



# NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

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**Date:** December 5, 2008

**To:** NCCTG Primary Clinical Research Associates

**From:** Sara Braun  
Protocol Development Coordinator

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

The purpose of this memorandum is to provide investigators with a recent industry report of an adverse event that has occurred in association with RAD-001 at a non-NCCTG institution. You may have also received this communication directly from the drug manufacturer.

**AE\_PHHO2008US14108**

Please note that all risks currently cited in the NCCTG consent form cannot be omitted; it is at the discretion of your local IRB as to whether they wish to add risks based on the enclosed information. If a determination has been made by the NCCTG Research Base that a protocol amendment is necessary, you will receive the NCI-approved protocol addendum at a later date; for purposes of cross-reference, this communication will cite the adverse event noted above

Please submit this adverse event to your Institutional Review Board.

If you have any questions concerning this communication, please contact Sara Braun at [braun.sara@mayo.edu](mailto:braun.sara@mayo.edu) or 507-538-8226.

SB/kjm  
enclosure



To: All Investigators in RAD001 Studies\*

Date: Dec 1, 2008

Re: Investigator Notification for RAD001  
Nephrolithiasis\_PHHO2008US14108

Dear Doctor,

In accordance with the Good Clinical Practice and specific national regulatory requirements, we would like to inform you of a serious, unexpected, possibly related adverse event of nephrolithiasis that occurred in a patient who enrolled in the investigator initiated trial CRAD001C2481 / AVF3961s, an exploratory study of Avastin (Bevacizumab) and RAD001 (Everolimus) in advanced low or intermediate grade neuroendocrine carcinoma.

Details of the adverse event as reported to Novartis are provided in the attached CIOMS I forms.

A search of the Novartis Clinical Safety Database for RAD001 for similar cases was performed using MedDRA 11.0 High Level Group Term of Urolithiasis. Nine cases were identified from the search including the current one. Only the current case is reported as suspected to be related to the study medication.

Given the available information, it is difficult to assess the causal relationship. Additional information has been requested.

We will keep you informed if further medically significant information becomes available. We ask that you please inform your Institutional Review Board or Ethics Review Board of this event, if you have such an obligation. For clinical trials in the U.S. only, if you are utilizing the services of a central Institutional Review Board (IRB) that has been contracted through Novartis, Novartis will submit the Investigator Notification on your behalf to the central IRB.

Sincerely,

Holly Zhang, MD  
Senior Pharmacovigilance Leader, Integrated Medical Safety  
Novartis Pharmaceuticals Corporation

East Hanover, New Jersey, 07936-1080  
United States

Attachment: CIOMS case report

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\* Novartis Investigator Notification: International Guidelines for Good Clinical Practice as well as specific health authority regulations require that clinical investigators be informed of any adverse drug reaction which is serious (according to specific regulatory criteria), unexpected (i.e. not specifically mentioned in the Investigator's Brochure) and which has a 'reasonable possibility' (in the opinion of the reporter and/or the Company) of being related to the study medication. While Novartis tries to obtain all meaningful information as soon as possible, we are required to communicate all available information within a specified time of its receipt. Since initial data is frequently incomplete, further information must be sent in the form of follow-up reports. Where they have such an obligation, investigators are expected to inform institutional review boards/ethics committees, of each investigator notification. Should Novartis believe that a change in protocol or other action needs to be taken on the basis of clinical reports or other available data, the company will communicate such changes to involved investigators.



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**ADDITIONAL INFORMATION**

**7+13. DESCRIBE REACTION(S) continued**

The investigator suspected a relationship between this event and the study medication.

Novartis Comment: Serious adverse drug reaction report (medically significant), assessed as unexpected according to the Investigators Brochure.

The information provided in this case does not warrant a change to the Investigators Brochure. The topic will be monitored closely. Investigator causality is suspected.