SUMMARY OF CHANGES
Amendment #4: April 1, 2011
(Broadcast: May 19, 2011)

RTOG 0420, A Phase II Study of Radiation Therapy Plus Low Dose Temozolomide Followed by Temozolomide Plus Irinotecan for Glioblastoma Multiforme

Study Chair: Frank S. Lieberman, MD; (412) 692-2600; liebermanf@upmc.edu

RTOG 0420 has been amended as follows:
As mandated by CTEP, beginning July 1, 2011, this study will utilize CTCAE version 4.0 for AdEERS reporting of adverse events. Related changes were made to Section 7.6.1 and 7.6.5.

NOTE: All AE reporting on the study case report forms will continue to use CTCAE version 3.0.

Cover Page: A document version history was added to the Cover Page per current RTOG standard.

Global: All weblinks to sub-pages of the RTOG website were updated.
RTOG 0420, A PHASE II STUDY OF RADIATION THERAPY PLUS LOW DOSE TEMOZOLOMIDE FOLLOWED BY TEMOZOLOMIDE PLUS IRINOTECAN FOR GLIOBLASTOMA MULTIFORME

Study Chair: Frank S. Lieberman, MD; (412) 692-2600; liebermanf@upmc.edu

RTOG 0420 has been updated as follows:

Section 3.1.14 and Section 11.1 footnote "e": For clarity, "triglycerides and cholesterol" have been deleted from blood chemistries.
SUMMARY OF CHANGES
Amendment 3, Version Date: August 10, 2005

RTOG 0420, A PHASE II STUDY OF RADIATION THERAPY PLUS LOW DOSE TEMOZOLOMIDE FOLLOWED BY TEMOZOLOMIDE PLUS IRINOTECAN FOR GLIOBLASTOMA MULTIFORME

Study Chair: Frank S. Lieberman, MD; (412) 692-2600; liebermanf@upmc.edu

RTOG 0420 has been amended to modify the dose of irinotecan as follows:

Section 1.6: This new section was added to address the rationale for modifying irinotecan/chemotherapy.

Section 7.2: The section was rewritten extensively to incorporate the dose modifications of irinotecan. A schematic was added to this section for clarity.

Section 7.3.13: In the third sentence, “in Section 7.2 if the toxicity occurs in cycles 1 to 3 or in Section 7.4.7 if toxicity occurs in subsequent cycles” was added to the end of the sentence for clarification.

Section 7.4.7.2: A new first sentence, “Guidelines for dose adjustments during the first 3 cycles are provided in Section 7.2” was added. The following text was added to the end of the section “and the dose given on day 15 of the cycle decreased by 50mg/m^2. Dose adjustment to below 100mg/m^2 of CPT-11 is not permitted, and patients who would require such a dose adjustment will be taken off study and continue with temozolomide only.”

Section 7.4.7.3: In the third and sixth sentences, “25%” was deleted and “50mg/m^2” was added. “Dose reduction below 100mg/m^2 per dose is not allowed” was added as a new fourth sentence. The following text was added at the end of the sixth sentence: “and the current dose is 150mg/m^2, a second dose reduction to 100mg/m^2 will be allowed.” A new sentence was added at the end of the section.

Section 7.4.7.4: At the end of the first sentence, “at any point in any cycle” was added.

Section 9.2.7: In the first sentence “permitted” was deleted and “mandated” was added. In the second sentence, “Use of G-CSF is permitted at any point in any cycle” was added at the beginning and “is not generally recommended” was deleted and “may be administered at the discretion of the investigator” was added at the end. “E-poietin may be used at any point in any cycle at the investigator’s discretion” was added as a new third sentence. In the fifth sentence, “However” and “recurrent” were deleted, “may be used at any point in any cycle at the investigator’s discretion” was added and “in subsequent cycles, or” was deleted. These changes were made for consistency with the rest of the protocol.
Section 13.6.2: CDUS version 1.1 was changed to CDUS version 3.0.

Consent: Under “What is Involved In The Study,” a new section “Modification in chemotherapy” was added to explain the change in irinotecan dose.
RTOG 0420, A PHASE II STUDY OF RADIATION THERAPY PLUS LOW DOSE TEMOZOLOMIDE FOLLOWED BY TEMOZOLOMIDE PLUS IRINOTECAN FOR GLIOBLASTOMA MULTIFORME

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RTOG 0420 has been amended to increase the required sample size to reflect the observed rate of inevaluability as follows:

**Schema:** The required sample size was changed from 99 to 157.

**Section 13.3:** Text was added to the end of this section providing the rationale for increasing the sample size.

**Section 13.4:** The projected distribution of patients for the study based upon the first 99 patients entered was added.

**Section 13.5:** A new paragraph was added to the end of this section addressing the accrual rate for the new sample size.

