

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 7 – September 24, 2004

**Summary**

**As of Addendum 7, Studies 1 and 2 will re-open to patient accrual.**

- This protocol is being amended to clarify the current dose level status, the addition of temozolomide and opening of Study 3 once either Study 1 or Study 2 is completed.
- Observation phase has been removed from entire protocol.
- Editorial/administrative changes.

**Replacement pages are provided. Please incorporate into the protocol and keep this addendum with your protocol**

Title page: Reflects addition of Addendum 7. The revised NCI version date has been added.

Page 3: The Index page has been revised to reflect:  
“14.0 Ancillary ~~Translational~~ **Translational/Pharmacologic** Studies”

Page 4: The schema has been revised as follows:

- OSI-774 given alone for 4 weeks.
- OSI-774 + TMZ will be given for 6 cycles rather than 6 months.
- Progression/Refusal/Excessive Toxicity → event monitoring for each study is now located in 1 text box.
- “for 15 years maximum from on-study” has been added to the last column under OSI-774 for all studies.

Page 14: Section 2.121 (Goals), the first sentence has been revised as follows:

- To assess treatment effectiveness of OSI-774 alone followed by OSI-774 + temozolomide + radiation therapy followed by OSI-774 and temozolomide **x 6 cycles followed by OSI-774 alone**, until progression in newly diagnosed glioblastomas primarily by survival at 52 weeks after entry into this study.

Page 15: Section 3.41 (Patient Eligibility), the first sentence has been revised as follows:

- Histologically confirmed glioblastoma multiforme (grade 4 of 4 astrocytoma). Gliosarcomas and other grade 4 astrocytoma variants (e.g., ~~oligoastrocytoma,~~ giant cell, ~~etc.~~) may be included.

Pages 17 & 18: Section 4.0 (Test Schedule) has been revised as follows:

- Reference to footnote 10 in the heading of the 6<sup>th</sup> column “End of RT” has been replaced with footnote 9.
- New 7<sup>th</sup> column has been added and reads “**(First 6 months after RT) before each TMZ cycle during maintenance OSI-774 + TMZ.**”
- Heading of the 8<sup>th</sup> column has been revised to read “**(Second 6 months after RT) Maintenance/Observation<sup>9</sup> During maintenance OSI-774** every 2 months x ~~1-year~~ **x 6 months**, every 3 months x 1 year, ~~then at least~~ every 6 months x 4 years, then annually x ~~5-years~~ **until 15 yrs. from on study**”
- The row labeled “Medical oncology consult” Xs have been inserted under “End of RT,” “Before each TMZ cycle during maintenance OSI-774 + TMZ,” and “During maintenance OSI-774 every 2 months x 6 months, every 3 months x 1 year, every 6 months x 4 years, then annually until 15 years from on study” columns.
- Xs with footnote 10 referenced have been added for the rows “Neuro History and Exam,” “MMSE (Appendix V),” “Chemistry group (alk phos, t. bili, creatine, glucose, SGOT [AST]),” “Serum free anticonvulsant level,” “MRI,” and “sEGFR assay.”
- Footnote 9 has been deleted and remaining footnotes renumbered.
- Footnote 10 is newly added.

Page 19: Section 6.3 has been revised for clarification as follows:

Randomization Center will register patients separately to the translational research component of this study (see Section 14.0) .**(This is optional.)**

- **Patient has/has not given permission to allow tissue samples to be used for the translational goals of this study**
- **Patient has/has not given permission to allow blood to be drawn and used for the translational goals of this study**

Page 19: Section 7.1 (Protocol Treatment), the first sentence has been revised as follows:

- For Studies 1 and 2, patients will be ~~observed~~ **assessed** for dose limiting toxicity (DLT).....

Page 20: Section 7.21 (Protocol Treatment), the table has been revised as follows:

Agent	Dose	Route	Day(s)	Retreat
Radiation*	6000 cGy (200 cGy x 30 fractions)		5 days/week x 6 weeks	
OSI-774	Call Randomization Center for assigned dose level	Oral	<b>Continues</b> daily throughout study	<b>Daily</b>
TMZ*	75 mg/m <sup>2</sup> /d x 7 days/week during RT, Starting 4 weeks after RT TMZ 200 mg/m <sup>2</sup> daily x 5 days every 28 days for 6 cycles	<b>Oral</b>	Daily after RT a 4 week break, then 5 days of treatment every 28 days for 6 cycles <b>7 days/week for 6 weeks</b> during RT	
<b>After completion of daily TMZ and RT, patient <u>continues</u> OSI-774 alone daily x 4 weeks</b>				
<b>TMZ</b>	<b>200 mg/m<sup>2</sup> daily</b>	<b>Oral</b>	<b>5 day/ week</b>	<b>Every 28 days for 6 cycles</b>
<b>OSI-774</b>	<b>TBD</b>	<b>Oral</b>	<b>Daily continuously</b>	<b>Daily</b>

\* Radiation and **daily** TMZ to start after 1 week of OSI-774 alone

Page 21: Section 7.31 (Protocol Treatment), the 4<sup>th</sup> sentence of the 1<sup>st</sup> paragraph has been revised as follows:

- After the radiation is completed the OSI-774 will continue on a daily basis **throughout the study** but the daily TMZ (75 mg/m<sup>2</sup>/day) will be stopped.

