

North Central Cancer Treatment Group

N0177: A Pilot and Phase II Study of OSI-774 and Temozolomide in Combination with Radiation Therapy in Glioblastoma Multiforme

Addendum 10 – February 17, 2006

Summary

- Clarification made to the eligibility criteria (Section 3.0) that women of childbearing potential must have a negative serum pregnancy test within 7 days of registration.
- Various editorial changes have been made to the test schedule section of the protocol.
- In order to allow more appropriate treatment flexibility, clarification has been made to the protocol treatment section of the protocol with regard to the starting dose of TMZ after radiation therapy (RT).
- For purposes of treatment flexibility, a dose reduction is allowed for the start of TMZ treatment after RT.
- In response to numerous inquiries, modifications have been made to the protocol treatment section of the protocol for further clarification.
- The timing of obtaining the EGFR samples was revised to be consistent throughout the protocol.
- The National Cancer Institute has requested that the Comprehensive Adverse Events and Potential Risks List (CAEPR) be included in all protocols that CTEP holds the IND. This listing has been incorporated into the drug information section of the protocol for OSI-774 and will replace the existing “known potential toxicities” section. Also additional side effects have been identified in this CAEPR listing and have been added to the model consent form.
- Contact information for Helen Tollefson has been updated throughout the protocol.
- Contact information for Dr. Maihle has been updated in the Translational/Pharmacologic Studies section (Section 14.2) of the protocol.
- Clarification made to the records and data collection (Section 18.0) as to the time points for collecting the MMSE in order to be consistent with the test schedule.
- Corrections have been made to the consent forms for consistency purposes that patients will be followed for 15 years rather than 5 years and that the total amount of additional blood draws will be 4 teaspoons rather than 1 teaspoon.
- Protocol resource personnel updates.
- Editorial/administrative changes.

**A Replacement protocol is provided. Please replace the current copy with the one attached.
Please keep this addendum with your protocol**

Title page: Now reflects Addendum 10 and revised NCI version date.

Page 2: The following corrections have been made to the protocol resource page:

- The NCCTG Research Base Protocol Development Coordinator’s name has been changed from Lori K. ~~Kelly~~ to Lori K. **Bratvold**.
- The fax number for Kathryn Scherger now reflects 507/284-1902 **266-7240**.
- The fax number for Helen Tollefson now reflects 507/284-1902 **9628**.
- The NCCTG Research Base SAE Coordinator has been added.
- The fax number for Vicki Bryhn now reflects 507/284-1902 **538-0906**.
- Contact information for Brenda J. Booth now reflects current contact information as follows:

Brenda J. Booth MLT (ASCP)
~~Tissue Acquisition and Cellular/Molecular Analysis~~ **Biospecimens**
Accessioning and Processing
Phone: 507/284-9730 **538-7062**
Fax: 507/284-8105 **538-7613**

Page 15: Section 3.31 (Patient Eligibility) has been revised as follows for clarification due to the MTD for patients on EIACs still being defined:

~~On or~~ **Off EIACs (until otherwise notified).**

Page 16: Section 3.47 (Patient Eligibility) is newly added to reflect that women of childbearing potential must have a negative serum pregnancy test within 7 days of registration.

Previous Section 3.47 now becomes Section 3.48.

Pages 17-18: Section 4.0 (Test Schedule), corrections and clarifications have been made as follows:

- Reference to footnote #10 has been deleted from the “Chemistry group” row under the column “(First 6 months after RT)...” as closer surveillance of lab values are needed during treatment.
- Reference to new footnote #12 is newly added to the “MRI or CT scan” row in order to clarify that MRI’s are preferred, but CT scans will be accepted.
- Reference to footnote #11 has been added to the “sEGFR assay” row under the column “First 6 months after RT)...” in order to decrease the burden of performing the number of EGFR assays without affecting the scientific values.
- The “X” has been deleted under the last column for the “sEGFR assay” as this is not needed at this timepoint.
- Footnote #1 has been revised to delete reference to the NCCTG pathology coordinator title and to reflect current fax number as follows: “If materials have been previously submitted to Dr. B. Scheithauer for a consult review or to a cooperative group pathologist for central pathology review for another cooperative group protocol, fax a copy of this review to ~~the NCCTG pathology coordinator~~ **Helen Tollefson** (507-284-1902 **9628**) to verify grade 4 astrocytoma. Then follow the pathology material procedures found in Section 18.0 so the process can be completed.”
- Footnote #11 is newly added.
- Footnote #12 is newly added.

