

North Central Cancer Treatment Group

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

Addendum 6 – September 24, 2004

Summary

- This protocol is being amended to include the addition of temozolomide due to the lack of overlapping dose-limiting toxicities, the different mechanisms of action of the agents, and evidence supporting synergistic activity of each agent with radiotherapy. In addition, alkylating agents have been shown to increase survival in high grade gliomas.
- Once either Study 1 or Study 2 is completed, Study 3 will be able to open to patient accrual.
- The first 3 dose levels for OSI-774 have been completed; therefore, the protocol has been updated to reflect the current dose level status.
- With the addition of cohorts, the sample size has been increased.
- The analytical procedures have been updated in the statistical section to reflect only performing one interim analysis.
- Clarification has been given to the decision rule.
- At the recommendation of Genentech, Inc., additional information has been added to the consent form. In a recently completed study of lung cancer, when serious side effects occurred, they were more likely to have lead to death for the patients who took OSI-774 plus chemotherapy as compared to those who took the placebo plus chemotherapy.
- Editorial/administrative changes.

A replacement protocol is provided. Please replace the current copy with the one attached.

Title page: Reflects addition of Addendum 6. The NCI version date of May 26, 2004 has been added.

The title of the study has been revised as follows:

A Phase I/II Study of OSI-774 **and Temozolomide** in Combination with Radiation Therapy in Glioblastoma Multiforme

Page 2: Protocol resource: The fax numbers and e-mail addresses are now reflected for the research base nurse and NCCTG nurse.

Page 4: The schema has been revised to include the addition of temozolomide.

Pages 12-14: Section 1.6 (Background) is newly added.

Page 14: Section 2.0 (Goals) has been revised to include the addition of temozolomide.

- Page 15: Section 3.41 (Patient Eligibility) has been revised as follows:
Histologically confirmed glioblastoma multiforme (grade 4 of 4 ~~glioma~~ **astrocytoma**). Gliosarcomas **and other grade 4 astrocytoma variants (e.g., oligoastrocytoma, giant cell, etc.)** may be included. Central pathology review is mandatory prior to study entry to confirm eligibility. It should be initiated as soon after surgery as possible.
- Page 15: Section 3.46 (Patient Eligibility) has been revised as follows:
- ANC \geq 1500/ μ L
 - **Hemoglobin \geq 9**
 - PLT \geq 100,000/ μ L
 - Total bilirubin \leq 1.5 x institutional upper limit of normal (ULN)
 - AST(SGOT) \leq 2.5 x institutional (ULN)
 - Creatinine \leq 1.5 x institutional (ULN)
- Page 16: Section 3.53 (Patient Eligibility) has been revised as follows:
Prior chemotherapy or radiation therapy for any brain tumor. **No prior temozolomide.**
- Section 3.58d (Patient Eligibility) is newly added as follows:
Any history of allergy or intolerance to Dacarbazine (DTIC).
- Page 17: Section 4.0 (Test Schedule): The following revisions have been made to Section 4.0:
- The heading of the fifth column has been revised as follows:
Weekly during OSI-774/**TMZ** and RT
 - A new seventh column “Before each cycle maintenance TMZ” has been added and the following tests and procedures will be performed at this timepoint:
Toxicity assessment
Exam, wt, PS
Hematology group (CBC with differential)
Anticonvulsant and steroid treatment log
 - Reference to footnote #5 has been deleted under the column entitled “Weekly during OSI-774/TMZ and RT for the “Hematology group”
 - Footnote #9 has been revised as follows:
This part of the schedule will start immediately after radiotherapy completed (i.e., 2 months after radiotherapy completed the patient will undergo testing as per the maintenance/observation schedule, which includes a MRI along with other tests). Blood draws not necessary for patients on observation not receiving **any protocol chemotherapy (OSI-774 or TMZ).**
 - New Footnote 11 added.

Pages 19-25: Entire Section 7.0 (Protocol Treatment) has been revised to include the addition of temozolomide.

The fourth and fifth bullets in Section 7.1 (Protocol Treatment) have been revised as follows:

- \geq grade ~~3~~4 thrombocytopenia
- \geq grade 3 **(other)** non-hematological toxicity

Page 22: The Dose Escalation Scheme in Section 7.32 (Protocol Treatment) has been revised to reflect the dose level status.

Page 26: The table in Section 8.0 (Dosage Modification Based on Adverse Event(s)) has been revised to include additional toxicities due to the addition of temozolomide.

