent hoarseness	persistent hoarseness, able to vocalize	whispered speech	tracheostomy or intubation
M04	Salivary	normal	mild mouth dryness or slightly thickened saliva	moderate to complete dryness		acute salivary gland necrosis
M05	Anorexia	no	yes (also code Weight Loss if it applies)			
M09	Dehydration	no	dry mucous membranes, diminished skin turgor	requires IV fluid replace-ment (brief)	requires IV fluid replacement (sustained); hospitalization	hypotensive; requires in-tensive care; hemo-dynamic collapse
				(also code applicable cause, if known)		
M07	Wound Dehiscence	no	skin or subcutaneous		fascial	
M08	Wound necrosis	no			yes	
M06	Rectal laceration	no			yes	
M99	Miscellaneous-Other (specify)		mild	moderate	severe	life-threatening

Last Revised 12/94 ds/mb