Page 22: Section 7.31 (Protocol Treatment), the table has been revised as follows:

Agent	Dose	Route	Day(s)	Retreat
Radiation*	6000 cGy (200 cGy x 30 fractions)		5 days/week x 6 weeks	
OSI-774	Call Randomization Center for assigned dose level	Oral	<b>Continues</b> daily throughout study	<b>Daily</b>
<b>TMZ*</b>	75 mg/m <sup>2</sup> /d x 7 days/week during RT. Starting 4 weeks after RT TMZ 200 mg/m <sup>2</sup> daily x 5 days every 28 days for 6 cycles	Oral	Daily <b>7 days/week for 6 weeks</b> during RT; after RT a 4 week break, then 5 days of treatment every 28 days for 6 cycles	
<b>After completion of daily TMZ and RT, patient <u>continues</u> OSI-774 alone daily x 4 weeks</b>				
<b>TMZ</b>	<b>200 mg/m<sup>2</sup> daily</b>	<b>Oral</b>	<b>5 day/ week</b>	<b>Every 28 days for 6 cycles</b>
<b>OSI-774</b>	<b>TBD</b>	<b>Oral</b>	<b>Daily continuously</b>	<b>Daily</b>

\*Radiation and **daily** TMZ to start after 1 week of OSI-774 alone

Page 23: Section 7.41 (Protocol Treatment), the 2<sup>nd</sup> sentence has been revised as follows:

- ...stipulate the phase II doses for the combined (TMZ/OSI+RT) and the maintenance (TMZ/+OSI ~~alone after OSI+RT~~) sections...

Section 7.41 (Protocol Treatment), the table has been revised as follows:

Arm**	Agent	Dose	Route	Day(s)	Retreat
C1	Radiation*	6000 cGy (200 cGy x 30 fractions)		5 days/week x 6 weeks	
	<b>OSI-774</b>	<del>To be determined</del> <b>Call Randomization Center for assigned dose level</b>	<b>Oral</b>	<b>Continues daily throughout study</b>	<b>Daily</b>
	<b>TMZ</b>	<del>75 mg/m2/d x 7 days/week during RT. Starting 4 weeks after RT, TMZ 200 mg/m2 daily x 5 days every 28 days for 6 cycles</del>	<b>Oral</b>	<del>Daily 7 days/week for 6 weeks during RT; after RT a 4 week break, then 5 days of treatment every 28 days for 6 cycles</del>	
<b>After completion of daily TMZ and RT, patient <u>continues</u> OSI-774 alone daily x 4 weeks</b>					
	<b>TMZ</b>	<b>200 mg/m2 daily</b>	<b>Oral</b>	<b>5 day/week</b>	<b>Every 28 days for 6 cycles</b>
	<b>OSI-774</b>	<b>TBD</b>	<b>Oral</b>	<b>Daily continuously</b>	<b>Daily</b>

\* Radiation and **daily** TMZ to start after 1 week of OSI-774 alone

\*\* Treatment assignment code for CDUS reporting

Page 26: Section 8.2 (Dosage Modification Based on Adverse Event(s)), the dose mod table has been revised to add solid lines under TMZ in the “Nausea” and “Hepatic” sections.

Pages 36 & 37: Section 13.0 (Treatment/Follow-up Decision at Evaluation of Patient) has been rewritten and reformatted to remove separation of items between studies 1, 2, and 3 and reference to the observation phase has been removed.

Page 37: Section 14.0 (Ancillary Studies), the title has been revised to read “~~Ancillary~~ **Translational/Pharmacologic** Studies”

Pages 55 & 56: Section 18.0 (Records and Data Collection Procedures) has been revised as follows:

- The heading “Maintenance/Observation Material” now reads “Maintenance Material”
- Reference to footnote 7 is now located by the X under the “At Each Evaluation” column for “MMSE”
- Footnote 7 is newly added.

Page 57: Section 19.1 (Budget) has been revised to reflect routine clinical care and TMZ are costs charged to patient.

Appendix IA: “What will happen in the study?” has been revised as follows:

- The 2<sup>nd</sup> sentence of the 2<sup>nd</sup> paragraph now reads “Daily OSI-774 will then continue ~~until~~ **unless** your disease gets worse.”
- The 4<sup>th</sup> sentence of the 3<sup>rd</sup> paragraph now reads “You will be required to keep a log of your steroid **and anticonvulsant** doses.”

“Will any biological sample(s) be stored and used in the future by the North Central Cancer Treatment Group (NCCTG)?” questions 3 and 4 are newly added.

Appendix IB: “What will happen in the study?” has been revised as follows:

- The 2<sup>nd</sup> sentence of the 2<sup>nd</sup> paragraph now reads “Daily OSI-774 will then continue ~~until~~ **unless** your disease gets worse.”
- The 3<sup>rd</sup> sentence of the 3<sup>rd</sup> paragraph now reads “...every 2 ~~weeks~~ **months** for 1 year, then every 3 months for 1 year, then every 6 months for 4 years.....”

“Will any biological sample(s) be stored and used in the future by the North Central Cancer Treatment Group (NCCTG)?” questions 7 and 8 are newly added.

Appendix IC: “What will happen in the study?” has been revised as follows:

- The 2<sup>nd</sup> sentence of the 1<sup>st</sup> paragraph now reads “Daily OSI-774 will then continue ~~until~~ **unless** your disease gets worse.”
- A new 4<sup>th</sup> sentence has been added and reads “**You will be required to keep a log of your steroid and anticonvulsant doses.**”

“Will any biological sample(s) be stored and used in the future by the North Central Cancer Treatment Group (NCCTG)?” questions 11 and 12 are newly added.