



NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

Date: October 3, 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_PHHO2008CA11400

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 1, 2008

Re: Investigator Notification for RAD001
Transient ischemic attack / PHHO2008CA11400

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 transient ischemic attack that occurred in a 61-year-old female patient that who received RAD001 in study CRAD001C2242, an open label, multicenter Phase 1 study investigating the combination of RAD001, cetuximab and irinotecan as second-line therapy after FOLFOX and bevacizumab in patients with metastatic colorectal adenocarcinoma.

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 Thromboembolic stroke, Embolic stroke, Ischaemic stroke, Cerebrovascular accident, Transient ischaemic attack, Cerebral ischaemia, Cerebral infarction and Ischaemia. A total of six cases were identified. Three cases were suspected including the current one. Of the two additional suspected cases, one cerebral infarction was reported in a patient with a history of hypertension, smoking and an old infarction in addition to the advanced metastatic disease; and one possible cerebrovascular accident was reported with limited information in a patient with advanced malignancy.

In the current case, the patient had a smoking history and advanced malignancy. Given the available information, a causal relationship between study drug and event occurrence cannot be established or excluded. The thromboembolic events are expected in the current IB, however, transient ischemic attack is currently 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) XXX	1a. COUNTRY XXX	2. DATE OF BIRTH			2a. AGE 61	3. SEX Female	3a. WEIGHT 59.80 kg	4-6 REACTION ONSET			8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION <input type="checkbox"/> PATIENT DIED <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			Day	Month	Year		
			Unk				17	SEP	2008		

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)
Transient ischemic attack [Transient ischaemic attack] ([Cerebral artery thrombosis], [Hemiparesis])

Case Description: Initial report received on 19 Sep 2008: This patient (patient no.X XX, centre no. XXX) was enrolled in protocol CRAD001C2242, an open label, multicenter Phase 1 study investigating the combination of RAD001, cetuximab and irinotecan as second-line therapy after FOLFOX and bevacizumab in patients with metastatic colorectal adenocarcinoma. The patient's medical history was not included. She received the first dose of study medication on 30 Jul 2008.

(Continued on Additional Information Page)

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name) #1) RAD001 + cetuximab and irinotecan (RAD001 + cetuximab and irinotecan) Tablet (Continued on Additional Information Page)		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) 30 mg qwkly	16. ROUTE(S) OF ADMINISTRATION #1) Oral	
17. INDICATION(S) FOR USE #1) Metastatic colorectal adenocarcinoma ((Continued on Additional Information Page)		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) 30-JUL-2008 / Ongoing	19. THERAPY DURATION #1) Unknown	

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
#1) CETUXIMAB (CETUXIMAB) ; 30-JUL-2008 / Ongoing
#2) IRINOTECAN (IRINOTECAN) ; 30-JUL-2008 / Ongoing

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergics, pregnancy with last month of period, etc.)
 From/To Dates: **Unknown** Type of History / Notes: Description: **Smoker (Smoker)**

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER Investigator's Notification Copy Novartis Pharma Headquarter		26. REMARKS
	24b. MFR CONTROL NO. PHHO2008CA11400	
24c. DATE RECEIVED BY MANUFACTURER 19-SEP-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 29-SEP-2008	25a. REPORT TYPE <input checked="" type="checkbox"/> INITIAL <input type="checkbox"/> FOLLOWUP:	

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

On 17 Sep 2008, the patient received cycle 3, day 8 treatment of RAD001 and cetuximab. On 18 Sep 2008, at about 2pm, the patient started to experience weakness in the left hand and left arm/face, which resulted in hospitalization for a possible stroke. A CT (computed tomography) scan of the head revealed a thrombus within the right middle cerebral artery (m-2 segment). The patient's symptoms spontaneously resolved and she was receiving intravenous (IV) heparin. The outcome was not reported.

Follow-up received on 22 Sep 2008 (prior to initial circulation): The diagnosis was confirmed as a transient ischaemic attack.

Follow-up received on 24 Sep 2008 (prior to circulation of initial report): The patient's condition was improving and she continued to receive intravenous heparin. Her cycle 3, day 15 dose was to be skipped. The patient is a smoker and it was considered that the stroke may be attributed to her smoking habit, however, the relationship between the event and study medication was reported as 'uncertain/unknown'.

Follow-up received on 26 Sep 2008 (prior to initial circulation and via email): The investigator reported that as the study medication could not be completely ruled out by the fact the event happened and that other IN CNS have been reported, he assessed the causality to be "suspected". "Not suspected" cannot be ticked as he cannot exclude completely the fact that the event may be related to study medication ("probably not related" in his AE assessment)".

Novartis Comment: Serious adverse drug reaction report, (hospitalisation), assessed as unexpected according to the Investigator Brochure due to greater specificity/severity. The following terms "thromboembolic event" and "thromboembolism" is already included in the Investigator's Brochure. Investigator causality is suspected.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1		Scan brain		
		Revealed a thrombus within the right middle cerebral artery (m-2 segment)		

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 + cetuximab and irinotecan (RAD001 + cetuximab and irinotecan) Tablet; Regimen #1	30 mg qwkly; Oral	Metastatic colorectal adenocarcinoma (Colorectal cancer metastatic)	30-JUL-2008 / Ongoing; Unknown