For **Protocol** Amendment to: RTOG 9813, A Phase III (Phase I Closed) Randomized Study of Radiation Therapy and Temozolomide (IND #60,265) Versus Radiation Therapy and Nitrosourea for Anaplastic Astrocytoma and Mixed Anaplastic Oligoastrocytoma (Astrocytoma Dominant)

NCI/Local Protocol #: RTOG 9813

NCI Protocol Version Date: May 30, 2014 (Broadcast June 9, 2014)

<table>
<thead>
<tr>
<th>Section</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global</td>
<td>Due to the transition to the NCTN, all RTOG terminology was revised to NRG Oncology terminology where applicable and additional references to RTOG have been removed where no longer applicable. Terminology was also adjusted for other NCTN organizations participating in this trial. The protocol was repaginated per current CTEP requirements.</td>
</tr>
<tr>
<td>Title page</td>
<td>Contact information was updated for Drs. Cairncross, Gilbert, Aldape, and Chakravarti. The amendment date was added.</td>
</tr>
<tr>
<td>10.5</td>
<td>Dr. Aldape’s email address was updated.</td>
</tr>
<tr>
<td>13.5.4</td>
<td>Event rates for the primary endpoint are much lower than anticipated for the original trial design. This has substantially extended the anticipated time to completion (which has already been exceeded). Thus, it is prudent to evaluate whether a determination of futility can be made before the requisite total number of events is reached. A futility analysis was therefore added as Section 13.5.4, and subsequent sections were renumbered accordingly.</td>
</tr>
<tr>
<td>Appendix VI</td>
<td>The information in these appendices was deleted because it is no longer needed.</td>
</tr>
<tr>
<td>Appendix VII</td>
<td></td>
</tr>
<tr>
<td>Informed Consent</td>
<td>No changes</td>
</tr>
</tbody>
</table>
For **Protocol Update** to: RTOG 9813, A Phase III (Phase I Closed) Randomized Study of Radiation Therapy and Temozolomide (IND #60,265) Versus Radiation Therapy and Nitrosourea for Anaplastic Astrocytoma and Mixed Anaplastic Oligoastrocytoma (Astrocytoma Dominant)

NCI/Local Protocol #: RTOG 9813

NCI Protocol Version Date: March 24, 2010
Update Date: May 1, 2014 (Broadcast May 1, 2014)

<table>
<thead>
<tr>
<th>Section</th>
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<tbody>
<tr>
<td>Title page</td>
<td>The update date was added.</td>
</tr>
<tr>
<td>7.5 Appendix V Appendix VI</td>
<td>These sections were updated to reflect the conversion to CTEP-AERS for all participating organizations.</td>
</tr>
<tr>
<td>7.6-7.7</td>
<td>These sections were deleted because all participating organizations will report adverse events via CTEP-AERs.</td>
</tr>
<tr>
<td>Informed Consent</td>
<td>No changes</td>
</tr>
</tbody>
</table>
RTOG 9813, A Phase III (Phase I Closed) Randomized Study Of Radiation Therapy And Temozolomide (IND #60,265) Versus Radiation Therapy And Nitrosourea For Anaplastic Astrocytoma and Mixed Anaplastic Oligoastrocytoma (Astrocytoma Dominant) **Study Chair**: Susan M. Chang, M.D., (415) 353-2966; FAX # (415) 353-2167; changs@neurosurg.ucsf.edu

RTOG 9813 has been 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 6.7
- Section 7.5.1
- Section 7.6
- Section 7.8
The statistical analysis plan for RTOG 98-13 was amended as follows:

**Section 1.3:** Three new paragraphs were added to the end of this section, which give the background and overview of the modified statistical analysis plan.

**Section 13.5.3:** This section was rewritten because the interim significance testing was revised.

**Section 13.5.4:** This section was amended because the final significance testing was revised.

**Section 13.5.4.1:** This section was rewritten because the significance level for final testing was revised. There is a new first sentence and the remainder of the original section was deleted.

