SUMMARY OF CHANGES
Update: July 24, 2008
(Broadcast July 24, 2008)

RTOG 0525, Phase III Trial Comparing Conventional Adjuvant Temozolomide With Dose-Intensive Temozolomide in Patients With Newly Diagnosed Glioblastoma
Study Chair: Mark R. Gilbert, MD; 713-792-4008; mrgilbert@mdanderson.org

RTOG 0525 has been updated as follows:

Section 7.3.4: Contact information for Biologics, Inc., was updated.

Section 10.0: The RTOG Tissue Bank has been renamed the RTOG Biospecimen Resource and has moved from LDS Hospital to the University of California San Francisco. This section was updated accordingly throughout.

Section 10.4: The link to the RTOG Patient Tissue Consent Frequently Asked Questions was updated.

Appendix V: In the diagram for proposed tumor tissue utilization and prioritization, the RTOG Tissue Bank was changed to the RTOG Biospecimen Resource.

Note: These are editorial/administrative changes to the protocol. NCI requires that these changes be documented on the protocol title page with the date of the update noted as "Update Date," not as an amendment.
RTOG 0525, Phase III Trial Comparing Conventional Adjuvant Temozolomide With Dose-Intensive Temozolomide in Patients With Newly Diagnosed Glioblastoma

Study Chair: Mark R. Gilbert, MD; 713-792-4008; mrgilbert@mdanderson.org

RTOG 0525 has been updated as follows:

Contact information was changed for Study Chair Terri Armstrong

Appendix I: Anemia was added to the Less Likely list of Temozolomide risks

NOTE: This is an editorial and/or 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 an amendment.
SUMMARY OF CHANGES
Update: January 8, 2008

RTOG 0525, Phase III Trial Comparing Conventional Adjuvant Temozolomide
With Dose-Intensive Temozolomide in Patients With Newly Diagnosed Glioblastoma
Study Chair: Mark R. Gilbert, MD; 713-792-4008; mrgilbert@mdanderson.org

RTOG 0525 has been updated as follows:

Index: Appendix VI and VII are dated as changed 01/08/08

Section 7.10: "MedDRA version 6.0" was added to the first sentence.

Section 11.6.4: Section 11.6.4.2 was changed to describe that the training video
procedures being available on the MD Anderson web site with a URL link provided.
Additionally the sentence about obtaining web site and password information was
changed to state "For questions about the certification test training"

Section 13.5: The accrual table was revised to current NCI standards, eliminating the
"More than one race and Unknown" categories.

Appendix VI: Information for how to access the neurocognitive training video web site
was added to Step 1, point (2)

Appendix VII: The "Dear Test Administrator letter" was added to the appendix and
noted that it is posted on the RTOG web site.

NOTE: This is an editorial and/or 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 an amendment.
RTOG 0525 has been amended as follows:

1) **Statistical Changes**
   In a June 2007 review of data for the first 313 patients enrolled on this trial, the prior projection for the percentage of patients not being randomized was significantly underestimated (10% vs 30%). In order to achieve 750 randomized patients, the target sample size was therefore increased from 834 to 1153. In addition, the percentage of patients with unmethylated MGMT was 12% more than projected and the percentage of patients with methylated MGMT was 12% less than projected. The observed monthly patient accrual rate was approximately 75% higher than expected. As a result of the June 2007 review, changes were made to the following sections:

**Cover Page:** The sample size was changed.

**Section 13.2.2:**
- In the fourth sentence, "with" was corrected to "will."
- The last sentence was replaced by the last 4 sentences to provide the new target sample size and related information.

**Section 13.2.3.2:** The last 3 sentences were added to provide statistical powers for a treatment comparison with a larger number of patients with unmethylated MGMT.

**Section 13.2.3.3:** The last 3 sentences were added to provide statistical powers for a treatment comparison with a smaller number of patients with methylated MGMT.

**Section 13.2.3.4:** The first, third, and fourth sentences were re-written to account for the new sample size and larger-than-anticipated monthly accrual rate.

**Section 13.3.1:** The last 7 sentences were added to provide updated information for the projected completion of patient accrual based on the increased sample size and larger-than-anticipated monthly accrual rate.