Pages 20,22,23: Sections 7.21, 7.31, and 7.41 (Protocol Treatment), a new footnote has been added after each table in order to allow more appropriate treatment flexibility as follows:

****At discretion of the treating physician, the patient may be treated at 150 mg/m²/day for 5 consecutive days at the first maintenance TMZ cycle (i.e., 4 weeks after radiation is completed). In the absence of grade 3 or 4 adverse events, a single dose escalation to 200 mg/m²/day may be attempted for the second maintenance TMZ cycle (i.e., 8 weeks after radiation is completed), and if tolerated should be continued for all subsequent cycles.**

Page 24: Section 7.5121 (Protocol Treatment) has been revised for clarification that an MRI or CT scan may be used for biopsy only patients as follows:

The localized contrast enhancement or mass and surrounding edema as estimated from the postoperative CT scan plus a 2 cm margin or the tumor plus edema based on the T2 weighted postoperative MRI scan plus a 2 cm margin will be the target volume for the initial fields (**for biopsy only patients a preoperative MRI or CT scan may be used to determine treatment volumes**). The dose to these initial fields will be 5000 cGy.

Page 24: Section 7.514 (Protocol Treatment) has been revised for clarification due to the possibility of treatment interruptions due to extenuating circumstances as follows:

Treatment will be given at 200 cGy per fraction, to isocenter for SAD treatments and to midplane for opposed SSD treatments or to the intersection of field centers at central axis for non-opposed SSD treatments, one fraction per day, **five days a week**, for a total dose of 6000 cGy. A minimum of two fields per fraction will be treated. Customized blocking should be utilized. **For extenuating circumstances (i.e. treatment interruptions due to holidays, inclement weather) one BID treatment may be delivered (treatments >6 hours apart) or 6 treatments a week (i.e. on a Saturday or Sunday) may be delivered.**

Page 25: Section 7.516 (Protocol Treatment) has been revised for further clarification as follows:

Port films of each field will be obtained and compared with initial simulator films at least ~~weekly~~ **once. At a minimum, port films will be obtained and compared with initial simulator reference films (i.e., reference films such as an orthogonal pair) at least weekly.**

Page 27: Section 8.0 (Dosage Modification Based on Adverse Event[s]), footnote * has been revised for purposes of treatment flexibility and clarification as follows:

Once a dose has been reduced, it should not be subsequently increased. **NOTE: When switching from daily TMZ during RT to maintenance TMZ after RT, at that point at the discretion of the treating physician one can start with 150 or 200 mgm²/day if there was a dose reduction during the daily TMZ during RT.**

Page 28: Section 10.12 (Adverse Event (AE) Reporting and Monitoring), the second sentence in the first bullet has been revised to correctly direct study personnel to the CAEPR as follows:

~~To access the CAEPR for an agent under a CTEP IND, contact the AdEERS MD Help Desk at adeersmd@tech-res.com.~~ **Refer to Section 15.0 to locate the CAEPR for the CTEP IND agent(s).**

Page 40: Section 14.171 (Translational/Pharmacologic Studies) has been revised to reflect current address for Helen Tollefson and to delete reference to NCCTG Pathology Coordinator as follows:

Paraffin blocks submitted from outside hospitals besides Mayo Clinic Rochester should be sent to ~~the NCCTG pathology coordinator~~ **Helen Tollefson** at the following address:

NCCTG Operations Office
~~Plummer 4~~ **NW Clinic 3-24**
200 First Street SW
Rochester, MN 55905
ATTN: Helen Tollefson, ~~Pathology Coordinator~~

~~The Pathology Coordinator~~ **Helen Tollefson** will forward the materials to: Dr. Robert B. Jenkins' laboratory at Mayo Clinic Rochester.

