RTOG 0227, Phase I/II Study of Pre-Irradiation Chemotherapy With Methotrexate, Rituximab, and Temozolomide and Post-Irradiation Temozolomide for Primary Central Nervous System Lymphoma

Study Chair: Jon Glass, M.D., (215) 503-7005; FAX # (215) 893-4873; jon.glass@jefferson.edu

RTOG 0227 was amended as follows:

As mandated by CTEP, CTC version 2.0 reporting requirements were converted to the CTEP Active Version of CTCAE.

Changes were made to the following sections:

- Section 6.5.1
- Section 6.5.2
- Section 7.8.1

Other changes

Section 3.1.6 and Eligibility Checklist question 16: Age ≥ 18 was added because it was inadvertently omitted.

Appendix I/Sample Consent: What Is Involved in the Study, last paragraph, second sentence and How Long Will I Be in the Study, first paragraph, last sentence: "Annually for five years was corrected to annually."
SUMMARY OF CHANGES
Amendment #6, Version Date: February 14, 2008
(Broadcast Date: February 28, 2008)

RTOG 0227, Phase I/II Study of Pre-Irradiation Chemotherapy With Methotrexate, Rituximab, and Temozolomide and Post-Irradiation Temozolomide for Primary Central Nervous System Lymphoma

Study Chair: Jon Glass, M.D., (215) 503-7005; FAX # (215) 893-4873; jon.glass@jefferson.edu

RTOG 0227 was amended as follows:

Title Page: The contact information for Dr. Glass was revised.

Section 7.4.6: The contact information for I.V. Solutions was updated.

Section 10: The information in this section pertaining to the RTOG Tissue Bank was updated to reflect its relocation to the University of California San Francisco. The new address for the RTOG Biospecimen Resource is included in Section 10.3.2.
RTOG 0227, Phase I/II Study of Pre-Irradiation Chemotherapy With Methotrexate, Rituximab, and Temozolomide and Post-Irradiation Temozolomide for Primary Central Nervous System Lymphoma

Study Chair: Jon Glass, M.D., (215) 728-3070; FAX # (215) 214-4015; Jon.Glass@fccc.edu

RTOG 0227 has been amended as follows:

NEUROIMAGING
Neuroimaging was revised to include head CT scans if MRIs are not feasible. Changes were made to the following sections:

- **Section 4.2.1:** "or head CT with and without contrast" was added parenthetically.
- **Section 7.7.3:** In the second sentence, "or head CT scan" was added parenthetically.
- **Section 11.1:** In the "Assessments" column, seventh row, "or head CT" was added parenthetically.
- **Section 11.2.1:** The second sentence was added.
- **Section 11.2.3.1:** The last three sentences were added.
- **Section 11.2.3.2:** In the first sentence, "or head CT scans" was added parenthetically and "if there has been tumor debulking or if there has been a greater than 4-week interval between the first scan and the date of enrollment" was added. In cases in which there has been a biopsy and less than a four-week interval between the pre-operative MRI or CT scan, the pre-operative MRI may be used as the baseline pre-treatment MRI.
- **Sections 11.2.3.3 and 11.2.3.4:** "MRIs" was changed to "neuroimaging."

Appendix I/What Is Involved in the Study?
Under "If you take part in this study, you will have the following tests and procedures," "or CT scan of your head" was added parenthetically to the third and second-to-last bullets, to the second sentence of the second-to-last paragraph, and to the last sentence of the last paragraph.

TIMING OF PRE-TREATMENT ASSESSMENTS
Pre-treatment assessments were revised from one week to four weeks prior to the first treatment cycle for the following assessments:

- MRI of the brain with and without gadolinium,
- screening for HBV infections and documentation of HBV vaccination history,
- slit lamp examination,
- CSF for cytology,
- pulmonary function testing in patients with known pulmonary or bronchospastic disease.

