

North Central Cancer Treatment Group

N057K: Phase I/II Evaluation of Everolimus (RAD001), Radiation and Temozolomide (TMZ)  
Followed by Adjuvant Temozolomide and Everolimus in Newly Diagnosed Glioblastoma

Addendum 4 – March 13, 2009

**Summary**

- Administrative/editorial changes.

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

**Title page** Updated to reflect the addition of Addendum 4 and revised NCI version date.

**Protocol Resource Page**

Page 2: Title change has occurred to the “Patient eligibility” contact. The current title for Butch Kvittem is NCCTG *Research Base* Quality **Assurance** Specialist.

The “Non-paraffin biospecimens” contact has been revised due to a staffing change. The person to contact is now **Roxann Neumann**. Both the fax and phone numbers remain the same.

**Section 7.0 Protocol Treatment**

Page 26:

In Section 7.122, a portion of the table has been revised for clarification, including a new triple asterisk footnote (\*\*\*). Changes are as follows:

	Agent	Dose Level	Route	Day(s)	ReRx
	<u>Pretreatment medication:</u> Prophylaxis for Pneumocystis carinii pneumonia (PCP) is required on this protocol (see Sections 7.12113 to 7.12117).				
Cycle 1:	Concomitant treatment with everolimus (RAD001) and temozolomide (TMZ)				
	Everolimus*	Call Registration Office for assigned dose level	Oral	1,8	Weekly
	THEN				
	Everolimus*	Continue same dose as assigned	Oral	<b>Starting on day 15, then weekly until RT is completed</b>	Weekly <del>until RT is completed</del>
	Radiation	6000 cGy (200 cGy x 30 fractions)		5 days/week (starting ≥day 8 but ≤ day 15, see section 7.12111)	x 6 weeks
	Temozolomide**	Call Registration Office for assigned dose level	Oral	Daily (starting on same day as RT)	x 6 weeks
Cycle 2:	4-6 WEEK REST PERIOD				
Cycle 3-8:	Adjuvant treatment with everolimus and temozolomide.				
	Everolimus*	Call Registration Office for assigned dose level – may be different from everolimus dose used in concomitant treatment.	Oral	1, 8, 15 and 22	28 days
	Temozolomide**	<del>200</del> <b>150</b> mg/m <sup>2</sup> /d	Oral	1-5	28 days
<b>Cycles 4-8</b>	<b>Everolimus</b>	<b>Dose level as in cycle 3</b>	<b>Oral</b>	<b>1, 8, 15, and 22</b>	<b>28 days</b>
	<b>Temozolomide</b>	<b>200 mg/m<sup>2</sup>/d***</b>	<b>Oral</b>	<b>1-5</b>	<b>28 days</b>
Cycles 9+:	Adjuvant treatment with everolimus alone until progression <sup>1</sup>				
	Everolimus*	Same as above	oral	1, 8, 15 and 22	28 days

1 Treatment may also be discontinued due to adverse events or patient refusal.

\* Tablets should be taken once ~~daily~~ **weekly**, preferably at night, with a glass (8 ounces) of water one hour before or after food. Patients should avoid foods with a high fat content 2 hours before and 2 hours after you take this medicine

\*\* Capsules should be taken once daily, preferably in the morning, with a glass (8 ounces) of water one hour before or after food.

\*\*\* **For cycles 4-8: Escalate temozolomide dose to 200 mg/m<sup>2</sup>/d only if no ≥ grade 3 adverse events attributable to TMZ occur in cycle 3.**

Pages 28: In Section 7.211, the table has been revised for clarification. Changes are as follows:

Agent	Dose Level	Route	Day(s)	ReRx	
<u>Pretreatment medication:</u> Prophylaxis for Pneumocystis carinii pneumonia (PCP) is required on this protocol (see Section 7.12113).					
<b>Cycle 1: Concomitant treatment with everolimus (RAD001) and temozolomide (TMZ)</b>					
<b>Cycle 1:</b>	Everolimus*	Dose level as determined in PHASE I	Oral	1, 8	Weekly
	THEN				
	Everolimus*	Dose level as determined in PHASE I	Oral	<b>Starting with day 15, then weekly until RT is completed</b>	Weekly until RT is completed
	Radiation	6000 cGy (200 cGy x 30 fractions)		5 days/week (starting $\geq$ day 8 but $\leq$ day 15, see section 7.12111)	x 6 weeks
	Temozolomide**	Dose level as determined in PHASE I	Oral	Daily (starting on same day as radiation)	x 6 weeks
<b>Cycle 2:</b>	<b>4-6 WEEK REST PERIOD</b>				
<b>Adjuvant treatment with everolimus and temozolomide for 6 cycles</b>					
<b>Cycles 3-8:</b>	Everolimus*	Dose level as determined in PHASE I	Oral	1, 8, 15 and 22	28 days
	Temozolomide**	<b>150</b> 200-mg/m <sup>2</sup> /d	Oral	1-5	28 days
<b>Cycles 4-8:</b>	Everolimus*	<b>Dose level as in cycle 3</b>	<b>Oral</b>	<b>1, 8, 15 and 22</b>	<b>28 days</b>
	Temozolomide**	<b>200 mg/m<sup>2</sup>/d***</b>	<b>Oral</b>	<b>1-5</b>	<b>28 days</b>
<b>Adjuvant treatment with everolimus alone until progression<sup>1</sup></b>					
<b>Cycles 9+:</b>	Everolimus*	Same as adjuvant treatment dose above	Oral	1, 8, 15 and 22	28 days

<sup>1</sup> Treatment may also be discontinued due to adverse events or patient refusal.

\* Tablets should be taken once ~~daily~~ **weekly**, preferably at night, with a glass (8 ounces) of water one hour before or after food. Patients should avoid foods with a high fat content 2 hours before and 2 hours after you take this medicine.

\*\* Capsules should be taken once daily, preferably in the morning, with a glass (8 ounces) of water one hour before or after food.

\*\*\* **For cycles 4-8: Escalate temozolomide dose to 200 mg/m<sup>2</sup>/d only if no  $\geq$  grade 3 adverse events attributable to TMZ occur in cycle 3.**

Page 29: In Section 7.313 the 8<sup>th</sup> sentence has been revised for clarification, as follows:  
**No Application of tissue inhomogeneity corrections are allowed at the treating physician's discretion** ~~will be made when using 3D conformal planning.~~

**Section 11.0 Treatment Evaluation**

Page 43: The table in Section 11.13 has been revised for clarification, as follows:

CR =	Total disappearance of all tumor. CR requires that patients be on no corticosteroids or on only adrenal replacement maintenance.
REGR =	unequivocal reduction in <del>size (but &lt;50% reduction)</del> <b>extent</b> of contrast-enhancement or a decrease in mass effect as agreed upon independently by primary physician and quality control physicians; no new lesions.
SD =	failure to qualify for CR, REGR, or PD.
PD =	unequivocal increase in size of contrast enhancement or increase in mass effect as agreed upon independently by primary physician and quality control physicians: appearance of new lesions.