**Section 13.3.3:** In the last sentence, "a revised rate of 35%" has replaced "10%," so that the targeted sample size may be further increased if the rate of patients not being randomized exceeds 35%.
Section 13.4.3:

- In the first sentence, "of patients on the study" was deleted for increased clarity.
- In the second sentence, "at the next RTOG meeting was added" for increased accuracy.
- In the second sentence, "of patients on the study and at least 300 deaths in each of the methylated and unmethylated subgroups" was replaced with "reported," because the final analysis will occur after there have been at least 647 deaths regardless of the number of deaths observed in the unmethylated MGMT and the methylated MGMT subgroups.

Section 13.4.5: In the first sentence, "three" was corrected to "four." The RTOG DMC will review the study four times per Section 13.4.2.

Section 13.5: The table has been updated to account for the increased sample size and the group distributions observed through June 2007.

Appendix I: Under "How many people will take part in the study?," the sample size was changed.

2) Other Changes

Cover Page: The contact information was updated for Dr. Armstrong, Dr. Stupp, and Dr. Hegi.

Schema Page: In the "stratify" box under "MGMT status," "unknown" was corrected to "indeterminate" for consistency with other sections of the protocol.

Section 1.0: In the 10th paragraph, 4th sentence, "administration" was corrected to "inactivation."

Section 5.3: The section was reworded to clarify that certification is for neurocognitive function testing only and to clarify that institutions with patients enrolling in the quality of life/neurocognitive function component must be certified. As a result, "quality of life" was deleted from the heading, and "with patients" and "for administering neurocognitive assessments" was added to the text.

Section 7.3.9: Leiomyosarcoma, pneumonia, and multi-organ failure were added under "other" at the request of the Central IRB.

Section 7.4: The upper limit for platelets was changed from 50 to 75 X10^9/L to be consistent with thrombocytopenia grades given elsewhere in the protocol. Changes were made to the following places:

- Third paragraph, second bullet
- Fourth paragraph, second bullet
• Summary of Temozolomide Delay or Discontinuation During Concomitant Radiation Therapy table: second cell under "Value" and first cell under "Action"

Section 7.5.1:

• In the first sentence under "Delay," the superscript 9 was added to the ANC and platelet values because it was inadvertently missing.
• In the last sentence under "Delay," 3 weeks was corrected to 4 weeks for consistency with other sections of the protocol.

Section 7.5.2:

• The heading of the fifth paragraph was corrected from "dose reductions" to "dose escalation."
• In the table titled "Worse Treatment-Related Hematologic AE During the Previous Cycle," the information in the cell corresponding to ANC ≥ 1.5 x 10^9/L and platelets ≥ 100 x 10^9/L was changed from "dose unchanged" to "Escalation to DL 1 (cycle 2 only) for consistency with other sections of the protocol.

Section 11.0: In footnote "i," a slash was added between "500" and "mm^3" because it was inadvertently missing.

Section 11.1:

• Footnote J: Due to inadvertent omissions: cycle 4 was added, cycle 9 was changed to cycle 10, and "1 month after" was added before cycle 12.
• Footnote k: For increased clarity, the text was rewritten so that it is presented in a fashion similar to footnote j.

Section 11.6.4.2: Information for how to access the training video was added to the second sentence and to the last three lines of the section.

Section 11.6.4.3:

• Neurocognitive evaluation summary form" was added to the 1st and 2nd sentences for increased accuracy.
• Appendix VI was corrected to Appendix VII in the first sentence.

Section 12.1:

• "Due" description for Net Clinical Benefit Instruments: Due to inadvertent omissions: cycle 4 was added, cycle 9 was changed to cycle 10, and "1 month after" was added before cycle 12.
• "Due" description for NCF Battery: For increased clarity, the text was rewritten so that it is presented in a fashion similar to the description for the Net Clinical Benefit Instruments.
Appendix I/Sample Consent:

- Under "What side effects or risks can I expect from being in the study?", the last sentence was added at the request of the Central IRB.
- Under "Risks and side effects related to temozolomide," vomiting was deleted from "likely" and added to "less likely" at the request of the Central IRB.
- Under "Risks and side effects related to temozolomide," anemia was added to the first bullet in "less likely" at the request of the Central IRB.
- Under "Risks and side effects related to temozolomide," leiomyosarcoma, development of another type of cancer, pneumonia, and multi-organ failure were added under "rare but serious" at the request of the Central IRB.
- For increased clarity and accuracy, in the consent form for the quality of life/neurocognitive function study: (1) "on day 15 of month 1 and 4" was added to the 2nd bullet of the 3rd paragraph; and (2) the entire 5th paragraph was added.