Page 27: Section 9.0 (Ancillary Treatment) has been revised as follows:

- 9.2 ~~Antiemetics – Since OSI-774 has not been associated with significant severe nausea/vomiting, we do not mandate the routine use of anti-emetics. If nausea and/or vomiting are encountered, the choice of anti-emetics will be left to the treating physician.~~ **Since TMZ may cause nausea, an appropriate anti-emetic (e.g., 1 mg dose of granisetron, or 4 mg of ondansetron) will be given one hour before the TMZ. Additional symptoms will be managed as per standard antiemetic guidelines.**
- 9.3 Anticonvulsants - Dosages must be recorded on concurrent treatment log. Anticonvulsant levels will be maintained in the therapeutic range and doses adjusted for maximal therapeutic efficacy, at the discretion of the patient's physician. Where medically appropriate, the use of a non-enzyme-inducing anticonvulsant will be encouraged. In patients already on EIACs and taking OSI-774, it is possible that discontinuing EIACs or switching to non-EIAC drugs could lead to OSI-774 overdose and toxicity. Extreme caution is advised in these scenarios. **If a patient is switched from an EIAC to a non-EIAC, the OSI-774 dose should be lowered to the maximally tolerated OSI-774 dose for patients not on EIACs.**

Pages 28-33: Section 10.0 (Adverse Events (AE) Reporting and Monitoring):

The following paragraphs under Section 10.1 have been updated to reflect current adverse event reporting procedures:

- 10.1 This study will utilize the Common Toxicity Criteria (CTC) version 2.0 for adverse event monitoring and reporting. The CTC version 2.0 can be downloaded from the CTEP home page (~~http://ctep.info.nih.gov/CTC3/ctc_ind_term.htm~~ <http://ctep.info.nih.gov/reporting/ctc.html>). All appropriate treatment areas should have access to a copy of the CTC version 2.0.

- Second paragraph under Section 10.11:

Expedited adverse event reporting requires submission of an **electronic** Adverse Event Expedited Reporting System (AdEERS) report. ~~Telephone~~ **Twenty-four (24) hour electronic** notification of NCI and NCCTG may also be required. ~~Telephone~~ **Twenty-four (24) hour electronic notification** and AdEERS reports are to be completed within the timeframes specified in Section 10.2. All expedited adverse event reports should also be submitted to the local Institutional Review Board (IRB).

Pages 28-33 (continued): The following has been updated in Section 10.2 to reflect current adverse event reporting procedures for studies with investigational agents:

10.21 Studies 1 and 2 (Mayo Rochester, Jacksonville, Scottsdale, and University of Alabama at Birmingham only)

<i>UNEXPECTED EVENT</i>		<i>EXPECTED EVENT</i>		<i>SECONDARY AML/MDS</i>
<i>GRADES 2 – 3</i> Attribution of Possible, Probable or Definite	<i>GRADES 4 and 5</i> Regardless of Attribution	<i>GRADES 1 – 3</i>	<i>GRADES 4 and 5</i> Regardless of Attribution	
<p>Grade 2 – Expedited report within 10 working days.</p> <p>Grade 3 – Report by phone 24-hour electronic notification to IDB and to the NCCTG Operations Office within 24 hrs. Expedited report to follow within 10 working days.</p> <p>(Grade 1 – Adverse Event Expedited Reporting NOT required.)</p>	<p>Report by phone 24-hour electronic notification to IDB and to the NCCTG Operations Office within 24 hrs. Expedited report to follow within 10 working days.</p> <p>This includes all deaths within 30 days of the last dose of treatment with an investigational agent regardless of attribution.</p> <p>Any late death attributed to the agent (possible, probable, or definite) should be reported within 10 working days.</p>	<p>Adverse Event Expedited Reporting NOT required.</p>	<p>Report by phone 24-hour electronic notification to IDB within 24 hrs and to the NCCTG Operations Office. Expedited report to follow within 10 working days.</p> <p>This includes all deaths within 30 days of the last dose of treatment with an investigational agent regardless of attribution.</p> <p>Any late death attributed to the agent (possible, probable, or definite) should be reported within 10 working days.</p>	<p>Reporting for this event required during and after completion of study treatment.</p> <p>Submit the NCI/CTEP Secondary AML/MDS Report form to the NCCTG Operations Office (see below next page) within 15 days per the instructions specified on the form.</p>

Pages 28-33 (continued):

The following has been updated in the footnotes for Section 10.2 to reflect current adverse event reporting procedures for studies with investigational agents:

- **For Hospitalizations only** - Any medical event equivalent to CTC Grade 3, 4, 5 which precipitated hospitalization (or prolongation of existing hospitalization) must be reported regardless of expected or unexpected and attribution.
- ~~Telephone reports to the Investigational Drug Branch at 301-230-2330 available 24 hours daily (recorder between 5 pm and 9 am EST). Also notify the NCCTG Operations Office within 24 hours. Call 507-284-3559. If after hours, record a detailed voicemail message or notify NCCTG Operations Office the next working day.~~
- Expedited reports are to be submitted electronically using the AdEERS application available at <http://ctep.info.nih.gov/AdEERS> <http://ctep.info.nih.gov/reporting/adeers.html>. The NCI Guidelines for expedited adverse event reporting are also available at this site.
- To submit written reports to NCCTG Operations Office, fax **or mail** reports to the NCCTG Operations Office, 200 First Street SW, Rochester, MN 55905, Fax: (507) 284-1902. The NCCTG Operations Office will submit the report to the NCI, IDB, if required, and provide copies to the Operations Office pharmacist and protocol development coordinator
- For this study refer to Section 15.152 for information regarding which adverse events should be considered as expected events.