**Section 13.5.4.2:** The section was revised for clarity.

**Section 13.5.4.3:** The toxicity analyses to be performed were delineated.

**Title page:** The email address for Dr. Chang was corrected.
SUMMARY OF CHANGES
Amendment #7, Version Date: September 26, 2006

RTOG 98-13, A Phase III (Phase I Closed) Randomized Study Of Radiation Therapy And Temozolomide (IND #60,265) Versus Radiation Therapy And Nitrosourea For Anaplastic Astrocytoma and Mixed Anaplastic Oligoastrocytoma (Astrocytoma Dominant)

Study Chair: Susan M. Chang, M.D., (415) 353-2966; FAX # (415) 353-2167; changs@neuro.ucsf.edu

RTOG 98-13 has been amended as follows to allow the use of CCNU as an alternative to BCNU and to allow submission of tissue specimen plugs:

Title Page: In the title of the protocol, "BCNU" was changed to "Nitrosourea" because the study was amended to allow either BCNU or CCNU. This change is reflected in the titles on the schema page, Appendix I (sample consent), and Appendix VII (study agent shipment form). Arnab Chakravarti, M.D was added as the Correlative Biology study chair and his contact information was included on the title page.

Index: Appendix VIII, "Specimen Plug Kit" was added here as it was added to the protocol.

Schema: Under Arm 2, "BCNU" was replaced with "nitrosourea (BCNU or CCNU)" and the dosing regimen for BCNU was deleted. Under Eligibility, "or CCNU" was added to the end of the no pre-existing lung disease exclusion.

Eligibility Checklist: "or CCNU" was added to the end of Question # 5. A new Question # 16 was added to correspond with new Section 3.1.6.

Section 1.3: In the last sentence of the first paragraph, BCNU was changed to nitrosourea. A new second paragraph was added to explain the inclusion of CCNU. In the third paragraph, starting with the fourth sentence and ending with the second to last sentence, new text was added discussing markers to be investigated.

Section 3.1.6: Age ≥18 eligibility was added.

Sections 3.2.12 and 3.2.13: "CCNU" was added to 3.2.12 and "or CCNU" was added to 3.2.13.

Section 5.1: A new sentence was added at the end of the section to clarify tissue submission.

Section 5.5.2: The zip code was corrected to 19013.
Section 7.1: "or CCNU" was added after "BCNU."

Section 7.1.2: Under Arm 2, "BCNU" was changed to "Nitrosourea" in the heading, and "Either BCNU or CCNU is allowed" was added.

Section 7.1.2.2: This is a new Section 7.1.2.2 providing CCNU dosing. The old Section 7.1.2.2 was renumbered as Section 7.1.2.1.1.

Section 7.3.4.2: The cross reference to Section 7.4 was changed to 7.5 due to renumbering of sections.

Section 7.4: New Section 7.4, "CCNU Information" was added. This necessitated the renumbering of old Section 7.4 as Section 7.5 and all subsequent sections through Section 7.8 (old Section 7.7). Cross references to these sections throughout the protocol were renumbered.

Section 9.2: This new section was added to provide pneumocystis carinii prophylaxis. As a result, old Section 9.2 was renumbered as Section 9.3.

Section 10.0: Section 10.0: "It is expected that tissue blocks, plugs, or slides be made available for tissue correlative studies" was added to the beginning of this section to clarify tissue submission.

Section 10.3: The heading "Pre-Randomization" was added for clarity.

Section 10.6.1: The third sentence was changed to: "All materials will be forwarded to the RTOG Tissue Bank for storage except those selected by the neuropathologist for the study files or those explicitly requested to be returned by the submitting institution."

Section 10.7.2: This section was changed to: "Representative paraffin block(s) or plugs for molecular analysis should be submitted for patients who have undergone a resection. If these are not available or the patient has undergone biopsy alone, five to ten representative slides of unstained tumor specimens should be submitted. Information regarding plug kits is located in Appendix VIII. Plug kits are available free of charge by contacting the RTOG Tissue Bank." The contact information for the RTOG Tissue Bank has been included.

Section 10.7.6: The reimbursement was amended to include "and $100 per case for serum."

