



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_PHHO2008US07899

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*

⇒ APLB

Date: July 01, 2008

NC

Re: Investigator Notification for RAD001
Enterovesicular Fistula / PHHO2008US07899

AC

Dear Doctors,

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 Enterovesicular Fistula that occurred in a 38-year-old male patient that was enrolled in study CRAD001C24111, an expanded cohort of patients with refractory metastatic colorectal cancer treated with bevacizumab and RAD001. 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 for Preferred Terms of Enterovesical Fistula, Anal Fistula, Colonic Fistula, Perineal Fistula, Enterocutaneous Fistula, Fistula and Enterocolonic Fistula. Four additional cases with various Fistula events were identified, of the four cases, one Enterocutaneous Fistula, one Perineal Fistula and two Anal Fistula events were identified. One event of Anal Fistula was assessed as suspected and remaining events were assessed as not suspected by the reporter. There was no other report of Enterovesical Fistula.

Considering the patient's baseline condition, the event Enterovesicular Fistula is likely to be related to the complications of underlying disease, however, a causal relationship to study drug cannot be excluded.

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,

Syed Sajjad, MD
SBSL, Integrated Medical Safety

CRAD001C 2241

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) XXX	1a. COUNTRY United States	2. DATE OF BIRTH Day XX Month XXX Year XXXX	2a. AGE XX Years	3. SEX Male	3a. WEIGHT 75.50 kg	4-6 REACTION ONSET Day 20 Month JUN Year 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) Enterovesicular fistula [Enterovesical fistula] ([Proctalgia]) UTI [Urinary tract infection]							<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	
Case Description: Initial report received on 24 Jun 2008. This patient (patient no. XXX) was enrolled in study CRAD001C24111, an expanded cohort of patients with refractory metastatic colorectal cancer treated with bevacizumab and RAD001. He received the first dose of study medication on 14 Dec 2007. Cycle 6, day 15 bevacizumab was given on 19 Jun 2008. On 20 Jun 2008, the patient reported to his local hospital for urinary signs and symptoms (s/s) and increased rectal pain that were ongoing for a urinary tract infection (UTI).								
(Continued on Additional Information Page)								

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name) #1) RAD001 + bevacizumab (RAD001 + bevacizumab) Tablet #2) BEVACIZUMAB (BEVACIZUMAB)		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 #2) UNK	16. ROUTE(S) OF ADMINISTRATION #1) Unknown #2) Unknown	
17. INDICATION(S) FOR USE #1) Metastatic Colorectal Cancer (Colorectal cancer metastatic) #2) Metastatic Colorectal Cancer (Colorectal cancer metastatic)		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) 07-DEC-2007 / Ongoing #2) 07-DEC-2007 / 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 Type of History / Notes Description Unknown

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER Investigator's Notification Copy Novartis Pharma Headquarter	26. REMARKS
24b. MFR CONTROL NO. PHHO2008US07899	25b. NAME AND ADDRESS OF REPORTER XXX XXX XXX XXX XXX XXX
24c. DATE RECEIVED BY MANUFACTURER 24-JUN-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 01-JUL-2008	25a. REPORT TYPE <input checked="" type="checkbox"/> INITIAL <input type="checkbox"/> FOLLOWUP:

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

The patient was given one dose of vancomycin intravenously and discharged home. The patient was informed that a computer tomography scan performed on 20 Jun 2008 showed an enterovesicular fistula. The patient was subsequently admitted to hospital on 21 Jun 2008 for a surgical consult and treatment. The outcome was not reported. The investigator stated that the enterovesicular fistula was possibly related to disease, bevacizumab and RAD001. In the absence of an investigator causality assessment, the Novartis medical safety physician provisionally assessed the UTI as suspected to be related to RAD001, based on current available information.

Novartis Comment: Serious adverse drug reaction, enterovesicular fistula, (hospitalisation), assessed as unexpected according to the Investigator's 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.

Serious adverse drug reaction, UTI (hospitalisation), assessed as expected according to the Investigator's Brochure. In the absence of a reporting healthcare professional causality, the Novartis medical safety physician has provisionally assessed the UTI as suspected to RAD001, based on the current available information.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	20-JUN-2008	Computerised tomogram		
		Showed an enterovesicular fistula		