**References:** A new reference, #31, was added.

**Consent:** Under “How Many People Will Take Part In The Study”, 99 was changed to 157 to reflect the increased sample size.
SUMMARY OF CHANGES
Amendment #1: Version: March 14, 2005

RTOG 0420, A PHASE II STUDY OF RADIATION THERAPY PLUS LOW DOSE TEMOZOLOMIDE FOLLOWED BY TEMOZOLOMIDE PLUS IRINOTECAN FOR GLIOBLASTOMA MULTIFORME

Study Chair: Frank S. Lieberman, MD; (412) 692-2600; liebermanf@upmc.edu

RTOG 0420 has been revised as follows:

Index: Appendix IV “Enzyme vs. Non-enzyme Inducing Anti-Seizure Medications” was added to the index because it was added to the protocol. Cross-references to it were added in Sections 3.1.10 and 9.2.2.

Eligibility Checklist, page 1: Question #12 “anti-seizure” was changed to “steroid.” Question #24 “Has the patient had prior chemotherapy?” was added.

Section 2.1: “compared with historical controls from the RTOG database” was deleted.

Section 3.1.12: Under “Hepatic” 0.5 was corrected to bilirubin 1.5 mg/dL.

Section 3.2.10: “Prior chemotherapy” was added as an ineligibility.

Section 7.1.1: The last sentence was revised to include “(or dapsone or atovaquone)” for prophylaxis of pneumocystis pneumonia for patients allergic to sulfa compounds who do not have access to pentamidine.

Section 7.1.1.3: New section added to include information about administering intravenous pentamidine.

Section 7.1.1.4: New section added to include information about dapsone.

Section 7.1.1.5: New section added to include information about atovaquone.

Section 7.2: The third sentence “One course of therapy is defined as 2 complete treatment cycles....” was deleted for consistency with the rest of the protocol.

Section 7.3.13: The dose modification table and corresponding footnote were deleted and the following text added: “The dose of temozolomide given in each cycle will be 150mg/m². No dose modification of the temozolomide dose is allowed. Subjects developing grade 3 hematologic toxicity will be managed by modifying the doses of CPT-11 as indicated below.”

Section 7.4.6: The second and third paragraphs were revised to clarify the irinotecan
shipping and drug returning procedures.

Section 9.1: The first paragraph under Section 9.0 “Other Therapy”, “Pneumocystis Prophylaxis” was reformatted to accommodate additional drug information. “or intravenous” was added to the second line of the first bullet because administration of intravenous pentamidine was added to the protocol. The second bullet includes information for dapsone and atovaquone.

Section 11.1: “SEE SECTION 11.2 FOR EVALUATION TIMEPOINTS” was added to heading. For “MRI or CT with contrast” footnote c was deleted under “Required Assessments” and added under “Pre-Treatment Evaluation.” In footnote d, “before every course” was deleted and “every 2 cycles (2 months)” was added for clarity and consistency with rest of protocol.

Section 11.2.4: In the first sentence, “2 cycles” was added between “every” and “(2 months).”

Consent:

- Under “What Is Involved In The Study?” # 2: The fourth paragraph was revised to reflect the additional choice of drugs a patient may receive for pneumocystis prophylaxis at the discretion of their doctor; the first sentence of the sixth paragraph was revised from “one month” to “2 weeks” for consistency with the protocol and the last sentence was added to include intravenous pentamidine; paragraphs seven and eight were added to include dapsone and atovaquone, which were added to the protocol.

- Under “Standard procedures being done because you are in this study,” in first bullet “glucose testing, blood tests to check liver and kidney function, urine tests” was deleted; “weekly” was changed to ”every 2 weeks” for consistency with protocol. The second bullet was revised to read: “Blood tests to determine the level of antiseizure medicine in your blood and blood tests to check liver and kidney function performed every 2 months or as clinically needed” for consistency with protocol.

- Under “How Long Will I Be In The Study?” the last sentence was revised to be consistent with the text of the protocol as: “You will be seen every month during the year of temozolomide and irinotecan chemotherapy, then in follow-up every 3 months for the next 2 years, and then every 6 months for 3 years, then annually.”

- The last sentence in the first paragraph under “Risks Associated with Temozolomide,” was revised to reflect the additional choices of treatment for pneumocystis pneumonia—the phrase “either as a pill treatment or using a type of inhaled antibiotic” was deleted.

- Under “Risks of antibiotic treatments to prevent pneumocystis pneumonia,” “Rash” was deleted from Uncommon risks of oral trimethoprim-sulfamethoxazole, and sections on Risks of dapsone and Risks of atovaquone were added.
Appendix III: In the last sentence of the first paragraph, “to process this form” was added; a space to provide an email address was added to the contact information; address information for sending completed forms was revised.