Appendix V/Molecular Correlative Studies: Under "Preliminary data and experimental plan, Aim 1," 7th paragraph 1st sentence, last clause: "in" was corrected to "is."

Appendix VI/Administration Procedures for the Neurocognitive Test Battery:

- Information for how to access the training video was added to point 2 and appendix VI was corrected to VII in point 5 in the following places:
  1. Under "Step 1- Examiner Approval for RTOG 0525" (at the beginning of the Appendix)
  2. Under "Requirements for Examiner Approval for RTOG 0525" (At the end of the Appendix)
- Under "Step 3/Controlled Oral Word Association Test/Recording and Scoring," the second bullet was rewritten so that the recording procedure is consistent throughout the appendix and consistent with the training video.

Appendix VII/Neurocognitive Certification Worksheet: This appendix has been deleted from the main protocol document and has been added as a fillable form on the RTOG web site next to the main protocol link.

Appendix X/NCCTG Group-Specific Information: Section 2/Neurocognitive Function Forms was added. All subsequent sections were appropriately renumbered.
RTOG 0525, Phase III Trial Comparing Conventional Adjuvant Temozolomide
With Dose-Intensive Temozolomide in Patients With Newly Diagnosed Glioblastoma

Study Chair: Mark R. Gilbert, MD; 713-792-4008; mrgilbert@mdanderson.org

RTOG 0525 has been updated as follows:

Eligibility Checklist/Step 1, last element: A sub-question was added to provide reasons for not participating in the quality of life/neurocognitive function components of the study.
RTOG 0525 has been amended as follows:

Quality of life and neurocognitive function were added to the study. As a result, the following sections were modified:

- **Title page:** Terri Armstrong added as Quality of Life Co-Chair.
- **Index:** Neuropsychological/QOL Assessments added as Appendix VI. Certification Worksheet for Test Administrator added as Appendix VII. All subsequent appendices renumbered.
- **Eligibility Checklist/Step 1, last element:** Added
- **Section 1.0:** Last 6 paragraphs added.
- **Section 2.3:** Added.
- **Section 5.3:** Added.
- **Section 11.1:** Last 3 rows of table (EORTC QLC3/BCM 20, MDASI-BT, NCF Battery) added. Footnotes j and k added.
- **Section 11.5.4:** New text inserted. All subsequent subsections renumbered.
- **Section 11.6:** New text inserted. Old text deleted (see below).
- **Section 12.1:** Information for EORTC QLC3/BCM 20, MDASI-BT, NCF Battery added.
- **Sections 13.1.3, 13.2.3.4, and 13.4.1.2:** Added.
- **Appendix I/Sample Consent:** Sample consent for quality of life study added.
- **Appendix VI:** Text changed to Neuropsychological/QOL Assessments.
- **Appendix VII:** Text changed to Certification Worksheet for Test Administrator.
- **Appendices VIII-X:** Renumbered from Appendices V-VIII.
- **REFERENCES:** Citation numbers 20-32 and 40-45 added, and all subsequent citations renumbered under REFERENCES and in the text.

The following additional changes were made:

- **Title page:** Contact information for Ken Aldape updated. Paul Brown identified as NCCTG Radiation Oncology Co-Chair, and Kurt Jaeckle added as NCCTG Medical Oncology Co-Chair.
- **Eligibility Checklist/Step 1, second-to-last last element and Section 3.2.12:** Added to prevent submission of tissue obtained by stereotactic biopsy.
- **Section 7.7:** $\text{mm}^3$ corrected from $\text{mm}^2$ in third-to-last sentence.
- **Section 10.2.2.1:** Specifications for tissue samples clarified.
- **Section 10.2.2.5:** Contact information for Ken Aldape updated.
• **Section 10.2.8**: Contact information for LDS Hospital updated.

• **Section 11.6**: Old text deleted because it described data submission practices that were not applicable to this protocol. New text inserted (see above).

