



# NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

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**Date:** June 13, 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\_PHHO2008US06493**

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/df  
enclosure



To: All Investigators in RAD001 Studies\*

Date: May 30, 2008

Re: Investigator Notification for RAD001  
Cytokine release syndrome/PHHO2008US06493

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 cytokine release syndrome that occurred in a 67-year-old male patient being treated with RAD001 during the course of the clinical trial entitled "A randomized, double-blind, placebo-controlled, multicenter phase III study in patients with advanced carcinoid tumor receiving Sandostatin LAR and RAD001 10 mg/d or Sandostatin LAR and placebo".

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 Cytokine release syndrome and Cytokine storm. No additional case was identified.

In the current case, the patient received RAD001 and Sandostatin, only the clinical manifestations were available at the time of this report. Based on the review of available data in this case, the sponsor cannot establish or exclude the possibility of a cause and effect relationship between administration of RAD001 and the event. 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,

CRAD001C 2241

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

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\* 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>XXX</b>	1a. COUNTRY <b>United States</b>	2. DATE OF BIRTH Day <b>XX</b> Month <b>XXX</b> Year <b>XX</b>	2a. AGE <b>XX</b>	3. SEX <b>Male</b>	3a. WEIGHT <b>91.80</b> kg	4-6 REACTION ONSET Day <b>15</b> Month <b>MAY</b> Year <b>2008</b>	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) <b>Cytokine release syndrome [Cytokine release syndrome] ([Skin exfoliation], [Pyrexia], [Confusional state], [Muscular weakness], [Skin reaction])</b>							<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 19 May 2005: This patient (centre no. XXX, patient no. XXX) was enrolled in the study CRAD001C2325, a randomised, double-blind, placebo-controlled, multicenter phase III study in patients with advanced carcinoid tumour receiving Sandostatin LAR and RAD001 10 mg/d or Sandostatin LAR and placebo. The patient's medical history included atrial fibrillation, mitral valve repair and rosacea. The patient received his first dose of study medication on 16 Apr 2008.							
(Continued on Additional Information Page)							

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

14. SUSPECT DRUG(S) (include generic name) #1 ) RAD001 Vs Placebo (RAD 666 RAD+TAB) Tablet #2 ) SANDOSTATIN LAR/ SMS 995A,B,G,H (OCTREOTIDE WITH POLY(D L-LACTIDE-CO-GLYCOLIDE)) Vial		20. DID REACTION ABATE AFTER STOPPING DRUG?  <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> NA <span style="float: right;">Unknown</span>
15. DAILY DOSE(S) #1 ) 10 mg, QD #2 ) 30 mg Q28days	16. ROUTE(S) OF ADMINISTRATION #1 ) Unknown #2 ) Unknown	
17. INDICATION(S) FOR USE #1 ) carcinoid tumour (Carcinoid tumour) #2 ) Carcinoid tumour (Carcinoid tumour)		21. DID REACTION REAPPEAR AFTER REINTRODUCTION?  <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> NA <span style="float: right;">Unknown</span>
18. THERAPY DATES(from/to) #1 ) 16-APR-2008 / 15-MAY-2008 #2 ) 16-APR-2008 / 15-MAY-2008	19. THERAPY DURATION #1 ) 30 days #2 ) 30 days	

**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	Description
Unknown	Rosacea (Rosacea)
Unknown	Mitral valve repair (Mitral valve repair)

**IV. MANUFACTURER INFORMATION**

24a. NAME AND ADDRESS OF MANUFACTURER Investigator's Notification Copy Novartis Pharma Headquarter	26. REMARKS
24b. MFR CONTROL NO. <b>PHHO2008US06493</b>	25b. NAME AND ADDRESS OF REPORTER XXXXXX XXXXXX XXXXXX XXXXXX
24c. DATE RECEIVED BY MANUFACTURER <b>19-MAY-2008</b>	
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 <b>30-MAY-2008</b>	25a. REPORT TYPE <input checked="" type="checkbox"/> INITIAL <input type="checkbox"/> FOLLOWUP:

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

On 15 May 2008, the patient presented with fever/rigors, confusion and profound new muscle weakness, which resulted in hospitalization. On arrival his temperature was 102 degrees Fahrenheit and the patient reported skin peeling of both hands and blister vesicles on fingertips. Urinalysis, CXR (chest x-ray) and blood cultures were negative, and ANC (absolute neutrophil count) was 6399. The study medication was held, but by the afternoon of 16 May 2008, the patient remained febrile. Work-up was negative for infection so no antibiotics were started. The patient was seen by Infectious Disease and placed on intravenous (IV) vancomycin and Fortaz for 48 hours prophylactically. The patient had recovery of fever, muscle weakness and confusion by 16 May 2008 but discharge was delayed, until 19 May 2008, for observation. The investigator felt, based on medical records, that the patient had cytokine release syndrome (grade 2) with hand/foot skin reaction (grade 3) on cycle 2, day 2 that were causing the symptoms. On 21 May 2008, the patient was seen for follow-up and was still experiencing peeling of skin, both hands, and fluid filled vesicles on 2-3 fingertips. The study medication would continue to be held until resolution of the events and would then restart with a dose reduction. At the time of reporting, the patient had recovered with sequelae. The investigator suspected a relationship between this event and the study medication (RAD001), including Sandostatin LAR (Novartis product).

Novartis Comment: Serious adverse drug reaction report (hospitalisation), assessed as unexpected for RAD001 according to the Investigators Brochure and unlisted for Sandostatin LAR according to the Core Data Sheet.

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 for RAD001 and Sandostatin LAR.

**13. Lab Data**

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	16-MAY-2008	White blood cell disorder Normal	7.9	10.8 4.5
2	17-MAY-2008	White blood cell disorder Low	3.0	10.8 4.5
3	18-MAY-2008	White blood cell disorder Low	3.8	10.8 4.5

**13. Relevant Tests**

(16 May 2008) Blood cultures : Negative

(16 May 2008) WBC (white blood cells) : 7.9

(17 May 2008) WBC : 3.0

(18 May 2008) WBC : 3.8

**23. OTHER RELEVANT HISTORY continued**

From/To Dates	Type of History / Notes	Description
Unknown		Atrial fibrillation (Atrial fibrillation);