Section 10.8.1: The last sentence was changed to "All material will be forwarded to the RTOG Tissue Bank for storage except those selected by the neuropathologist for the study files or those explicitly requested to be returned by the submitting institution."

Section 10.8.2: The beginning of this section was amended for consistency with changes made to Section 10.7.2.
Section 10.9.2.1: "or plugs" was added to the third bullet for consistency with other changes to the protocol.

Section 10.9.2.2: The name of the contact at NCCTG was updated in the last paragraph.

Section 11.1: Footnote "f" was revised for clarity: "Every 3 months in year 1; q 6 months in years 2 and 3 and then annually." A new footnote, "h" was added and the superscript under "Follow-up" for "MRI or CT Brain/contrast" was changed from "c" to "h."

Section 13.2.1: In the first and second sentences, BCNU was changed to nitrosourea.

Section 13.2.2: The third sentence was changed to: "These factors along with CDKN2A and methyl guanine methyl transferase (MGMT) methylation, which was found to be of prognostic value in glioblastoma multiforme, will be examined for their association with survival." A new last sentence was added. These changes were made to clarify the molecular analysis.

Section 13.3: A new last sentence was added.

Section 13.5.3: Stopping rules were amended so as to include boundaries for stopping due to futility.

Section 13.5.4: A new sentence was added to the end of this section.

Section 13.5.4.1: BCNU was changed to nitrosourea in the first sentence and a new second paragraph was added.

Section 13.5.4.4: The first sentence was revised for consistency with other changes to the protocol text.

Consent:

- BCNU was changed to nitrosourea throughout the consent for consistency with the changes made to the protocol text.
- Under Description of Procedures: Under Treatment 2, the second sentence was changed to "You will receive nitrosourea as either BCNU by vein or CCNU capsules orally as an outpatient" and a new last sentence was added to incorporate the possible use of CCNU. In the last paragraph of this section, "surgery or" was added to the first sentence; the second to last sentence was rewritten; and a new last sentence was added.
- Under Risks of Nitrosourea: The text was rewritten to incorporate CCNU.
- Under Tissue and Blood Testing: Two new paragraphs were added for clarification. Under Making Your Choice, in the third sentence, "treatment" was changed to "main" and "the" was deleted and "optional future" was added for consistency with changes made to the protocol text.
RTOG 98-13, A Phase I/III Randomized Study Of Radiation Therapy And Temozolomide Versus Radiation Therapy And BCNU For Anaplastic Astrocytoma (IND #60,265)

Study Chair: Susan M. Chang, M.D., (415) 353-2966; FAX # (415) 353-2167; changs@neuro.ucsf.edu

RTOG 98-13 has been updated as follows:

Section 6.0 — For clarity, the statement “Note: Intensity Modulated RT (IMRT) Is Not Allowed” was added to section title.

NOTE: This is an editorial/administrative change to the protocol. NCI now requires that these changes be documented on the protocol title page with the date of the update noted as “Update Date”, not as a revision.

An updated protocol is available (no password required) on the RTOG website: http://www.rtog.org/
RTOG 98-13, A Phase III (Phase I Closed) Randomized Study Of Radiation Therapy And Temozolomide (IND #60,265) Versus Radiation Therapy And BCNU For Anaplastic Astrocytoma and Mixed Anaplastic Oligoastrocytoma (Astrocytoma Dominant)

Study Chair: Susan M. Chang, M.D., (415) 353-2966; FAX # (415) 353-2167; changs@neuro.ucsf.edu

RTOG 98-13 has been amended as follows:

Section 5.5.2 – In the last sentence, the number “5” was changed to “6” to be consistent with information in other areas of the protocol. The sentence now reads: “Therapy should start within 6 weeks after tissue diagnosis.”

Section 7.2.6 – In the third column of the table, all instances of the word “and” were changed to “or.”

Section 7.3.4.1 – In the second-to-last sentence, the number “1400” was changed to “1440” to be consistent with information in other areas of the protocol. The sentence now reads: “It is mandatory that BCNU be stopped at a maximum of 1440 mg/m^2 or 1 full year of therapy.”