The timing for the pre-treatment MRI was changed because an MRI within four weeks of the initiation of chemotherapy follows the general guidelines for glioma trials. The timing for HBV screening, slit lamp examinations, CSF, and pulmonary function was changed because these tests may be difficult to schedule within a one-week time frame and are not expected to change substantially between the time of diagnosis and the time of treatment start. Changes were made to the following sections:

- **Sections 4.0-4.2.6:** The entire section was restructured
- **Section 11.1:** Footnotes were changed as follows:
  - Row 1: Dagger reference deleted
  - Rows 2-6, 12, 13: Dagger reference added pre-study
  - Rows 7-11: Double dagger reference added pre-study
  - Row 7: Reference to footnote k added
  - Dagger footnote: "First" added immediately before "treatment cycle"
  - Double dagger footnote: Added
  - Footnote k: Added

**OTHER CHANGES**

**Section 4.2.1.1:** Added because unless there has been tumor debulking, a post-operative MRI is not necessary for treatment initiation

**Section 7.1.4:** The timing requirement for the initiation of prophylactic antibiotics was changed from "no later than five days prior to the initiation of rituximab" to "at the time of the initiation of rituximab" because it is not necessary to start these medications five days prior to chemotherapy

**Section 7.7.2:** In the first sentence, formatting of "mm³" was corrected.

**Section 11.1:** Row 3: The timing for CBC was switched from weekly during TMZ to every 4 weeks during TMZ, and footnote j was added. These modifications were made because there is no medical necessity to perform weekly CBCs during monthly temozolomide treatment. Testing in the third and fourth weeks, with a change to monthly CBCs provided there are no toxicities, reflects the general standard for temozolomide use with malignant gliomas.
SUMMARY OF CHANGES
Amendment #4, Version Date: May 31, 2006

RTOG 0227, Phase I/II Study of Pre-Irradiation Chemotherapy With Methotrexate, Rituximab, and Temozolomide and Post-Irradiation Temozolomide for Primary Central Nervous System Lymphoma Study Chair: Jon Glass, M.D., (215) 728-3070; FAX # (215) 214-4015; Jon.Glass@fccc.edu

The phase I portion of RTOG 0227 recently established a temozolomide MTD of 100 mg/m². The phase II portion of this study opened on 2/24/06, with temozolomide administered at that dose. The following sections of the protocol have been amended to reflect this information:

- **Schema:** "100 mg/m²" was added after the description of Arm 4.
- **Section 7.1.3:** The last sentence was added.
- **Appendix IA/Sample Consent:**
  - Introductory section: The last paragraph was added.
  - "What Is Involved in This Study?," second paragraph: The last two sentences were added.

**Other Changes**

**Section 7.8:** RTOG's AE reporting language has been revised to reflect that sites should report AEs and SAEs via AdEERS and that they should not call RTOG Headquarters to report this information. As a result, the following changes were made:

- **Section 7.8.2:** Heading/first paragraph: Information for RTOG's AE phone line was deleted.
- **Section 7.8.3:**
  - Heading/first paragraph: Information for RTOG's SAE phone line was deleted. Instructions were added to report via AdEERS and to contact the CTEP Help Desk for assistance.
  - Second paragraph: All but the last line was deleted.
  - Third paragraph: Instructions to report via the RTOG phone line were deleted and instructions to report via AdEERS were added.

**Section 10.3.2:** Contact information was updated for information for LDS Hospital.

**Section 11.1:** Footnotes for post-treatment slit lamp and CSF evaluations were modified to clarify that these evaluations are needed only at the time of recurrence. As a result, the following changes were made:

- First row, last column: The superscript "h" and "or death" were deleted.
- Slit-lamp and CSF rows, last column: "X^m" was changed to "X^{h,m}".
- Hepatitis B screening row: All instances of "X^i" were changed to "X^i".
- Footnotes: Footnote h from the previous version has been deleted, and footnote i from the previous version is the new footnote h. Footnote j from the previous version is the new footnote i. Footnote j has been deleted.

An updated protocol is available (no password required) on the RTOG website: 
www.rtog.org
RTOG 0227, Phase I/II Study of Pre-Irradiation Chemotherapy With Methotrexate, Rituximab, and Temozolomide and Post-Irradiation Temozolomide for Primary Central Nervous System Lymphoma Study Chair: Jon Glass, M.D., (215) 728-3070; FAX # (215) 214-4015; Jon.Glass@fccc.edu

RTOG 0227 has been updated as follows:

Section 7.1.4: In the first bullet point, (1) the spelling of "sulfamethoxazole" was corrected and (2) the dose of trimethoprim/sulfamethoxazole was corrected to "160 mg/800 mg" from "160 mg/180 mg."

