



# NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

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**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\_PHHO2008AU08078**

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](mailto:braun.sara@mayo.edu) or 507-538-8226.

SB/kjm  
enclosure



APLB

To: All Investigators in RAD001 Studies\*

=> NC

Date: July 9, 2008

AL

Re: Investigator Notification for RAD001  
Perianal abscess / PHHO2008AU08078

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 perianal abscess that occurred in a 63-year-old female patient that was enrolled and treated in study CRAD001C2114, a two-step, phase 1 study investigating the combination of RAD001 with carboplatin, paclitaxel and bevacizumab in non-small-cell lung cancer (NSCLC) patients not treated previously with systemic therapy. The two steps include: Step 1 - RAD001, carboplatin and paclitaxel (CP) and step 2 - RAD001, carboplatin, paclitaxel and bevacizumab (CPB).

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 that contain abscess. A total of 28 cases were identified, four cases were suspected including the current one. The remaining 24 cases were assessed as not suspected by the reporters. Of the additional three suspected cases, one perirectal abscess was the complication of skin infection in a patient with recurrent glioblastoma. One rectal abscess occurred in a prostate cancer patient along with possible proctitis and anal fistula. One liver abscess developed along with biliary sepsis in a patient with advanced pancreatic neuroendocrine tumor with multiple liver and bone metastases.

In the current case, the patient experienced constipation leading to the development of anal fissures and subsequent perianal abscess. The event of perianal abscess seems to be related to the complications of constipation. 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,

Holly Zhang, MD  
Senior Pharmacovigilance Leader, Integrated Medical Safety  
Novartis Pharmaceuticals Corporation  
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.

<b>SUSPECT ADVERSE REACTION REPORT</b>	

**I. REACTION INFORMATION**

1. PATIENT INITIALS (first, last) <b>X</b>	1a. COUNTRY <b>X</b>	2. DATE OF BIRTH			2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET			8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
		Day	Month	Year	Years		Day	Month	Year		
		<b>18</b>	<b>MAR</b>	<b>1945</b>	<b>63</b>	<b>Female</b>	<b>82.80</b>		<b>JUN</b>	<b>2008</b>	

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)  
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)  
**Perianal abscess [Perianal abscess] ([Purulent discharge])  
Increased GGT [Gamma-glutamyltransferase increased]  
Anal fissure [Anal fissure] ([Proctalgia])  
Constipation [Constipation]**

Case Description: Initial report received on 27 Jun 2008. This patient (X) from centre (X) was enrolled in study CRAD001C2114, a two-step, phase 1 study investigating the combination of RAD001 with carboplatin, paclitaxel and bevacizumab in non-small-cell lung cancer (NSCLC) patients not treated previously with systemic therapy.

(Continued on Additional Information Page)

PATIENT DIED  
 INVOLVED OR PROLONGED INPATIENT HOSPITALISATION  
 INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY  
 LIFE THREATENING

**II. SUSPECT DRUG(S) INFORMATION**

14. SUSPECT DRUG(S) (include generic name) #1 ) RAD001 (RAD001) Tablet #2 ) PACLITAXEL (PACLITAXEL) <p style="text-align: right;">(Continued on Additional Information Page)</p>		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 ) 5 mg / day #2 ) 370 mg	16. ROUTE(S) OF ADMINISTRATION #1 ) Oral #2 ) Intravenous	
17. INDICATION(S) FOR USE #1 ) Non-small cell lung cancer (Non-small cell lung cancer) #2 ) Non-small cell lung cancer (Non-small cell lung 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 ) 06-JUN-2008 / 25-JUN-2008 #2 ) 05-JUN-2008 / 05-JUN-2008	19. THERAPY DURATION #1 ) 20 days #2 ) 1 day	

**III. CONCOMITANT DRUG(S) AND HISTORY**

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction) #1 ) KEFLEX (CEFALEXIN MONOHYDRATE) ; 13-JUN-2008 / Ongoing #2 ) LACTULOSE (LACTULOSE) ; 08-JUN-2008 / Ongoing #3 ) SENOKOT (SENNA ALEXANDRINA FRUIT) ; 08-JUN-2008 / Ongoing #4 ) MOVICOL (MACROGOL, POTASSIUM CHLORIDE, SODIUM BICARB #5 ) COLOXYL WITH SENNA (DOCUSATE SODIUM, SENNOSIDE A+B) <p style="text-align: right;">(Continued on Additional Information Page)</p>		
23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)		
From/To Dates	Type of History / Notes	Description
Unknown	Current Condition	Anxiety (Anxiety)
Unknown	Current Condition	Dyslipidemia (Dyslipidaemia)