Section 7.3.5.3 – In the second column of the table, all instances of the word “and” were changed to “or.”

Section 7.4.2 – The mailing address for RTOG Headquarters was updated. The address also was updated in 7.6, 10.7.6, 12.0, 12.3.3, and Appendix VI.

Section 11.1 – An “X” was added to the Pre-Treatment Evaluation column for PFT and DLCO.

Section 11.2.2 – The word “preferably” was added to the instructions for obtaining a contrast enhanced MRI or CT scan. The sentence now reads: “A contrast enhanced MRI or CT scan must be obtained (preferably within 72 hours after the surgical procedure) to determine the extent of residual tumor prior to further treatment.”
SUMMARY OF CHANGES
Update Date: May 17, 2004

RTOG 98-13, A Phase III (Phase I Closed) Randomized Study Of Radiation Therapy And Temozolomide (IND #60,265) Versus Radiation Therapy And BCNU For Anaplastic Astrocytoma and Mixed Anaplastic Oligoastrocytoma (Astrocytoma Dominant)

Study Chair: Susan M. Chang, M.D., (415) 353-2966; FAX # (415) 353-2167; changs@neuro.ucsf.edu

RTOG 98-13 has been updated as follows:

Title Page – David Schiff, M.D. is the new ECOG Co-Chair for R9813. ECOG’s contact information has been updated to reflect the change.

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 Web site, http://www.rtog.org
SUMMARY OF CHANGES  
Update Date: January 28, 2004

RTOG 98-13, A Phase III (Phase I Closed) Randomized Study Of Radiation Therapy And Temozolomide (IND #60,265) Versus Radiation Therapy And BCNU For Anaplastic Astrocytoma and Mixed Anaplastic Oligoastrocytoma (Astrocytoma Dominant)

Study Chair: Susan M. Chang, M.D., (415) 353-2966; FAX # (415) 353-2167; changs@neuro.ucsf.edu

RTOG 98-13 has been updated as follows:

The Eligibility Checklist page 1 Question # 5 has been corrected.

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”.

A updated protocol is available (no password required) on the RTOG Web site, http://www.rtog.org
SUMMARY OF CHANGES
Update Date: January 27, 2004

RTOG 98-13, A Phase III (Phase I Closed) Randomized Study Of Radiation Therapy And Temozolomide (IND #60,265) Versus Radiation Therapy And BCNU For Anaplastic Astrocytoma and Mixed Anaplastic Oligoastrocytoma (Astrocytoma Dominant)

Study Chair: Susan M. Chang, M.D., (415) 353-2966; FAX # (415) 353-2167; changs@neuro.ucsf.edu

RTOG 98-13 has been updated as follows:

Section 7.4.2: This section was updated to clarify all of the addresses to which the completed FDA Form 3500 must be mailed or faxed.

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”.

A updated protocol is available (no password required) on the RTOG Web site, http://www.rtog.org
SUMMARY OF CHANGES  
Revision 5, Version Date: December 22, 2003

RTOG 98-13, A Phase III (Phase I Closed) Randomized Study Of Radiation Therapy And Temozolomide (IND #60,265) Versus Radiation Therapy And BCNU For Anaplastic Astrocytoma and Mixed Anaplastic Oligoastrocytoma (Astrocytoma Dominant)

Study Chair: Susan M. Chang, M.D., (415) 353-2966; FAX # (415) 353-2167; changs@neuro.ucsf.edu

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

RTOG 98-13 has been revised as follows:

Title page, Schema title, Appendix IA title, Appendix VII title: The title has been amended to reflect the closure of Phase I and to make more prominent that mixed glioma histology is allowed.

Title page: The email contact information for Drs. Bushunow, Jaeckle, and Barger was added.

Version Date: Changed to December 22, 2003 to reflect the date of the submission of this amendment to NCI.

Eligibility Checklist: Question #5 has been reworded from “Patient’s Name” to “Patient’s Initials (First, Middle, Last).”

