



NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

Date: October 24, 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_PHHO2008FR08382

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: July 18, 2008

Re: Investigator Notification for RAD001
Cerebrovascular accident/ PHHO2008FR08382

APL B
NC
AL

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 cerebrovascular accident (fatal) that occurred in a 60-year-old female patient that was enrolled and treated in study CRAD001C24117, a multi-centre phase II prospective open study trial evaluating the tolerance and efficacy of RAD001 (everolimus) in patients with endometrial cancer in relapse or metastatic.

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 Terms of Cerebrovascular accident and Cerebrovascular disorder. No additional case was identified.

In the current case, a 60-year-old female patient with advanced endometrial cancer passed away at home. Her study medication was discontinued 13 days before her death due to a grade 2 thrombocytopenia (platelets 49,000 / mm³). The investigator suspected underlying disease progression and probable cerebrovascular accident as the cause of death. In the absence of a documented cause of death, no causal relationship can be established between the event and treatment with the study drug. Considering the patient's deteriorating condition, most likely patient died of progressive metastatic endometrial cancer. Death due to disease progression is expected in this population.

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.

CRAD001C 2241

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

cc: US ICRO Investigator
Local Trial Leader
Field Monitor
Central IRB (if applicable)
mDOC

* 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) XX	1a. COUNTRY XXX	2. DATE OF BIRTH Day Month Year	2a. AGE 60 Years	3. SEX Female	3a. WEIGHT Unk	4-6 REACTION ONSET Day Month Year 02 JUL 2008	8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data) Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas) Probable cerebro-vascular accident [Cerebrovascular accident] Cancer progression [Malignant neoplasm progression] ([Metastasis]) Grade 2 thrombocytopenia (platelets 49,000 / mm³) (non-serious) [Thrombocytopenia]							<input checked="" type="checkbox"/> PATIENT DIED Date: 04-JUL-2008 <input type="checkbox"/> INVOLVED OR PROLONGED INPATIENT HOSPITALISATION <input type="checkbox"/> INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY <input type="checkbox"/> LIFE THREATENING
Case Description: Initial report received on 4 Jul 2008: This patient (patient no. XX, centre no. XXX) was enrolled in CRAD001C24117, a multi-centre phase II prospective open study trial evaluating the tolerance and efficacy of RAD001 (everolimus) in patients with endometrial cancer in relapse or metastatic. The patient's medical history was not reported.							
(Continued on Additional Information Page)							

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name) #1) RAD001 (RAD001) Tablet		20. DID REACTION ABATE AFTER STOPPING DRUG?
(Continued on Additional Information Page)		<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	21. DID REACTION REAPPEAR AFTER REINTRODUCTION? <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> NA Unknown
17. INDICATION(S) FOR USE #1) Endometrial cancer (Endometrial cancer)		
18. THERAPY DATES(from/to) #1) 06-JUN-2008 / 21-JUN-2008	19. THERAPY DURATION #1) 16 days	

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)		
#1) INNOHEP (HEPARIN-FRACTION, SODIUM SALT) ; Unknown #2) ARANESP (DARBEPOETIN ALFA) ; Unknown #3) OXYNORM (OXYCODONE HYDROCHLORIDE) ; Unknown #4) LYRICA (PREGABALIN) ; Unknown #5) LANTUS (INSULIN GLARGINE) ; Unknown #6) EUPANTOL (PANTOPRAZOLE) ; Unknown		
23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)		
From/To Dates	Type of History / Notes	Description
Unknown		Obesity (Obesity)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER Investigator's Notification Copy Novartis Pharma Headquarter		26. REMARKS
	24b. MFR CONTROL NO. PHHO2008FR08382	25b. NAME AND ADDRESS OF REPORTER XXX XXX XXX XXX XXX XXX
24c. DATE RECEIVED BY MANUFACTURER 16-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 18-JUL-2008	25a. REPORT TYPE <input checked="" type="checkbox"/> INITIAL <input type="checkbox"/> FOLLOWUP:	
(Continued on Additional Information Page)		

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

The patient was enrolled in the study on 21 May 2008. The patient received the last dose of study medication prior to the event on 21 Jun 2008. The patient was not receiving study medication at the time of the event. On 2 Jul 2008, the patient presented with probable cerebrovascular accident. This was considered medically significant and life threatening. The patient died on 4 Jul 2008, an autopsy was not performed. The investigator did not suspect a relationship between this event and the study medication but considered the event to be related to underlying disease / progression of cancer.

Follow-up received on 7 Jul 2008 combined with follow-up received on 8 Jul 2008: The patient had medical history of obesity. The investigator clarified that the patient was enrolled in the study from 2 Jun 2008 (not 21 May 2008 as previously reported). The patient commenced study medication on 6 Jun 2008. Study medication was discontinued on 21 Jun 2008 due to grade 2 thrombocytopenia (platelets 49,000 / mm³). The cause of death was considered to be possible cerebrovascular accident or metastases or related to study medication.

11 Jul 2008 upon internal review of documents receive 07 and 08 Jul 2008 corrections were made. Cerebrovascular accident causal assessment is considered as not suspected as previously reported. Drug toxicity was added as a suspect event.

Follow-up received on 16 Jul 2008: The patient received 10 mg / day of RAD001 from 6 Jun 2008. Platelet count on 21 Jun 2008 was 49,000 / mm³ and study medication was discontinued on this date. The patient was not hospitalised and the investigator confirmed that the thrombocytopenia was considered non-serious. The patient died at home on 4 Jul 2008 and no autopsy was performed. Although cerebrovascular accident (CVA) was not medically confirmed, the cause of death was considered to be probable CVA. The investigator considered the probable CVA, cancer progression and possible metastases to be suspected to be related to study medication.

Novartis Comment: Serious adverse drug reaction report, probable cerebrovascular accident (death), assessed as unexpected according to the Investigator's Brochure. However, other alternative causes (disease progression) provide a possible explanation for the reported adverse event. Investigator causality is suspected.

Serious adverse drug reaction report, cancer progression (death), assessed as expected according to the Investigator's Brochure. Investigator causality is suspected.

All remaining reported leading events and associated symptoms were assessed as non-serious by the investigator.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	21-JUN-2008	Platelet count	49,000 / mm ³	

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 #2	UNK; Unknown	Endometrial cancer (Endometrial cancer)	22-JUN-2008 / Unknown; Unknown

25b. Name And Address of Reporters continued

XXX
 XXX
 XXX
 XXX
 XXX
 XXX

XXX
 XXX
 XXX
 XXX
 XXX
 XXX