• **Appendix I/Sample Consent**:  
  o Under "How long will I be in this study?," the last paragraph, describing follow-up visits, was deleted because it was inaccurate. Follow-up visits are already accurately described in the preceding section ("When I am finished taking the study treatment").  
  o Under "What are the costs of taking part in this study?," the second paragraph was added to clarify that patients whose tumor samples contain insufficient tissue for MGMT analysis will not be randomized to the second part of the study and will not be able to receive temozolomide without cost.

• **Appendix X/NCCTG Group-Specific Information**: Section 2.0 modified because NCCTG sites will submit data to RTOG Headquarters, not the Mayo Clinic. Sections 3.0 and 4.0 added to clarify that NCCTG sites should follow the protocol guidelines for adverse event reporting and tissue/specimen submission.
SUMMARY OF CHANGES
Update Date: September 21, 2006

RTOG 0525, Phase III Trial Comparing Conventional Adjuvant Temozolomide With Dose-Intensive Temozolomide in Patients With Newly Diagnosed Glioblastoma

Study Chair: Mark R. Gilbert, MD; 713-792-4008; mrgilbert@mdanderson.org

RTOG 0525 has been updated as follows:

Section 11.2.2: In the first sentence, "every 2 cycles" was corrected to "every 3 cycles" for consistency with the rest of the protocol.

Appendix I/Sample Consent: In the study plan diagram, "Group 1" was corrected to "Group 2" in the last box on the right.
SUMMARY OF CHANGES
Amendment #1, Version Date: June 12, 2006

RTOG 0525, Phase III Trial Comparing Conventional Adjuvant Temozolomide With Dose-Intensive Temozolomide in Patients With Newly Diagnosed Glioblastoma

**Study Chair:** Mark R. Gilbert, MD; 713-792-4008; mrgilbert@mdanderson.org

RTOG 0525 has been amended as follows:

**Title Page**

- To conform with current RTOG standards, the coordinating group’s study chairs were moved to the left side of the page and the study chairs for all other groups were moved to the right.
- The phone and fax numbers for Dr. Mehta were updated.
- The fax number for Dr. Hegi was updated.
- Dr. Brown was added as the NCCTG Study Chair because NCCTG has joined the study.

**Index:** Appendix VIII was added as instructions for NCCTG sites because NCCTG has joined the study.

**Schema Page:**

- Stratification of radiation by standard US criteria or according to the EORTC revised criteria was added to the end of the stratification section. See description of changes under Appendix VII for additional details.
- Under Patient Population, "multiforme" was deleted because it is no longer part of the official name of "glioblastoma."

**Eligibility Checklist, Step 1:**

- Page 2, 1st question: (1) "Gliosarcoma" was added because it is a variant of glioblastoma and is therefore an eligible diagnosis; (2) "multiforme" was deleted because it is no longer part of the official name of "glioblastoma."
- Page 2, 17th question: "Surgery" was revised to "most recent brain tumor surgery" for increased clarity.
- Page 5, final question: This question was added due to the addition of Section 11 in Appendix VII. See description of changes under Appendix VII for additional details.

**Section 2.2.6:** This objective was added in an attempt to confirm the hypothesis that, in some brain tumors, lack of disease progression at 6 months is associated with longer overall survival.
Section 3.1.1: (1) "Gliosarcoma" was added because it is a variant of glioblastoma and is therefore an eligible diagnosis; (2) "multiforme" was deleted because it is no longer part of the official name of "glioblastoma."

Section 3.1.3: Due to the likelihood that stereotactic biopsy will not yield enough tissue to render the patient eligible for Step 2 registration, this criterion was revised to reflect that diagnosis must be made by open biopsy or tumor resection.

Section 3.1.6: The first and second sentences were modified to more accurately reflect the timing for the postoperative scan.

Section 3.1.6.1: The former Section 3.1.6.1 was deleted because patients diagnosed with stereotactic biopsy are no longer eligible for this trial. The former Section 3.1.6.2 has become the new Section 3.1.6.1.

Section 3.1.7: "Surgery" was revised to "most recent brain tumor surgery" for increased clarity.

Section 3.2.4: This section was modified to reflect that prior use of all intramural or intracavitary treatments is excluded.

Section 5.0: Instructions were added for NCCTG sites to consult Appendix VIII.

Section 5.1: The third bullet point was added to clarify how institutions will know that the MGMT test results have been received and when institutions can proceed to the second step of registration.