Eligibility: Section 3.1.4 was changed to “Therapy must begin within 6 weeks” rather than 5 weeks to allow more time for central pathology review. Section 3.1.5, DLCO criterion was deleted and replaced by Section 3.2.13. These changes were made to Schema eligibility also.

Ineligibility: Section 3.2.13, “Any pre-existing lung disease that in the investigator’s opinion will prevent administration or completion of therapy of BCNU” was added here and to the Schema eligibility also. For consistency, this also replaced the previous question #5 on the Eligibility Checklist.

Section 4.2: Pre-treatment evaluation changed to allow for CT. “CT scans are allowed for patients who cannot undergo MRI. The same type of scan must be used throughout the protocol treatment period.” was added at the end of the section in order to permit the use of CT.
Section 5.5.4: In the second sentence, the telephone number for ECOG was corrected and “name or” was deleted from the third sentence to be consistent with change to question #5 on Eligibility Checklist.

Section 6.2: In this section, “4 to 8 MV” was changed to “4 to 18 MV photons” in the first sentence to reflect current practice and availability of the radiation machine capabilities.

Section 6.6: In the second sentence, “attempts should be made to limit the dose to the optic chiasm” was changed from 60 Gy to 54 Gy to maximize the safety of administration of the radiation to the optic apparatus.

Section 7.1: “Patients should take BCNU and Temozolomide on consecutive days with no interruptions for weekends or holidays.” was added for clarification.

Section 10.7.6: This section on Reimbursement was added to clarify reimbursement procedures. The original sentence concerning reimbursement was replaced with this more detailed explanation.

Section 11.1: Under “Study Parameters,” the following changes were made for consistency with the protocol text: Under Required, “or CT” was added to MRI Brain; in footnote c, “Pre-treatment MRI” and “CT scans allowed for patients who cannot undergo MRI—same type of scan must be used throughout protocol treatment” were added; pre-treatment evaluation “PFT or DLCO” was deleted along with the corresponding footnote e; and footnotes “f, g, h” re-lettered as “e, f, g,” respectively. In new footnote e, “DLCO only (excluding Arm 1)” was deleted. Changes were made accordingly both in the table and in the footnotes themselves.

Section 11.2.2: “or CT scan” was added because CT scans are now permitted.

Section 11.2.3: In the first sentence, “CT” was deleted because this does not apply to the MRI technique.

Section 12.1: Due date for MR and ME forms changed to “For grade ≥3 neuro-toxicity and for progression. See Section 12.2 for submission details.”

Section 12.2.3: “Subsequent MRI scans and MRI reports, other than the pre-entry, should be forwarded to RTOG Headquarters only in the event of a suspected ≥3 neuro-toxicity and/or progression.” was added for clarification.

Appendix III: The P4 form has been revised to request “Participant’s Initials,” Participant’s I.D.No.,” in the label area; in the Eligibility box the following was added in order to try and capture additional eligibility data—“Slides with Pathology reports that indicate grade II tumor but reference anaplasia can be submitted to Dr. Aldape for central pathology review.”
Appendix VI: Under 1. Registration, in the last sentence, “in Section 5.5.4” was corrected to “in Section 5.5.”

A revised protocol is available (no password required) on the RTOG Web site, http://www.rtog.org
RTOG 98-13, A Phase I/III Randomized Study Of Radiation Therapy And Temozolomide Versus Radiation Therapy And BCNU For Anaplastic Astrocytoma (IND #60,265)

Study Chair: Susan M. Chang, M.D., (415) 353-2966; FAX # (415) 353-2167; changs@neuro.ucsf.edu

RTOG 98-13 has been updated as follows:

Title Page — Updated Dr. Dolinskas’ e-mail address to cadoli@pahosp.com.

Section 5.6 — Deleted remote registration information for NCCTG Institutions.

NOTE: This is an editorial/administrative change to the protocol. NCI now requires that these changes be documented on the protocol title page with the date of the update noted as “Update Date”, not as a revision.

