



# 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\_PHHO2008IT11948**

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: Oct 17, 2008

Re: Investigator Notification for RAD001  
Osteoarthritis / PHHO2008IT11948

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 osteoarthritis that occurred in a 58-year-old female patient that who received RAD001 in the study CRAD001C2325, a randomized, double-blind, placebo-controlled, multicentre phase III study in patients with advanced carcinoid tumor receiving Sandostatin LAR and RAD001 10 mg/d or Sandostatin LAR and placebo.

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

A search of the Novartis Clinical Safety Database for RAD001 for similar cases was performed using MedDRA 11.0 Preferred Term of Osteoarthritis. No additional case was identified from the search.

In the current case, a 58-year-old female patient with advanced carcinoid tumor experienced bilateral osteoarthritis. The osteoarthritis is expected in this age group. However, a causal relationship to study drug cannot be excluded. No medical history was provided, 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**

On 26 Feb 2008, the patient showed osteoarthritis of the left knee which then progressed to her right knee on 18 Jun 2008. The patient was diagnosed with bilateral osteoarthritis. On 12 Aug 2008 the patient's bilateral osteoarthritis worsened and developed into a severe walking disability. The investigator stated that he considered the event to be a significant disability but it did not require hospitalisation. Treatment was not reported. The patient's condition was reported as improving. The investigator stated that once the patient stopped taking study medication the situation improved. Therefore study medication was permanently discontinued on 09 Sep 2008. The investigator suspected a relationship between this event and the study medication (RAD001C). The investigator did not provide a causality assessment for Sandostatin LAR. In the absence of an investigator causality, the Novartis medical safety physician has provisionally assessed the event as not suspected to be related to Sandostatin LAR, based on the current available information.

Novartis Comment: Serious adverse drug reaction (significant disability), assessed as unexpected according to the Investigator Brochure for RAD001C. The information provided in this individual case does not warrant a change to the Investigator Brochure text. The topic will be monitored closely. Investigator causality is suspected to be related to the study medication (RAD001C).