Section 6.4: In the second paragraph, the second-to-last and third-to-last sentences were modified to reflect more accurate specifications for preoperative and postoperative scans.

Section 7.3: In the temozolomide heading, "Temodal®" was added for increased clarity, since the trade name varies according to country.

Section 7.4: In the table, right hand column, "plt" was expanded to "platelet" for consistency with the remainder of the protocol.

Section 7.10: 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 7.10.1: Heading/first paragraph: Information for RTOG's AE phone line was deleted.
- Section 7.10.2
Section 10.2.8: Contact information was added for the RTOG Tissue Bank.

Section 11.1, Footnote b: The last line was deleted because patients diagnosed with stereotactic biopsy are no longer eligible for this trial.

Section 12.0: Instructions were added for NCCTG sites to consult Appendix VIII.

Section 13.1.2.1: The acronym for progression-free survival (PFS) was deleted for consistency with terminology used in the remainder of the protocol.

Section 13.1.2.6: This endpoint was added in an attempt to confirm the hypothesis that, in some brain tumors, lack of disease progression at 6 months is associated with longer overall survival.

Section 13.2.1:

- Second sentence: "Multiforme" was deleted because it is no longer part of the official name of "glioblastoma."
- Second-to-last sentence: Stratification of radiation by standard US criteria per Section 6 of the protocol or according to the EORTC revised criteria was added. See description of changes under Appendix VII for additional details.

Section 13.2.2: The sixth sentence was modified to reflect that there will be five, not three, planned data analyses.

Section 13.2.3.1: In the last sentence, the acronym for progression-free survival (PFS) was deleted for consistency with terminology used in the remainder of the protocol.

Appendix I/Sample Consent

- **During the study...**: Text was modified to reflect that side effect questionnaires are not a part of this study and that side effect information will be documented by the treating site during routine study visits. Changes were made to the second paragraph/second bullet point and to the third paragraph/first sentence.
- **"Will my medical information be kept private?"**: The first two sentences were added to clarify that data are kept in a password-protected database at RTOG Headquarters and that, for patients enrolling through EORTC and NCCTG sites, data are also kept in confidential files maintained by EORTC and NCCTG, as applicable.
Appendix VII/EORTC Group-Specific Information: Section 11 has been added. European centers now have separate guidelines for radiation therapy volumes and treatment definitions.

Appendix VIII/NCCTG Group-Specific Information: This appendix was added for NCCTG sites because NCCTG has joined the study.
SUMMARY OF CHANGES
Update Date: January 17, 2006

RTOG 0525, Phase III Trial Comparing Conventional Adjuvant Temozolomide With Dose-Intensive Temozolomide in Patients With Newly Diagnosed Glioblastoma

Study Chair: Mark R. Gilbert, MD; 713-792-4008; mrgilbert@mdanderson.org

RTOG 0525 has been updated as follows:

Eligibility Checklist, page 1 - EORTC institution number was deleted because it is no longer necessary for registration of EORTC patients.

Section 3.1.4 - "A" was added before "supratentorial" because it was inadvertently omitted.

Section 3.1.5 - The hyphen was deleted in "postoperative" for consistency with the rest of the protocol and to conform with AMA style.

Section 5.1, Step 1, 2nd bullet - "Histologic confirmation" has replaced "tissue evaluation" for increased clarity.

Section 5.1, Step 2, 1st bullet - "A second" was added before "web registration" and "and entering the stratification variables into the second step checklist" was deleted in order to more accurately reflect the registration process.

Section 5.2 - Instructions were added as the second to last paragraph for sites not receiving confirmation of web registration.

Section 7.3.4 - The email address for submitting study agent shipment forms was added to the second paragraph.

Section 11.5.2 - The timeframe for progression-free survival was added because it was inadvertently omitted.

Section 12.0-12.1 - Footnotes regarding submission of data forms that are available for web entry were added to the address information and to the end of Section 12.1. Electronic submission of forms is required for the following forms: A5, T1, TF, AE, SR, F1. In addition, the AO was deleted because this information is being collected at registration.

Section 13.4.6 - CDUS information was added based on NCI's current analysis plan.

Appendix VI - The study agent shipment form was deleted from the protocol, and a note to see the electronic version on the RTOG website was added.
NOTE: These are editorial/administrative changes 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 an amendment.

An updated protocol is available on the RTOG website: http://www.rtog.org