An updated protocol is available (no password required) on the RTOG website: http://www.rtog.org/
SUMMARY OF CHANGES
Update Date: September 15, 2003

RTOG 98-13, A Phase I/III Randomized Study Of Radiation Therapy And Temozolomide Versus Radiation Therapy And BCNU For Anaplastic Astrocytoma (IND #60,265)

Study Chair: Susan M. Chang, M.D., (415) 353-2966; FAX # (415) 353-2167; changs@neuro.ucsf.edu

RTOG 98-13 has been updated as follows:

Section 5.5.1 — ECOG Institutions must submit the Study Agent Shipment Form to the CTSU Regulatory Office in Philadelphia.

Section 5.6 — Updated registration procedures for NCCTG Institutions.

NOTE: This is an editorial/administrative change to the protocol. NCI now requires that these changes be documented on the protocol title page with the date of the update noted as “Update Date”, not as a revision.

An updated protocol is available (no password required) on the RTOG website: http://www.rtog.org/
SUMMARY OF CHANGES
Update Date: August 20, 2003

RTOG 98-13, A Phase I/III Randomized Study Of Radiation Therapy And
Temozolomide Versus Radiation Therapy And BCNU For Anaplastic Astrocytoma (IND #60,265)

Study Chair: Susan M. Chang, M.D., (415) 353-2966; FAX # (415) 353-2167;
changs@neuro.ucsf.edu

RTOG 98-13 has been updated as follows:

Section 5.2 — Sites in the U.S. will submit the Study Agent Shipment Form to the CTSU
Regulatory Office versus RTOG Headquarters; this change also was made in Section
7.2.1 and Appendix VII.

Section 7.2.1 — Updated Biologics contact information

NOTE: This is an editorial/administrative change to the protocol. NCI now requires that
these changes be documented on the protocol title page with the date of the update noted
as “Update Date”, not as a revision.

An updated protocol is available (no password required) on the RTOG website:
http://www.rtog.org/
SUMMARY OF CHANGES
Revision 4, Version Date: June 23, 2003

RTOG 98-13, A Phase I/III Randomized Study Of Radiation Therapy And Temozolomide Versus Radiation Therapy And BCNU For Anaplastic Astrocytoma (IND #60,265)

Study Chair: Susan M. Chang, M.D., (415) 353-2966; FAX # (415) 353-2167; changs@neuro.ucsf.edu

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

RTOG 98-13 has been revised as follows:

Title page — The contact information for Dr. Cairncross was updated; Dr. Jaeckle replaced Dr. Buckner as NCCTG co-chair.

Schema page — For clarity, Arm 3 was indicated as “Dropped” with a reference to Section 1.3; the date of closure of Pilot #2, Arm 5 was corrected to 1/25/02, and this correction also was made in Section 7.1.4; the phrase “by central review” was added in the first item in the Eligibility list to correspond to Section 3.1.1.

Eligibility Checklist — Question 14 was added to page 1 to correspond to Section 3.2.10, and question 21 was added to page 2 to correspond to Section 3.1.1; subsequent questions were appropriately renumbered on both pages.

Section 3.1.1 — The phrase concerning “oligodendrogial component” was revised from “less than 25%” to “≤ 25%”; this change also was made to the Eligibility list on the Schema page and to question 1, page 1 of the Eligibility Checklist.

Section 3.1.6 was deleted as this pretreatment evaluation is discussed in Section 4.2. The text of Section 3.1.6.1 was moved to Section 4.2, and Section 3.1.6.1 also was deleted; the subsequent section was appropriately renumbered.

Sections 5.2, 7.2.1, and Appendix VII were revised to clarify the drug shipment procedure.

Section 7.3.5.1 was revised for clarity.

Section 10.0 — The following changes were made:
At the request of the North Central Cancer Treatment Group (NCCTG), “NCCTG” was deleted from the title of the section;

Section 10.1 — “Central review” was added at the beginning of this section for clarity;

Section 10.7.2 — The text of Section 10.7.3 was added to this section, and it was revised for clarity; Section 10.7.3 was deleted, and subsequent sections were appropriately renumbered;

Section 10.7.3 (formerly Section 10.7.4) was revised for clarity;

Section 10.7.6 (formerly Section 10.7.7) was updated to RTOG standard.