NOTE: This is an editorial/administrative change to the protocol. NCI now requires that these changes be documented on the protocol title page with the date of the update noted as "Update Date". An updated protocol is available on the RTOG website: www.rtog.org
SUMMARY OF CHANGES
Amendment #3, Version Date: August 18, 2005

RTOG 0227, Phase I/II Study of Pre-Irradiation Chemotherapy With Methotrexate, Rituximab, and Temozolomide and Post-Irradiation Temozolomide for Primary Central Nervous System Lymphoma

Study Chair: Jon Glass, M.D., (215) 728-3070; FAX # (215) 214-4015; Jon.Glass@fccc.edu

RTOG 0227 has been amended to exclude active hepatitis B, change the slit lamp exam and CSF time frames, and incorporate the revised NCI AE Reporting Guidelines as follows:

Schema: “no active hepatitis B” was added to the Eligibility list for consistency with the addition of Section 3.2.9 excluding patients with active hepatitis B.

Eligibility Checklist: Question # 15 was added for consistency with Section 3.2.9.

Section 4.4: This section was rewritten as: “Screening for hepatitis B virus (HBV) infections and documentation of HBV vaccination history.”

Section 5.1: This section was amended for clarity and consistency with the revised Study Agent Shipment Form.

Section 5.2: The website for the Human Subject Training was updated.

Section 6.5.1: The words “reported and” were deleted for consistency with the revised NCI AE reporting guidelines.

Section 6.5.4: This section was deleted and replaced with: “See Section 7.8 for AdEERS Adverse Event Reporting.” Sections 6.5.5 and 6.5.6 were deleted. These changes were for consistency with the revised NCI AE reporting guidelines.

Section 7.4.1: In the third sentence, “Investigator Brochure” was replaced with “package insert.”

Section 7.4.6: In the second paragraph, the third sentence was rewritten for consistency with Appendix V. In the third paragraph, in the first sentence, “temozolomide” replaced “patient-specific drug supply” and “registered” replaced “randomized”; the third sentence “Canadian shipments may require additional time” replaced “For Canadian shipments, allow 7-10 days lead time” for clarity.

Section 7.8: The heading was changed to “Adverse Events.”
Section 7.8.1: In the first paragraph, CDUS version 2 was updated to version 3. Two new paragraphs were added to the end of the section.

Sections 7.8.2 through 7.8.4: These sections were replaced with the revised NCI AE reporting guidelines text.

Section 7.9: This section on AdEERs expedited reporting was added as required per the revised NCI AE reporting guidelines.

Section 11.1: Under Study Parameters:

• The slit lamp exam and CSF were deleted for the timeframes Week 10 of Tx, Week 13, and Every two months during TMZ.
• Hepatitis B screening was added for the timeframes Every two weeks during Pre-RT chemo, Week 13, and Every two months during TMZ.
• Footnote “j” referring to the hepatitis B screening was revised as: “Any patient with a previous history of hepatitis B or abnormalities on screening in the absence of previous vaccination will need to have re-screening done at the 4-week mark, pre- and post-RT, and every 2 months for a total of 1 year from receiving rituximab.”

Consent: Under “What Is Involved In The Study,” the following text was deleted for consistency with the changes made to the protocol text:

• under “Then periodically during treatment, you will have,” bullets # 4 and 5 for the slit lamp and lumbar puncture were deleted;
• in the second to last paragraph, the text “will be performed prior to beginning treatment with temozolomide, at the completion of treatment with temozolomide, and” was delete;
• in the last paragraph, “a slit lamp examination, and a lumbar puncture” was deleted.

• Under “What Are The Costs,” a new second paragraph was added.

Appendix V: The Study Agent Shipment Form was revised for clarity.
SUMMARY OF CHANGES
Update Date: April 13, 2005

RTOG 0227, Phase I/II Study of Pre-Irradiation Chemotherapy With Methotrexate, Rituximab, and Temozolomide and Post-Irradiation Temozolomide for Primary Central Nervous System Lymphoma Study Chair: Jon Glass, M.D., (215) 728-3070; FAX # (215) 214-4015; Jon.Glass@fccc.edu

RTOG 0227 has been updated as follows:

Appendix V – CTSU’s fax number corrected to read 215-569-0206.

