



NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

Date: August 8, 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_PHHO2008US05802

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 or 507-538-8226.

SB/df
enclosure



To: All Investigators in RAD001 Studies*

Date: Aug 1, 2008

Re: Investigator Notification for RAD001
Convulsion / PHHO2008US05802

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 convulsion that occurred in a 56-year-old male patient that was enrolled and treated in study CRAD001C2410, a multicenter, open label study of RAD001 in patients with recurrent glioblastoma.

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 10.1 Preferred Term of convulsion. A total of 19 cases were identified including 18 not suspected cases and the current suspected case.

In the current case, the convulsion is most likely due to complications of the underlying malignancy (recurrent glioblastoma). A causal relationship to study drug is unlikely, but cannot be excluded.

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 (first, last) XXX	1a. COUNTRY XXX	2. DATE OF BIRTH			2a. AGE 56	3. SEX Male	3a. WEIGHT Unk	4-6 REACTION ONSET			8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
		Day	Month	Year			Day	Month	Year		
										<input type="checkbox"/> PATIENT DIED <input checked="" type="checkbox"/> INVOLVED OR PROLONGED INPATIENT HOSPITALISATION <input checked="" type="checkbox"/> INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY <input checked="" type="checkbox"/> LIFE THREATENINGCCC	
7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data) Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas) Seizures [Convulsion] ([Vomiting], [Aspiration]) Pneumothorax [Pneumothorax] Severe respiratory infection [Respiratory tract infection] Collapsed lung [Collapse of lung] Disease progression [Disease progression] Case Description: Initial report received on 05 May 2008: This patient (XXX XXX) was enrolled in the trial CRAD001C2410, a multicenter, open label study of RAD001 in patients with recurrent glioblastoma. <p style="text-align: right;">(Continued on Additional Information Page)</p>											

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name) #1) RAD001 (RAD001) Tablet		20. DID REACTION ABATE AFTER STOPPING DRUG? <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> NA Unknown
(Continued on Additional Information Page)		
15. DAILY DOSE(S) #1) 5mg	16. ROUTE(S) OF ADMINISTRATION #1) Unknown	
17. INDICATION(S) FOR USE #1) Chemotherapy multiple agents systemic (Not Coded)		21. DID REACTION REAPPEAR AFTER REINTRODUCTION? <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> NA Unknown
18. THERAPY DATES(from/to) #1) 02-MAY-2008 / 04-MAY-2008	19. THERAPY DURATION #1) 3 days	

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction) #1) HYDROCHLOROTHIAZIDE (HYDROCHLOROTHIAZIDE) ; Unknown #2) DEXAMETHASONE (DEXAMETHASONE) ; Unknown #3) NEXIUM (ESOMEPRAZOLE MAGNESIUM) ; Unknown	
23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.) From/To Dates	Description
Unknown	Hypertension (Hypertension)
Unknown	Chemotherapy NOS (Chemotherapy)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER Investigator's Notification Copy Novartis Pharma Headquarter		26. REMARKS
	24b. MFR CONTROL NO. PHHO2008US05802	25b. NAME AND ADDRESS OF REPORTER XXX XXX XXX XXX XXX
24c. DATE RECEIVED BY MANUFACTURER 22-JUL-2008	24d. REPORT SOURCE <input checked="" type="checkbox"/> STUDY <input type="checkbox"/> LITERATURE <input checked="" type="checkbox"/> HEALTH PROFESSIONAL <input type="checkbox"/> OTHER:	
DATE OF THIS REPORT 01-AUG-2008	25a. REPORT TYPE <input checked="" type="checkbox"/> INITIAL <input type="checkbox"/> FOLLOWUP:	

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

The study enrolls patients in two parallel arms based on plans for salvage surgery. The patient's medical history included: hypertension, status post resection 28 Jan 2008, radiation therapy, and chemotherapy with Temodar. He received the first dose of study medication on 02 May 2008. On 04 May 2008, the patient experienced three seizures in one hour requiring hospitalization (that same day). The patient required intubation. During intubation the patient vomited and there was a concern that the patient aspirated. Subsequently, the patient was found to have a collapsed lung and a chest tube was placed. The patient was transferred to another facility where he continued to be intubated and sedated with propofol and a fentanyl drip. Further evaluation is ongoing regarding this event. The study medication was temporarily interrupted, due to the event. At the time of reporting, the patient's condition was not reported. The investigator did not suspect a relationship between the events and the study medication.

Follow-up received on 22 Jul 2008: The study medication was permanently discontinued on 04 May 2008. During the intubation the patient sustained a pneumothorax, in addition to the collapsed lung. He was also treated for a severe respiratory infection and was eventually able to come off his ventilator. The events were assessed as life-threatening and also involved persistent or significant disability/incapacity. MRI (magnetic resonance imaging) on 15 May 2008, showed recurrent/residual tumor was stable. The patient was stabilized and discharged to a rehabilitation facility on 16 May 2008. He was considered to have recovered with sequelae. The investigator suspected a relationship between the seizure (grade 4) and the study medication and also indicated that the event was due to underlying disease progression. The investigator did not suspect a relationship between the pneumothorax (grade 2) and the study medication. In the absence of the investigator's causality assessment for severe respiratory infection the Novartis Medical Safety Physician provisionally assessed this event as not suspected to be related to study medication, based on current available information.

Novartis Comment: Serious adverse drug reaction report, seizure (life-threatening), 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.

All remaining reported leading events and associated symptoms were assessed as not suspected by the investigator/Novartis medical safety physician.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	15-MAY-2008	Nuclear magnetic resonance imaging	Showned recurrent / residual tumor was stable.	

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	5mg; Unknown	Chemotherapy multiple agents systemic (Not Coded) Glioblastoma (Glioblastoma)	02-MAY-2008 / 04-MAY-2008; 3 days

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown		Radiation therapy (Radiotherapy);
Unknown		Surgery (Surgery);
28-JAN-2008 to Unknown		Glioblastoma multiforme (Glioblastoma multiforme);