



NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

Date: March 27, 2009

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-01 at a non-NCCTG institution. You may have also received this communication directly from the drug manufacturer.

AE_PHHO2008TR15236

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 at 507-538-8226.

SB/kjm
enclosure



To: All Investigators in RAD001 Studies*

Date: Jan 6, 2009

Re: Investigator Notification for RAD001
Radiation Esophagitis /PHHO2008TR15236

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 radiation esophagitis that occurred in 49-year-old female patient who enrolled in the study CRAD001L2401, an open-label, multi-center, expanded access study of RAD001 in patients with metastatic carcinoma of the kidney who have progressed despite vascular endothelial growth factor receptor tyrosine kinase inhibitor therapy.

A search of the Novartis Clinical Safety Database for RAD001 was performed using MedDRA 11.0 preferred term of Radiation oesophagitis. Two cases were identified including the current case. The additional case was not suspected.

In the current case, the investigator reported that the event was caused by palliative radiation to the bone and the event was also suspected to be related to RAD001. Considering the patient's history of palliative radiation, it is unlikely that the event was caused by the study drug, however, a contribution by the study drug cannot be excluded. 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

* 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.

SUSPECT ADVERSE REACTION REPORT												

I. REACTION INFORMATION

1. PATIENT INITIALS <small>(first, last)</small>	1a. COUNTRY Turkey	2. DATE OF BIRTH			2a. AGE 49 Years	3. SEX Female	3a. WEIGHT 81.00 kg	4-6 REACTION ONSET			8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION <input type="checkbox"/> PATIENT DIED <input checked="" type="checkbox"/> INVOLVED OR PROLONGED INPATIENT HOSPITALISATION <input type="checkbox"/> INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY <input type="checkbox"/> LIFE THREATENING
7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data) Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas) Radiation esophagitis gr IV caused by palliative radiation to bone [Radiation oesophagitis] Case Description: Initial report received on 24 Dec 2008: This patient (centre no. xxx, patient no. xxx) was enrolled in the study CRAD001L2401, an open-label, multi-center, expanded access study of RAD001 in patients with metastatic carcinoma of the kidney who have progressed despite vascular endothelial growth factor receptor tyrosine kinase inhibitor therapy. The patient had no significant history. She received the first dose of study medication on 10 Sep 2008. (Continued on Additional Information Page)											

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name) #1) RAD001 (RAD001) Tablet #2) RADIATION (NO INGREDIENTS/SUBSTANCES) (Continued on Additional Information Page)		20. DID REACTION ABATE AFTER STOPPING DRUG? <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> NA <input type="checkbox"/> Unknown
15. DAILY DOSE(S) #1) 10 mg, daily #2) Unknown	16. ROUTE(S) OF ADMINISTRATION #1) Oral #2) Unknown	
17. INDICATION(S) FOR USE #1) Metastatic renal cell carcinoma (Metas) #2) Unknown (Continued on Additional Information Page)		21. DID REACTION REAPPEAR AFTER REINTRODUCTION? <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> NA <input type="checkbox"/> Unknown
18. THERAPY DATES(from/to) #1) 10-SEP-2008 / 10-NOV-2008 #2) Unknown	19. THERAPY DURATION #1) 62 days #2) Unknown	

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergics, pregnancy with last month of period, etc.) From/To Dates Type of History / Notes Description Unknown

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER Investigator's Notification Copy Novartis Pharma Headquarter		26. REMARKS
24b. MFR CONTROL NO. PHHO2008TR15236		
24c. DATE RECEIVED BY MANUFACTURER 24-DEC-2008	24d. REPORT SOURCE <input checked="" type="checkbox"/> STUDY <input type="checkbox"/> LITERATURE <input checked="" type="checkbox"/> HEALTH PROFESSIONAL <input type="checkbox"/> OTHER:	25b. NAME AND ADDRESS OF REPORTER
DATE OF THIS REPORT 06-JAN-2009	25a. REPORT TYPE <input checked="" type="checkbox"/> INITIAL <input type="checkbox"/> FOLLOWUP:	

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

On 10 Nov 2008, the patient presented with radiation esophagitis grade IV, which involved hospitalisation. The event was reported to be caused by palliative radiation to the bone. The study medication was temporarily interrupted on 10 Nov 2008. The patient's condition was improving. The investigator suspected a relationship between this event and the study medication.

Novartis Comment: Serious adverse drug reaction (hospitalisation), assessed as unexpected according to the Investigator Brochure for RAD001. 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.

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
#1) RAD001 (RAD001) Tablet; Regimen #1	10 mg, daily; Oral	Metastatic renal cell carcinoma (Metastatic renal cell carcinoma)	10-SEP-2008 / 10-NOV-2008; 62 days