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

An updated protocol is available (no password required) on the RTOG website: www.rtog.org
RTOG 0227, Phase I/II Study of Pre-Irradiation Chemotherapy With Methotrexate, Rituximab, and Temozolomide and Post-Irradiation Temozolomide for Primary Central Nervous System Lymphoma

Study Chair: Jon Glass, M.D., (215) 728-3070; FAX # (215) 214-4015; Jon.Glass@fccc.edu

RTOG 0227 has been updated as follows:

Index – Added: Appendix V, Study Agent Shipment Form, due to the addition of this appendix.

Appendix V – Added, due to change in temozolomide supply information per Amendment #2.
SUMMARY OF CHANGES
Amendment #2, Version Date: December 14, 2004

RTOG 0227, Phase I/II Study of Pre-Irradiation Chemotherapy With Methotrexate, Rituximab, and Temozolomide and Post-Irradiation Temozolomide for Primary Central Nervous System Lymphoma

Study Chair: Jon Glass, M.D., (215) 728-3070; FAX # (215) 214-4015; Jon.Glass@fccc.edu

RTOG 0227 has been amended as follows:

Title page – Updated: (1) Dr. Glass’s contact information; (2) Dr. Schultz’s email address.

Index – Added: Appendix IV, Sample Methotrexate Orders, due to the addition of this appendix.

Section 5.1 – Updated: Registration procedures were updated to reflect mandatory web-based registration.

Section 6.5.5 – Amended because non-standard fractionated radiation therapy is not applicable to this protocol.

- Deleted: First paragraph/first sentence, “non-standard fractionated radiation therapy.”
- Changed: Second paragraph/first sentence, “standard fractionated radiation therapy” to “whole brain radiation therapy.”
- Deleted: “Standard fractionated radiotherapy is defined as 1.8 – 2.0 Gy once daily radiation to a dose of 70.2 Gy or less, including 2D and 3D conformal radiotherapy. Non-standard fractionated radiation therapy is treatment administered using brachytherapy, radiopharmaceuticals, high LET radiation, radiosurgery, intensity modulated radiation therapy (IMRT) and conventional radiotherapy with fraction size or total dose not within the parameters specified above.”

Section 7.1.2 – Added: “Sample orders are detailed in Appendix IV” due to the addition of this appendix.

Section 7.4.5 – Renumbered: This section was previously misnumbered 7.4.4.

Section 7.4.6

- Renumbered: This section was previously misnumbered 7.4.5.
• Changed: Temozolomide supply information, to reflect that temozolomide is now being supplied by the manufacturer and can be ordered through I.V. Solutions.

Section 7.7.1.2 – Added: “A recurrence of the same toxicity at the lower dose will result in the discontinuation of temozolomide,” due to an omission regarding hematological toxicity as a criterion for determining dose limiting toxicity.

Section 7.8.2.6 – Updated: Mailing address for RTOG Headquarters. The address also was updated in Sections 7.8.4 and 12.0.

Section 10.3.2 – Updated: Email address for LDS Hospital.

Section 11.1
• 6th column heading corrected from “Week 13 (During TMZ)” to “Week 13 (Prior to TMZ)”
• Last column heading changed from “Following Completion of Tx and After” to “Following Completion of Tx and at Time of Recurrence or Death” to make this table consistent with the data submission schedule in Section 12.1
• Reference to footnote “i” deleted from last column of “MRI brain” row due to a change in the meaning of footnote “i” (see below)
• Reference to footnote “i” added to last column of “Slit-lamp for examination” and “CSF for cytology” rows due to a change in the meaning of footnote “i” (see below)
• Reference to footnote “h” deleted from last column of “MMSE” and “Spitzer QOL Assessment” rows due to a change of column heading (see bullet 2 above)
• Footnote “i” changed from “MRI done at time of recurrence during follow-up period” to “Slit-lamp examination and lumbar puncture performed at time of recurrence” to reduce the number of CSF evaluations per reconsideration of study chairs

Section 13.2.1 – Added to end of second sentence: “or any hematological toxicity resulting in the discontinuation of temozolomide as defined in Section 7.7.1.2,” due to an omission regarding hematological toxicity as a criterion for determining dose limiting toxicity.

