



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_PHHO2008US07823

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



APLB

To: All Investigators in RAD001 Studies*

→ NC

Date: June 26, 2008

AK

Re: Investigator Notification for RAD001
Rectal abscess with anal fistula, Proctitis / PHHO2008US07823

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 events of Proctitis, Rectal abscess with anal fistula that occurred in a 71-year-old male patient that was enrolled and treated in study CRAD001C24124, a phase I/II trial of RAD001 and Bicalutamide for androgen independent prostate 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 10.1 Preferred Terms of Proctitis, Rectal abscess and Anal fistula. A total of 3 cases with events of rectal abscess and anal fistula were identified, all of which were assessed as not suspected by the reporters. Of these, progression of the underlying disease was the attributed cause in 2 cases. There was no other report of Proctitis.

Based on the review of available data, the sponsor cannot establish or exclude the possibility of a cause and effect relationship between administration of RAD001 and the events. 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,

Mary Aghoghovbia, MD
Senior Pharmacovigilance Leader, Integrated Medical Safety
Novartis Pharmaceuticals Corporation

CRAD001C 2241

East Hanover, New Jersey, 07936-1080
United States

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

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) XX	1a. COUNTRY XX	2. DATE OF BIRTH			2a. AGE 71 Years	3. SEX Male	3a. WEIGHT 107.00 kg	4-6 REACTION ONSET			8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
		Day 07	Month SEP	Year 1936			Day 11	Month JUN	Year 2008		
7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data) Event Verbatim (PREFERRED TERM) (Related symptoms if any separated by commas) Rectal abscess with possible communication with anal wall and base of penis [Rectal abscess] ([Pyrexia], [Proctalgia], [Anal discomfort], [Rectal discharge], [Anal fistula]) Possible proctitis [Proctitis] Flu like symptoms [Influenza like illness] ([Pain]) Constipation [Constipation] Generalized body aches and arthralgias [Arthralgia]										<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 checked="" type="checkbox"/> LIFE THREATENING	
Case Description: Initial report received on 20 Jun 2008: This patient (XX)										(Continued on Additional Information Page)	

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name) #1) RAD (RAD) Tablet #2) CASODEX (BICALUTAMIDE)		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 / day #2) 50 mg / day	16. ROUTE(S) OF ADMINISTRATION #1) Oral #2) Unknown	
17. INDICATION(S) FOR USE #1) Prostate cancer (Prostate cancer) #2) Unknown		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) 14-APR-2008 / 12-JUN-2008 #2) Unknown	19. THERAPY DURATION #1) 60 days #2) Unknown	

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction) #1) OMEPRAZOLE (OMEPRAZOLE) ; Unknown #2) LUPRON (LEUPRORELIN ACETATE) ; Unknown #3) CALCIUM (CALCIUM) ; Unknown #4) VITAMIN D (ERGOCALCIFEROL) ; Unknown #5) OMEGA 3 (FISH OIL) ; Unknown #6) ASPIRIN (ACETYLSALICYLIC ACID) ; Unknown		
(Continued on Additional Information Page)		
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. PHHO2008US07823	25b. NAME AND ADDRESS OF REPORTER XX XX XX XX XX XX XX XX
24c. DATE RECEIVED BY MANUFACTURER 20-JUN-2008	24d. REPORT SOURCE <input checked="" type="checkbox"/> STUDY <input type="checkbox"/> LITERATURE <input type="checkbox"/> HEALTH PROFESSIONAL <input type="checkbox"/> OTHER:	
DATE OF THIS REPORT 25-JUN-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**

XX) was enrolled in study CRAD001C24124, a phase I/II trial of RAD001 and bicalutamide for androgen independent prostate cancer. The patient's medical history was not included. He received the first dose of study medication on 14 Apr 2008. On 11 Jun 2008, the patient complained of flu-like symptoms, constipation, rectal pain, generalized body aches and arthralgias, with a temperature of 102. On 12 Jun 2008, the patient presented to clinic for examination. Palpation of the perirectal area revealed no abnormalities, but the patient continued to experience generalized tenderness in the perianal area. Study therapy was held and the patient was to return in 1 week for follow-up. On 13 Jun 2008, the patient complained of rectal drainage and was sent to ED (emergency department). A CT (computed tomography) revealed possible proctitis but no fluid collection. There was no visible abscess. The patient was dispensed clindamycin and returned home. On 19 Jun 2008, the patient experienced continued pain and low grade temperature. An MRI (magnetic resonance imaging) revealed a large loculated rectal abscess with possible communication with anal wall and base of penis (rectal fistula). The event was considered life-threatening. At the time of reporting, the patient was being admitted to hospital for IV (intravenous) antibiotics and surgical evaluation. The investigator suspected a possible relationship between this event and RAD001.

Novartis Comment: Serious adverse drug reaction report, rectal abscess, possible proctitis, (life-threatening), assessed as unexpected according to the Investigators Brochure. The information provided in this case does not warrant a change to the Investigators Brochure. The topic will be monitored closely. Investigator causality is suspected.

Serious adverse drug reaction report, arthralgia, constipation, flu-like symptoms (life-threatening), assessed as expected according to the Investigators Brochure. Investigator causality is suspected.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	13-JUN-2008	Computerised tomogram		
			Possible proctitis but no fluid collection - there was no visible abscess	
2	19-JUN-2008	Nuclear magnetic resonance imaging		
			Revealed a large loculated rectal abscess with possible communication with anal wall and base of penis	

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION continued

#7) VEMMA ESSENTIAL MINERALS (MINERALS NOS) ; Unknown

#8) IBUPROFEN (IBUPROFEN) ; Unknown

#9) TYLENOL (PARACETAMOL) ; Unknown

25b. Name And Address of Reporters continued

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