



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_PHHO2008US12593

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 31, 2008

Re: Investigator Notification for RAD001
Cardio-respiratory arrest (Fatal)/ PHHO2008US12593

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 cardio-respiratory arrest (fatal) that occurred in a 50-year-old female patient who received RAD001 in the study CRAD001J2101, an open-label, multi-centre, dose escalation phase 1b study of RAD001 in combination with trastuzumab and paclitaxel in patients with HER2-overexpressing metastatic breast cancer.

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 Terms of cardio-respiratory arrest, cardiopulmonary failure, and cardio-respiratory distress for events with fatal outcome. Five cases were identified from the search. Two cases were suspected including the current one; and three cases were not suspected. The additional suspected event occurred secondary to esophageal perforation.

In the current case, the patient had metastatic breast cancer. 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) XXX	1a. COUNTRY XXX	2. DATE OF BIRTH			2a. AGE 50 Years	3. SEX Female	3a. WEIGHT Unk	4-6 REACTION ONSET			8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
		Day 04	Month JAN	Year 1958			Day 18	Month OCT	Year 2008		
7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data) Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas) Cardiopulmonary arrest [Cardio-respiratory arrest] ([Unresponsive to stimuli])										<input checked="" type="checkbox"/> PATIENT DIED Date: 22-OCT-2008 <input checked="" type="checkbox"/> INVOLVED OR PROLONGED INPATIENT HOSPITALISATION <input type="checkbox"/> INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY <input checked="" type="checkbox"/> LIFE THREATENING	
Case Description: Initial report received on 20 Oct 2008: This patient (number XXX, centre XXX) was enrolled in study CRAD001J2101, an open-label, multi-centre, dose escalation phase 1b study of RAD001 in combination with trastuzumab and paclitaxel in patients with HER2-overexpressing metastatic breast cancer. Medical history included hypertension, depression, insomnia, chronic pain, heartburn, constipation and hypokalaemia. The patient started study medication on 22 Aug 2008. On 18 Oct 2008 she experienced a cardiopulmonary arrest. The patient was found unresponsive at home.										(Continued on Additional Information Page)	

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name) #1) RAD001+Trastuzumab and Paclitaxel (RAD001+Trastuzumab and Paclitaxel) Tablet		20. DID REACTION ABATE AFTER STOPPING DRUG? <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> NA Unknown
15. DAILY DOSE(S) #1) 10 mg, QD	16. ROUTE(S) OF ADMINISTRATION #1) Oral	
17. INDICATION(S) FOR USE #1) Breast cancer (Breast cancer)		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) 22-AUG-2008 / 18-OCT-2008	19. THERAPY DURATION #1) 58 days	

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction) #1) TRASTUZUMAB (TRASTUZUMAB) ; Unknown #2) PACLITAXEL (PACLITAXEL) ; Unknown					
23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)					
From/To Dates Unknown Unknown	Description <table style="width: 100%; border: none;"> <tr> <td style="width: 30%; text-align: center;">Type of History / Notes Current Condition</td> <td>Hypertension (Hypertension)</td> </tr> <tr> <td></td> <td>Hypokalemia (Hypokalaemia)</td> </tr> </table>	Type of History / Notes Current Condition	Hypertension (Hypertension)		Hypokalemia (Hypokalaemia)
Type of History / Notes Current Condition	Hypertension (Hypertension)				
	Hypokalemia (Hypokalaemia)				

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER Investigator's Notification Copy Novartis Pharma Headquarter		26. REMARKS
	24b. MFR CONTROL NO. PHHO2008US12593	
24c. DATE RECEIVED BY MANUFACTURER 20-OCT-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 XXX XXX XXX XXX
DATE OF THIS REPORT 30-OCT-2008	25a. REPORT TYPE <input checked="" type="checkbox"/> INITIAL <input type="checkbox"/> FOLLOWUP:	

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

Resuscitation was performed prior to arrival at ER (emergency room). She was intubated in ER and transferred to ICU (intensive care unit). At the time of reporting the patient was on a ventilator. Extubation and palliative care was anticipated based on the family's wishes. The event was considered to be life-threatening and involved hospitalisation. The study medication was permanently discontinued due to the event on 18 Oct 2008. The patient was not improving but arrest was not present. The investigator did suspect a relationship between this event and the study medication.

Follow-up received on 22 Oct 2008, prior to circulation of initial report: The family elected to remove the patient's ventilator support and provide palliative measures only. The patient died on 22 Oct 2008, no autopsy was performed.

Novartis Comment: Serious adverse drug reaction report, death, assessed as unexpected according to the Investigator's Brochure. It is Novartis' policy to assess a case with a fatal outcome as unexpected unless the label specifically mentions death as a possible outcome of the listed risks. Investigator causality is suspected.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	18-OCT-2008	Alanine aminotransferase	138 IU/l	
2	19-OCT-2008	Alanine aminotransferase	161 IU/l	
3	20-OCT-2008	Alanine aminotransferase	243 IU/l	
4	18-OCT-2008	Aspartate aminotransferase	270 IU/l	
5	19-OCT-2008	Aspartate aminotransferase	371 IU/l	
6	20-OCT-2008	Aspartate aminotransferase	499 IU/l	
7	18-OCT-2008	Blood creatine phosphokinase	1000 IU/l	
8	19-OCT-2008	Blood creatine phosphokinase	2709 IU/l	
9	18-OCT-2008	Blood creatinine	1.1 mg/dl	
10	19-OCT-2008	Blood creatinine	2.9 mg/dl	
11	20-OCT-2008	Blood creatinine	3.9 mg/dl	
12	18-OCT-2008	Blood glucose	370 mg/dl	
13	19-OCT-2008	Blood glucose	367 mg/dl	
14	20-OCT-2008	Blood glucose	123 mg/dL	
15	18-OCT-2008	Blood potassium	2.7 mmol/l	
16	19-OCT-2008	Blood potassium	4.0 mmol/l	
17	18-OCT-2008	Blood urea	10 mg/dl	
18	19-OCT-2008	Blood urea	23 mg/dl	
19	20-OCT-2008	Blood urea	26 mg/dl	
20	18-OCT-2008	Troponin I	2.010 ng/ml	

ADDITIONAL INFORMATION**13. Lab Data**

#	Date	Test / Assessment / Notes	Results	Normal High / Low
21	19-OCT-2008	Troponin I	5.830 ng/ml	

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown		Constipation (Constipation);
Unknown		Heartburn (Dyspepsia);
Unknown		Chronic pain (Pain);
Unknown		Insomnia (Insomnia);
Unknown		Depression (Depression);