



NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

Date: November 28, 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_PHHO2008DE11094

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/kjm
enclosure



To: All Investigators in RAD001 Studies*

Date: Oct 24, 2008

Re: Investigator Notification for RAD001
Pulmonary embolism (fatal) / PHHO2008DE11094

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 pulmonary embolism (fatal) that occurred in a 63-year-old female patient who received RAD001 in the study CRAD001C2325, a randomized, double-blind, placebo-controlled, multicenter 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 pulmonary embolism for events with fatal outcome. Nine cases were identified from the search. Two cases were suspected including the current one; and seven cases were not suspected.

In the current case, a 63-year-old female patient with advanced carcinoid tumor suddenly died. Pulmonary embolism was reported as a cause of death. No autopsy or any diagnostic test was performed to confirm the event occurrence. Pulmonary embolism was reported to be related to underlying carcinoid tumor and RAD001 administration. Pulmonary embolism is expected in the IB, but fatal outcome of this event is not specified.

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)	1a. COUNTRY	2. DATE OF BIRTH			2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET			8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION <input checked="" type="checkbox"/> PATIENT DIED Date: 24-SEP-2008 <input checked="" type="checkbox"/> INVOLVED OR PROLONGED INPATIENT HOSPITALISATION <input type="checkbox"/> INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY <input type="checkbox"/> LIFE THREATENING
		Day	Month	Year	63 Years	Female	62.00 kg	Day	Month	Year	
		24	SEP	1944			02	SEP	2008		
7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data) Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas) Pulmonary embolism [Pulmonary embolism] Urosepsis [Urosepsis] ([Pyrexia], [C-reactive protein increased]) Case Description: Initial report received on 12 Sep 2008: This patient (centre no. xxx, patient no. xxx) was enrolled in the study CRAD001C2325, a randomised, double-blind, placebo-controlled, multicenter phase III study in patients with advanced carcinoid tumour receiving Sandostatin LAR and RAD001 10 mg/d or Sandostatin LAR and placebo. The patient's medical history included: hypertension, strumectomy, ureter stent, dyspnoea, cardiac arrhythmia and uronephrosis. (Continued on Additional Information Page)											

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name) #1) RAD001 Vs Placebo (RAD 666 RAD+TAB) Tablet #2) SANDOSTATIN LAR (OCTREOTIDE WITH POLY(D L-LACTIDE-CO-GLYCOLIDE)) Unknown		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) Double blind #2) Double blind	16. ROUTE(S) OF ADMINISTRATION #1) Oral #2) Unknown	
17. INDICATION(S) FOR USE #1) Carcinoid tumour (Carcinoid tumour) #2) Carcinoid tumour (Carcinoid tumour)		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) 22-APR-2008 / Unknown #2) 22-APR-2008 / Unknown	19. THERAPY DURATION #1) Unknown #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, allergies, pregnancy with last month of period, etc.)	
From/To Dates Unknown Unknown	Type of History / Notes Description Lymph node metastases (Metastases to lymph nodes) Stenosis ureteral (Ureteric stenosis)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER Investigator's Notification Copy Novartis Pharma Headquarter		26. REMARKS	
24b. MFR CONTROL NO. PHHO2008DE11094		25b. NAME AND ADDRESS OF REPORTER	
24c. DATE RECEIVED BY MANUFACTURER 21-OCT-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 24-OCT-2008	25a. REPORT TYPE <input checked="" type="checkbox"/> INITIAL <input type="checkbox"/> FOLLOWUP:		

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

The patient received her first dose of study medication on 22 Apr 2008. On 02 Sep 2008 the patient presented with urosepsis , which resulted in hospitalisation. The study medication was temporarily interrupted. At the time of this report the patient's condition was still present and unchanged. The investigator did not suspect a relationship between this event and the study medication (RAD001 or Sandostatin).

Follow up received on 01 Oct 2008: The patient died on 24 Sep 2008 due to urosepsis. The investigator reassessed the causality and suspected a relationship between this event and RAD001, but did not suspect a relationship to Sandostatin.

Follow-up received on 14 Oct 2008: The investigator confirmed that an autopsy was not performed. The cause of death as reported on the death certificate was pulmonary embolism. The investigator suspected a relationship between the pulmonary embolism and RAD001. In the absence of the investigator's causality assessment for pulmonary embolism and Sandostatin LAR, the Novartis medical safety physician provisionally assessed this event as not suspected to be related to Sandostatin LAR pending further information.

Internal review on 20 Oct 2008: No new information. Report resubmitted following unblinding due to regulatory reporting requirements.

Follow up received on 21 Oct 2008: The patient's medical history included septicemia with Candida and stenosis of the ureter due to lymph node metastases. The investigator also stated that the carcinoid tumour was relevant history leading up to the pulmonary embolism. Signs and symptoms of the urosepsis included fever and elevated CRP. Blood cultures were performed (results not provided). Treatment for the urosepsis included Fluconazole. No diagnostic tests or treatment was given for the pulmonary embolism . The patient had a sudden and unexpected death. At the time of death the patient's disease was stable. The investigator did not suspect a relationship between the pulmonary embolism and Sandostatin LAR.

Novartis Comment: Serious adverse drug reaction, pulmonary embolism (death), assessed as unexpected according to the Investigator's 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 RAD001 (not Sandostatin LAR).

Serious adverse drug reaction report, urosepsis (death), assessed as expected according to the Investigator's Brochure for RAD001C. Investigator causality is suspected to RAD001 (not Sandostatin LAR).

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1		Blood culture		
		results not provided		

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown		Septicaemia candida (Candida sepsis);
Unknown		Hydronephrosis (Hydronephrosis);
Unknown		Cardiac arrhythmia (Arrhythmia);
Unknown		Dyspnoea (Dyspnoea);
Unknown		Ureteral stent insertion (Ureteral stent insertion);
Unknown		Strumectomy (Thyroidectomy);
Unknown		Hypertension (Hypertension);