Pages 28-33 (continued):

The following changes have been made to Section 10.22 to reflect current adverse event reporting procedures for Study 3:

- 10.22 Study 3 (entire NCCTG membership)

<i>Unexpected Event</i>		<i>Expected Event</i>		<i>Grade 4 Myelosuppression or Hospitalizations During Treatment Not Otherwise Reportable</i>	<i>Secondary AML/MDS</i>
<i>Grades 2 and 3 Attribution of Possible, Probable or Definite</i>	<i>Grader 4 and 5 Regardless of Attribution</i>	<i>Grades 1 through 3</i>	<i>Grades 4 and 5 Regardless of Attribution</i>		
<p>Expedited report within 10 working days.</p> <p>(Grade 1 Adverse Event Expedited Reporting NOT required.)</p>	<p>Report by phone 24-hour electronic notification to IDB and to the NCCTG Operations Office within 24 hrs. Expedited report to follow within 10 working days.</p> <p>This includes all deaths within 30 days of the last dose of treatment with an investigational agent regardless of attribution.</p> <p>Any late death attributed to the agent (possible, probable, or definite) should be reported within 10 working days.</p>	<p>Adverse Event Expedited Reporting NOT required.</p>	<p>Expedited report, including Grade 5 aplasia in leukemia patients, within 10 working days.</p> <p>This includes all deaths within 30 days of the last dose of treatment with an investigational agent regardless of attribution.</p> <p>Any late death attributed to the agent (possible, probable, or definite) should be reported within 10 working days.</p>	<p>Submit a Notification Form: Grade 4 or 5 Non-AER Reportable Events/Hospitalization Form to NCCTG Operations Office (see below next page) within 5 working days.</p> <p>If AdEERS report has been submitted, this form does not need to be submitted.</p>	<p>Reporting for these events required during and after treatment.</p> <p>Submit NCI/CTEP Secondary AML/MDS Report Form to the NCCTG Operations Office (see below next page) within 15 working days.</p>

Pages 28-33 (continued):

The following has been updated in the footnotes for Section 10.22 to reflect current adverse event reporting procedures for Study 3:

- **For Hospitalizations only** - Any medical event equivalent to CTC Grade 3, 4, 5 which precipitated hospitalization (or prolongation of existing hospitalization) must be reported regardless of expected or unexpected and attribution.
- ~~Telephone reports to the Investigational Drug Branch at 301-230-2330 available 24 hours daily (recorder between 5 pm and 9 am EST). Also notify the NCCTG Operations Office within 24 hours. Call 507-284-3559. If after hours, record a detailed voicemail message or notify NCCTG Operations Office the next working day.~~
- Expedited reports are to be submitted electronically using the AdEERS application available at <http://ctep.info.nih.gov/AdEERS> <http://ctep.info.nih.gov/reporting/adeers.html>. The NCI Guidelines for expedited adverse event reporting are also available at this site.
- To submit written reports to NCCTG Operations Office, fax ~~or mail~~ reports to the NCCTG Operations Office, 200 First Street SW, Rochester, MN 55905, Fax: (507) 284-1902. The NCCTG Operations Office will submit the report to the NCI, IDB, if required, and provide copies to the Operations Office pharmacist and protocol development coordinator.
- For this study refer to Section 15.152 for information regarding which adverse events should be considered as expected events.

- Page 31: Section 10.3 (Adverse Event (AE) Reporting and Monitoring) has been revised as follows:
- A new category “Blood/Bone Marrow” has been added to include neutropenia and thrombocytopenia which will be graded at each evaluation.
 - Nausea has been added to the “Gastrointestinal” category and will be graded at each evaluation.
- Page 36: Section 13.17 (Treatment/Follow-up Decision at Evaluation of Patient), an additional paragraph has been added as follows:
- As with OSI-774, treatment with maintenance TMZ will continue until one of the following criteria listed above applies or a total of 6 cycles have been completed.**
- Pages 36-37: Renumbering and other revisions have occurred in Section 13.0 (Treatment/Follow-up Decision at Evaluation of Patient) as follows:
- Previous Section 13.3 now becomes Section 13.223.
 - Previous Section 13.4 now becomes Section 13.23.
 - Previous Section 13.5 now becomes Section 13.3 and has also been revised as follows:
 - **For Studies 1, 2, and 3:** Patients who PROG or
 - Previous Section 13.6 has been deleted.
 - Previous Section 13.7 now becomes Section 13.4.
 - Previous Section 13.8 now becomes Section 13.5.
- Page 39: Section 14.142 (Ancillary Studies), the reference number has been revised to reflect #80 rather than #66.
- Page 40: Section 14.16 (Pathology – Collection): Helen Tollefson’s name has been added to the address reflected in this section.
- 14.161 Paraffin blocks submitted from outside hospitals besides Mayo Clinic Rochester should be sent to the NCCTG pathology coordinator at the following address:
- NCCTG Operations Office
Plummer 4
200 First Street SW
Rochester, MN 5905
ATTN: **Helen Tollefson**, Pathology Coordinator
- Page 44-47: Section 15.2 (Drug Information) is newly added to reflect the addition of temozolomide.