Appendix I — Under “Description of Procedures”, the third paragraph was revised to clarify when patients would be asked to complete the MMSE.

At the request of the North Central Cancer Treatment Group (NCCTG), the following sections were revised for NCCTG investigators: Sections 5.6, 7.7, 10.9.2.1, 10.9.2.2, and 12.3.3.

At the request of the Eastern Cooperative Oncology Group (ECOG), the following sections were revised for ECOG investigators: Sections 5.2, 5.5.1, 5.5.2, 5.5.4, 7.6, 10.8.2, 12.3.1, Appendix VI, and Appendix VII.

A revised protocol is available (no password required) on the RTOG Web site, http://www.rtog.org
SUMMARY OF CHANGES
Revision 3, Version Date: 8/15/02

RTOG 98-13, A PHASE I/III RANDOMIZED STUDY OF RADIATION THERAPY AND TEMOZOLOMIDE VERSUS RADIATION THERAPY AND BCNU FOR ANAPLASTIC ASTROCYTOMA (IND #60,265)

Study Chair: Susan M. Chang, M.D., (415) 353-2966; FAX # (415) 353-2167; changs@neuro.ucsf.edu

IRB Review Requirements:

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

Based on the toxicity analyses of pilot Arms 4 and 5, the proposed Arm 3 of the phase III component of RTOG 98-13 has been dropped; the study will randomize patients between radiation therapy and temozolomide (Arm 1) or radiation therapy and BCNU (Arm 2).

The following sections of the protocol have been revised to reflect this change:

- The title of the study was revised throughout the protocol to reflect the current two-arm design.
- The Schema page was revised, including the sample size for the Phase III component of the study;
- Section 1.2.7 was added;
- Sections 1.3 and 2.1.3 were revised;
- Section 7.1.3 was deleted and subsequent sections appropriately renumbered;
- Sections 13.1.3 and 13.2.1 were revised;
- Section 13.2.2 was deleted and subsequent sections appropriately renumbered;
- Sections 13.3, 13.5.3, 13.5.4, 13.5.4.1, 13.5.4.2, and the Gender/Minority table in Section 13.6 were revised;
- In references, citations 59 and 61 were deleted, and the citations were appropriately renumbered;
- Appendix I, “Purpose of This Study” and “Description of Procedures” were revised.

Other Changes: The terminology in Sections 6.4.1 and 6.4.2 was changed to the correct RTQA scoring criteria; these categories are used for every study chair review.

Section 6.4.1 — The phrase “deviation unacceptable” has replaced the phrase “major deviation”.
Section 6.4.2 — The phrase “variation acceptable” has replaced the phrase “minor variation”.

A revised protocol is available (no password required) on the RTOG website: http://www.rtog.org/
The following changes have been made:

**Title Page** — Ken Aldape, M.D. is now study chair for Neuropathology and Molecular Genetics; Dr. Aldape’s contact information is provided in Section 10.5; sections 10.6 through 10.9.2.2 were updated with his name and/or contact information as necessary.

**Schema** — Arm 2: The BCNU schedule was corrected to include the cycle on days 56, 57, and 58, and the maximum BCNU dose was corrected to 1440 mg/m²; Arms 3 and 5: After “Repeat every eight weeks for a total of 6 cycles”, the sentence, “BCNU will be given on day 5 of Temozolomide during these cycles” was added, and the maximum BCNU dose was corrected to 900 mg/m². These revisions also were made in Sections 7.1.2, 7.1.3, and 7.1.5; in the paragraph above “Eligibility”, the 4th sentence was corrected to read “Refer to Section 7.1.5 for details”.

**Section 3.2.2** — was revised to read, “Any oligodendroglial component > 25%”.

**Section 7.2.1** — Kim Adams, Director of Pharmacy, is now the Biologics, Inc. contact.

**Section 10.2** — The last sentence, “Patients with oligoastrocytomas are not eligible”, was deleted.

**Section 10.7.2** — was revised to read “Representative paraffin block(s)”; Sections 10.8.2 and 10.9.2.1 were revised to correspond.