Section 13.4 – Section changed to: “Based on RTOG accrual to 93-10, patient accrual is expected to be 1.8 cases per month. At this rate, it will take 29 months to accrue the required 52 cases. If the average monthly accrual rate is consistently less than 1 patient, the study will be re-evaluated with respect to feasibility.” Changed for increased accuracy and because the expected accrual for this trial was incorrectly computed from the total accrual rate to RTOG 93-10, which included SWOG accrual, rather than from the RTOG contribution to the accrual rate, which was 1.8 cases per month.

Section 13.6 – Changed: Number of not Hispanic or Latino males from 24 to 34 and total number of males in ethnic category from 25 to 35, due to miscalculations.
Appendix IA/What is Involved in the Study?

- Changed: First paragraph, second sentence rewritten to indicate that hospitalization is strongly suggested but not mandatory during methotrexate administration.
- Changed: Second to last paragraph, second sentence rewritten for consistency with changes made to section 11.1. The applicable portion of this paragraph now states: “A brain MRI will be performed every two months. A slit lamp examination and a lumbar puncture will be performed prior to beginning treatment with temozolomide, at the completion of treatment with temozolomide, and may also be performed if the tumor begins to grow again.”

Appendix IA/What Are the Risks of the Study?

Due to an overstatement of risks and for consistency with Section 6.5

- Changed: Risks Associated With Brain Irradiation to Risks Associated With Whole Brain Radiation
- Deleted from Very Likely: (1) Dry mouth or altered taste; (2) Headaches; (3) Weakness; (4) Seizure
- Deleted from Less Likely: (1) Fever, chills, or heavy sweating
- Added to Less Likely: (1) “possible” immediately before “vomiting”; (2) General weakness; (3) Dry mouth or altered taste; (4) Cataract information, typically several years after radiation treatment; (5) Dry and/or itchy eyes; (6) Middle ear congestion
- Deleted from Less Likely But Serious: (1) Blood clots; (2) Mental slowness; (3) Severe damage to normal brain tissue that may require additional surgery
- Added to Less Likely But Serious: (1) Diminished memory, and/or mental slowing, immediately after “behavioral changes”; (2) Local brain swelling requiring long-term steroid use and/or surgery

Appendix IV – Added, due to requests from treating sites.
RTOG 0227 has been amended as follows, in response to a memo circulated by Dr. Thomas Davis regarding the development of HBV reactivation with fulminant hepatitis and hepatic failure:

Section 4.4. – Added: “Screening of patients at high risk of hepatitis B virus (HBV) infections”; subsequent sections of 4.0 renumbered accordingly.

Section 7.2.3 – Added: “Hepatitis B virus (HBV) reactivation: HBV reactivation with fulminant hepatitis, hepatic failure, and death has been reported in some patients with hematologic malignancies treated with rituximab. The majority of patients received rituximab in combination with chemotherapy. The median time to the diagnosis of hepatitis was approximately four months after the initiation of the rituximab and approximately one month after the last dose.”

Section 7.7.4 – Added: “Carriers of hepatitis B should be closely monitored for clinical and laboratory signs of active HBV infection and for signs of hepatitis throughout their study participation”; subsequent sections of 7.0 renumbered accordingly.

Section 7.7.5 – Added: “Criteria for Treatment Discontinuation: Rituximab should be discontinued in any patient who develops active HBV infection or hepatitis”; subsequent sections of 7.0 renumbered accordingly.

Section 11.1– Added: “Hepatitis B screening” and corresponding footnote j to Pre-Study Assessments.

Appendix IA/Risks Associated with Rituximab– Added: “Additional Risk Information
In people who have ever been infected with hepatitis B virus, there is a risk that the virus can flare up during treatment with drugs that affect your immune system, such as rituximab. This could lead to liver failure or even death. The risk of hepatitis B virus flaring up may continue for several months after you stop taking rituximab. If you become jaundiced (yellowing of the skin and eyes) or develop viral hepatitis while taking rituximab or after stopping treatment, you should tell your study doctor immediately. Your study doctor will discuss this risk with you and explain what testing is recommended to check for hepatitis.”