Page 47-54: The following revisions have been made to Section 16.0 (Statistical Considerations and Methodology):

- Section 16.1 now reflects the addition of temozolomide.
- Section 16.11 has been revised as follows:
 - Study design: The cohorts-of-3 **or -6** design described in Section 7.0 will be used, with MTD and DLT as defined therein. Dose-level decisions for succeeding cohorts will be made approximately 3 weeks after the 3rd **last** patient in a specific cohort has completed radiation therapy, i.e., about 10 weeks after the patient begins study therapy.
- Section 16.12 now reflects a maximum of 36 patients rather than 18.
- Section 16.13 has been rewritten to reflect revised analysis plans.
- New Section 16.131 (Adverse event profile) and new Section 16.132 (Toxicity profile) and all remaining sections have been renumbered.
- Previous Section 16.131 (now Section 16.133), the following has been added to the end of the first sentence:
 - in the two patient populations (Study 1 and Study 2). Within each patient population summaries will be prepared for the entire group as well as by the treatment received (OSI-774 only and OSI-774+TMZ).**
- Previous Section 16.132 (now Section 16.134) has been rewritten to clarify timed endpoints.
- Section 16.21 has been revised to reflect performing one interim analysis rather than two.
- Section 16.23 has been rewritten.
- Section 16.24 has been revised to reflect performing one interim analysis rather than two.
- Section 16.26 has been revised to reflect that Study 3 can open to patient accrual before Study 1 or Study 2 is complete.
- Section 16.27 is newly added and previous Section 16.27 now becomes 16.28.
- Section 16.2815 has been revised to reflect one interim analysis. The reference number has been revised to reflect #84 rather than #70.
- Section 16.5, the first 2 bullet items have been revised to reflect the addition of temozolomide and to reflect that Study 3 can open after Study or Study 2 is complete.
- The table in Section 16.63 has been updated to accurately represent desired patient accrual.

Page 54: Section 17.0 (Pathology Considerations): Editorial correction:

17.0 Pathology Considerations:

Central pathology review is mandatory prior to study entry to confirm eligibility. It should be initiated ... 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 ~~data monitor~~ **coordinator** (507/284-1902) to verify grade 4 astrocytoma. Then follow the pathology material procedures found in Section 18.0 so the process can be complete.

Page 56: Section 18.0 (Records and Data Collection Procedures):

- The “x” has been deleted from the row “Anticonvulsant and Steroid Treatment Log” and column “Prior to study entry” and relocated to the column “≤14 days after registration.”
- The “x” has been deleted from the row “CTEP Report Variables Form” and column “Prior to study entry” and relocated to “≤14 days after registration.”
- Editorial correction in Footnote 2 to add the pathology coordinator’s name:
 2. Within 30 days of registration, submit the paraffin block to Pathology Coordinator **Helen Tollefson**, NCCTG Operations Office, Plummer 4, 200 First Street SW, Rochester, MN 55905.

Pages 61-63: The following revisions have been made to Section 20 (References):

- References #65 and 66 are newly added.
- Previous reference #65 now becomes #79.
- Previous reference #66 now becomes reference 67.
- References #68-78 are newly added and all other references have been renumbered.

Appendices
IA, IB, and IC:

The following revisions have been made to each of the consent forms:

- The study title has been updated.
- The consent forms have been revised to include the addition of temozolomide.
- Appendices IA and IB: The second sentence of the third paragraph under the section titled “What will happen in the study?” has been revised to include that patients will also have blood tests during their course of radiation treatments. *Note:* Appendix IC: The same information applies except it occurs in the second sentence of the second paragraph rather than the third paragraph.
- The last sentence of the third paragraph under the section titled “What will happen in the study?” is newly added. *Note:* Appendix IC: The same information applies except it occurs in the second paragraph rather than third paragraph.
- Under the section “What are the risks of the study?” a new paragraph has been added under the OSI-774 side effects which includes the additional information requested by Genentech, Inc.
- Side effects for temozolomide have been added to the “What are the risks of the study?” section.