Page 41: Section 14.22 (Translational/Pharmacologic Studies) has been revised in order to be consistent with the test schedule and to reflect Dr. Maihle's current location as follows:

The sEGFR concentrations will be determined by Nita J. Maihle, Ph.D.; **at Yale University School of Medicine and her staff at Mayo Clinic Rochester.** Maihle and colleagues have identified a 110-kDa soluble EGFR (p110 sEGFR) protein in human sera and have developed an ALISA (Acridinium Linked ImmunoSorbent Assay) to quantify this p110 sEGFR protein (81). Where possible, pre-operative blood samples will be obtained. In all cases, samples will be obtained at registration, **during fifth week of OSI-774 (after patient has received at least 28 days of OSI-774) at initiation of radiation therapy and at subsequent intervals the beginning of the third cycle of combined TMZ/OSI following the completion of radiotherapy.**

Section 14.232 (Translational/Pharmacologic Studies), the fourth sentence of the second paragraph has been revised to reflect the correct shipping addresses as follows:

Ship on dry ice within 24 hours to the ~~Tissue Acquisition and Cellular/Molecular Analysis Shared Resource laboratory~~ **Biospecimens Accessioning and Processing**, Guggenheim 10364, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, Attention Brenda Booth, who will process the sample and forward to Dr. Nita Maihle's laboratory (Department of Biochemistry and Molecular Biology, Guggenheim 1402, Mayo Clinic, 200 First Street SW, Rochester, MN 55905), attention Jackie Lafky **Lori Carria, Maihle Laboratory, Yale University – School of Medicine, 300 George Street, Suite 8100, New Haven, CT 06511**, within 2 hours of receipt.

Pages 43-44: Section 15.15 (Drug Information) has been replaced in its entirety due to the inclusion of the CAEPR listing for OSI-774 at the request of the National Cancer Institute.

Pages 44-65: Due to the inclusion of the CAEPR listing, repagination has occurred.

Page 55: Section 17.0 (Pathology Considerations), the fifth sentence has been revised to delete reference to the NCCTG pathology coordinator title and to reflect the current fax number as follows:

If materials have been previously submitted to Dr. B. Scheithauer for a consult review or to a cooperative group pathologist for central pathology review for another cooperative group protocol, fax a copy of this review to ~~the NCCTG pathology coordinator~~ **Helen Tollefson (507/284-1902 9628)** to verify grade 4 astrocytoma.

Pages 56: Section 18.2 (Records and Data Collection Procedures), the "X" has been deleted from the column "End of RT" for the MMSE in order to be consistent with the test schedule, this is not needed at this time point.

Page 57: Section 18.2 (Records and Data Collection Procedures), the first paragraph of footnote #1 and the first and third paragraphs of footnote #2 have been revised to delete reference to the NCCTG pathology coordinator as follows:

1. A call needs to be made to ~~the NCCTG pathology coordinator~~ **Helen Tollefson** (507/266-0724) prior to forwarding the following material:
2. Within 30 days of registration, submit the paraffin block to ~~Pathology Coordinator~~ **Helen Tollefson**, NCCTG Operations Office, ~~Plummer 4~~ **NW Clinic 3-24**, 200 First Street SW, Rochester, MN 55905.

Following patient registration, submit the packaged blocks/slides to the NCCTG Operations Office, ~~pathology coordinator~~ **Helen Tollefson**.

Section 18.2 (Records and Data Collection Procedures), the third sentence of footnote #3 has been revised for clarification as follows:

For patients who do not receive any scheduled radiation therapy, submit ~~a the~~ **the** radiation therapy reporting form ~~explaining why~~ **with the reason** radiation was not given.

Appendix IA: Correction has been made to the third sentence of the third paragraph under the section “What will happen in the study?” to reflect that patients will be followed annually for **15** years rather than 5 years.

Correction has been made to the fourth paragraph under the section “What will happen in the study?” to reflect that **4** teaspoons of additional blood will be drawn rather than 1 teaspoon.

