



NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

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_PHHO2008BE12855

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: No 17, 2008

Re: Investigator Notification for RAD001
Renal tubular necrosis (fatal)/ PHHO2008BE12855

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 renal tubular necrosis (fatal) that occurred in a 74-year-old male patient who received RAD001 in the study CRAD001C2324, a randomized double-blind phase III study of RAD001 plus best supportive care versus placebo plus best supportive care in the treatment of patients with advanced pancreatic neuroendocrine tumor (NET).

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 renal tubular necrosis. One additional case was identified from the search. The case involved a patient with advanced renal cancer. Renal tubular necrosis was reported as related to the underlying cancer progression.

In the current case, the patient had advanced pancreatic neuroendocrine tumor and a history of hypertension, hypercholesterolemia and hyperlipidemia. Kredex (carvedilol), Coversyl (perindopril erbumine) and simvastatin were given concomitantly. The available information is inadequate for full assessment. 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 (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: 27-OCT-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	74 Years	Male	68.00 kg	Day	Month	Year	
		13	JUL	1934				17	OCT	2008	
7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data) Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas) Tubulus necrosis [Renal tubular necrosis] ([Renal failure acute], [Blood creatinine increased]) Anorexia [Anorexia]											
Case Description: Initial report received on 24 Oct 2008: This patient (centre no. xxx, patient no. xxx) was enrolled in the study CRAD001C2324, a randomised double-blind phase III study of RAD001 plus best supportive care versus placebo plus best supportive care in the treatment of patients with advanced pancreatic neuroendocrine tumor (NET). The patient's medical history included arterial hypertension and hypercholesterolaemia/hyperlipidaemia.											
(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+CMAS) 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) Double blind	16. ROUTE(S) OF ADMINISTRATION #1) Oral	
17. INDICATION(S) FOR USE #1) pancreatic neuroendocrine tumour (Pancr)		21. DID REACTION REAPPEAR AFTER REINTRODUCTION? <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> NA Unknown
(Continued on Additional Information Page)		
18. THERAPY DATES(from/to) #1) 03-OCT-2008 / 22-OCT-2008	19. THERAPY DURATION #1) 20 days	

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction) #1) KREDEX (CARVEDILOL) ; Ongoing #2) COVERSYL (PERINDOPRIL ERBUMINE) ; Ongoing #3) SIMVASTATIN (SIMVASTATIN) ; Ongoing	
23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.) From/To Dates	Description
Unknown	Hyperlipidaemia (Hyperlipidaemia)
Unknown	Hypercholesterolaemia (Hypercholesterolaemia)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER Investigator's Notification Copy Novartis Pharma Headquarter		26. REMARKS
	24b. MFR CONTROL NO. PHHO2008BE12855	25b. NAME AND ADDRESS OF REPORTER
24c. DATE RECEIVED BY MANUFACTURER 05-NOV-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 13-NOV-2008	25a. REPORT TYPE <input checked="" type="checkbox"/> INITIAL <input type="checkbox"/> FOLLOWUP:	

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

The patient received his first dose of study medication on 3 Oct 2008. On 17 Oct 2008, the patient presented with the first signs/symptoms of anorexia, which resulted in hospitalisation on 22 Oct 2008. Extra fluids were given. Blood samples also showed high creatinine. At the time of this report the patient's condition was still present and unchanged. In the absence of an investigator causality, a Novartis medical safety physician provisionally assessed that this event was suspected to be due to study medication, based on current available information.

Follow up received on 05 Nov 2008: The onset date of the high creatinine was 22 Oct 2008 which involved hospitalization. The study medication was permanently discontinued on 22 Oct 2008. During hospitalization the patient's condition deteriorated further due to increased creatinine up to 9.32 ml/dl, despite extra fluids and intravenous diuretics, with acute renal insufficiency as a consequence. Renal biopsy showed tubulus necrosis. The patient died on 27 Oct 2008, autopsy was not performed. The cause of the acute renal insufficiency and tubulus necrosis was not clear. The investigator did not suspect a relationship between the high creatinine and anorexia and the study medication. The investigator could not exclude a relationship between the acute renal insufficiency and tubulus necrosis and the study medication.

Novartis Comment: Serious adverse drug reaction report, tubular necrosis (death), assessed as unexpected according to the Investigator Brochure.

The information provided in this individual case does not warrant a change to the Investigator's 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.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1		Biopsy Acute renal insufficiency		
2	22-OCT-2008	Blood creatinine High	6.29 mg/dL	
3	27-OCT-2008	Blood creatinine	9.32 mg/dl	

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 Vs Placebo (RAD 666 RAD+TAB+CMAS) Tablet; Regimen #1	Double blind; Oral	pancreatic neuroendocrine tumour (Pancreatic neuroendocrine tumour)	03-OCT-2008 / 22-OCT-2008; 20 days

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown		Hypertension arterial (Hypertension);