**IV. MANUFACTURER INFORMATION**

24a. NAME AND ADDRESS OF MANUFACTURER Investigator's Notification Copy Novartis Pharma Headquarter		26. REMARKS
24b. MFR CONTROL NO. <b>PHHO2008AU08078</b>		
24c. DATE RECEIVED BY MANUFACTURER <b>27-JUN-2008</b>	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 X X X X X X
DATE OF THIS REPORT <b>07-JUL-2008</b>	25a. REPORT TYPE <input checked="" type="checkbox"/> INITIAL <input type="checkbox"/> FOLLOWUP:	

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

The two steps include: Step 1 - RAD001, carboplatin and paclitaxel (CP) and step 2 - RAD001, carboplatin, paclitaxel and bevacizumab (CPB). Medical history included hypertension, dyslipidemia and anxiety. The patient received the first dose of study medication on 05 Jun 2008 and was in step 2 of the study. In Jun 2008, the patient presented with increasing anal pain due to anal fissure. The patient described a 3 week-history of constipation, grade 2 (likely related to anti-emetics, tropisetron and metoclopramide), refractory to aperients. This constipation led to anal fissures developing. On 25 Jun 2008, the patient developed purulent discharge secondary to perianal abscess, which developed despite prophylactic Keflex (commenced on 13 Jun 2008). A physical examination was not completed due to anal pain. The patient was admitted to hospital for treatment with intravenous (IV) antibiotics (ampicillin, ceftriaxone and metronidazole). A CT (computed tomography) pelvis was to be arranged to assess for collection, and surgical review post CT scan. Cycle 2 of the study treatment was not initiated, due to grade 3 increased GGT (gamma glutamyl transferase). The study medication was temporarily interrupted due to the events. At the time of reporting, the patient's condition was still present and unchanged. The investigator assessed the relationship between the perianal abscess and study medication as suspected stating that the fissures, together with the patient's immuno-compromised state increased the likelihood of the perianal abscess. In the absence of an investigator causality for the constipation and anal fissure the Novartis medical safety physician has provisionally assessed these events as not suspected to be related to study medication based on the current available information.

Novartis Comment: Serious adverse drug reaction report, perianal abscess (hospitalisation), 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, increased gamma-GT (hospitalisation), assessed as expected according to the Investigators Brochure. Investigator causality is suspected.

All remaining reported leading events and associated symptoms were assessed as not suspected by the Novartis medical safety physician.

**13. Lab Data**

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	25-JUN-2008	Gamma-glutamyltransferase	249 U/L	
2	25-JUN-2008	Neutrophil count	3.1 x 10 <sup>9</sup> /L	

**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
#3 ) CARBOPLATIN (CARBOPLATIN); Regimen #1	900 mg; Intravenous	Non-small cell lung cancer (Non-small cell lung cancer)	05-JUN-2008 / 05-JUN-2008; 1 day
#4 ) BEVACIZUMAB (BEVACIZUMAB); Regimen #1	255 mg; Intravenous	Non-small cell lung cancer (Non-small cell lung cancer)	05-JUN-2008 / 05-JUN-2008; 1 day
#5 ) TROPISETRON (TROPISETRON); Regimen #1	5 mg ONCE; Intravenous	Unknown	05-JUN-2008 / 05-JUN-2008; 1 day
#5 ) TROPISETRON (TROPISETRON); Regimen #2	5 mg / day; Oral	Unknown	06-JUN-2008 / 07-JUN-2008; 2 days
#6 ) METOCLOPRAMIDE (METOCLOPRAMIDE); Regimen #1	10 mg, PRN; Oral	Unknown	07-JUN-2008 / Ongoing; Unknown

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**ADDITIONAL INFORMATION**

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

#4 ) MOVICOL (MACROGOL, POTASSIUM CHLORIDE, SODIUM BICARBONATE, SODIUM CHLORIDE) ; 11-JUN-2008 / Ongoing

**23. OTHER RELEVANT HISTORY** *continued*

From/To Dates	Type of History / Notes	Description
Unknown	Current Condition	Hypertension (Hypertension);