Under the “What are the risks of the study?” section for OSI-774, additional side effects have been identified and realignment and reformatting have also occurred to reflect the information provided in the CAEPR listing as follows:

~~More common~~ **Likely** side effects:

Diarrhea
 Skin rash
 Nausea
 Dizziness
Headache
~~Vomiting~~
 Fatigue
~~Loss of appetite~~
Skin dryness
Itchiness

Appendix IA
Con't:

Less ~~common~~ **likely** side effects:

Mouth dryness

Vomiting

Headache

Fatigue

Loss of appetite

~~Skin dryness~~

~~Itchiness~~

Fever

Hair loss

Heartburn

Mouth sores

Taste changes

Eye dryness

Dry cough

Shortness of breath

Eye pain

Eye infections

Liver injury

Rare **but serious** side effects:

~~Eye dryness~~

~~Eye pain~~

~~Eye infections~~

~~Fever~~

~~Dry cough~~

~~Shortness of breath~~

~~Lung damage~~

~~Mouth sores~~

~~Taste changes~~

~~Heartburn~~

~~Hair loss~~

~~Liver injury~~

Skin sores/ulcers

Side effects reported by patients, but not proven to be caused by OSI-774:

Dehydration

Stomach or intestine ulcers

Bleeding

Infections

Kidney damage

Eye inflammation and blurred vision

Appendix IB: Correction has been made to the third sentence of the third paragraph under the section “What will happen in the study?” to reflect that patients will be followed annually for **15** years rather than 5 years.

Correction has been made to the fourth paragraph under the section “What will happen in the study?” to reflect that **4** teaspoons of additional blood will be drawn rather than 1 teaspoon.

Under the “What are the risks of the study?” section for OSI-774, additional side effects have been identified and realignment and reformatting have also occurred to reflect the information provided in the CAEPR listing as follows:

~~More common~~ **Likely** side effects:

Diarrhea
Skin rash
Nausea
Dizziness
~~Headache~~
~~Vomiting~~
Fatigue
~~Loss of appetite~~
Skin dryness
Itchiness

~~Less common~~ **likely** side effects:

Mouth dryness
Vomiting
Headache
Fatigue
Loss of appetite
~~Skin dryness~~
~~Itchiness~~
Fever
Hair loss
Heartburn
Mouth sores
Taste changes
Eye dryness
Dry cough
Shortness of breath
Eye pain
Eye infections
Liver injury

Appendix IB
Con't:

Rare **but serious** side effects:

~~Eye dryness~~

~~Eye pain~~

~~Eye infections~~

~~Fever~~

~~Dry cough~~

~~Shortness of breath~~

~~Lung damage~~

~~Mouth sores~~

~~Taste changes~~

~~Heartburn~~

~~Hair loss~~

~~Liver injury~~

Skin sores/ulcers

Side effects reported by patients, but not proved to be caused by OSI-774:

Dehydration

Stomach or intestine ulcers

Bleeding

Infections

Kidney damage

Eye inflammation and blurred vision

Appendix IC: Correction has been made to the third sentence of the third paragraph under the section "What will happen in the study?" to reflect that patients will be followed annually for **15** years rather than 5 years.

Correction has been made to the fourth paragraph under the section "What will happen in the study?" to reflect that **4** teaspoons of additional blood will be drawn rather than 1 teaspoon.

Appendix IC
Con't:

Under the "What are the risks of the study?" section for OSI-774, additional side effects have been identified and realignment and reformatting have also occurred to reflect the information provided in the CAEPR listing as follows:

~~More common~~ **Likely** side effects:

Diarrhea
Skin rash
Nausea
Dizziness
~~Headache~~
~~Vomiting~~
Fatigue
Loss of appetite
Skin dryness
Itchiness

~~Less common~~ **likely** side effects:

Mouth dryness
Vomiting
Headache
Fatigue
Loss of appetite
~~Skin dryness~~
~~Itchiness~~
Fever
Hair loss
Heartburn
Mouth sores
Taste changes
Eye dryness
Dry cough
Shortness of breath
Eye pain
Eye infections
Liver injury

Appendix IC
Con't:

Rare **but serious** side effects:

Eye dryness

Eye pain

Eye infections

Fever

Dry cough

Shortness of breath

Lung damage

Mouth sores

Taste changes

Heartburn

Hair loss

Liver injury

Skin sores/ulcers

Side effects reported by patients, but not proved to be caused by OSI-774:

Dehydration

Stomach or intestine ulcers

Bleeding

Infections

Kidney damage

Eye inflammation and blurred vision