**Section 10.7.3** — was revised to read “Five to ten representative slides of unstained tumor sections *(if block(s) not available for distribution)”; Sections 10.8.2 and 10.9.2.1 were revised to correspond.

**Section 10.7.4** — was revised to require one serum separator tube of blood, preferably frozen; Section 10.8.2 was revised to correspond.

**Section 10.7.7** — was revised.

**Section 10.9.2.2** — The phrase “within 24 hours” was added to the first sentence of the first paragraph; the last sentence of the second paragraph was deleted.

**Section 11.3.2.3** — was revised to read “A zero to 25% or zero to 50% decrease…”.
Section 11.3.2.4 — The second sentence, “Time to progression is defined as time from initial diagnosis to tumor progression”, was added.

Section 13.2.1 — The fifth sentence of the second paragraph was revised.

Appendix I, sample consent — Under “Description of Procedures”, Treatment 2: The third sentence was corrected to read “The BCNU will begin on the first three days of radiation and will be given on days 56, 57, and 58”; Treatment 3: The fifth and sixth sentences were revised to read “The Temozolomide and the BCNU will be repeated every eight weeks up to six times. The BCNU is given over 3 hours at each of these visits”.

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

RTOG 98-13, Astrocytoma

August 17, 2001

The following changes are in effect:

1. **NCCTG has joined this study**; the following sections were updated: the Cover page, Sections 5.2, 5.6, 7.7, 10.0, 12.3, and Appendices I (Confidentiality) and VII.

2. **This study has re-opened** to collect additional phase I information (designated as Arm 5) for 15 new patients. The dose of temozolomide will be 150 mg/m2 p.o. daily on days 1-5 with BCNU 150 mg/m2 to be given i.v. on day 5. The rationale is the dose reduction necessary for the majority of patients in the initial pilot (Arm 4) due to grades 3 and 4 melosuppression. There is also scientific rationale for the sequencing of the agents based on the depletion of alkyl transferase by temozolomide and to potential sensitization to BCNU. This will be given every eight weeks (instead of six weeks) to be consistent with Arm 2. Toxicities will be assessed prior to proceeding to the phase III study. The following sections were updated: the Schema, Sections 7.1, 7.1.2.1, 7.1.3.1, 7.2.1, 7.3.4.1, 7.3.5-7, 13.2.4, 13.6, and Appendix I (Description of Procedures). **This amendment requires IRB approval**; **documentation of approval must be received at RTOG (from RTOG members) prior to study entry.**

3. **Other Changes:**

   **Cover Page** – Dr. Chang has replaced Dr. Thoron as the primary study chair. Also, telephone and fax numbers were updated for Drs. Cairncross, Gilbert, Bahary, and Louis.

   **Schema** – Mixed oligodendroglial/astrocytic tumors are eligible if the oligodendroglial component is less than 25%. Also affects the Eligibility Checklist (Q1), Sections 3.1.1, 10.2, and Appendices I (Purpose) and III.

   **Schema** – Prestudy liver and renal function limits have been added. Also affects the Eligibility Checklist (Q3), Sections 3.1.3, and 4.5, and 11.1.

   **Schema** – Eligible DLCO is ≥ 70%. Also affects the Eligibility Checklist (Q5), and Section 3.1.5.

   **Section 3.2.12** was added.

   **Section 5.1** – Added that same-day review cannot be guaranteed. Also affects Section 10.1 and 10.6.
**Section 5.3** – was updated for patient registrations.

**Sections 7.1.2, 7.1.3.1, and 7.3.4.1** – Corrected the maximum dose of BCNU to 1400 mg/m2.

**Section 7.2.7** – Schering Plough will not supply temozolomide free of charge for patients who go off study per protocol definition, for either disease progression or toxicity. Also affects Section 11.6.3 (new) and Appendix I (costs).

**Section 13.2.1**, paragraph 2, line 4, was corrected to “It is assumed that 67% of the patients will be in class I . . .”

*A replacement protocol is attached.*