



NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

Date: September 5, 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_PHHO2007US21124_F1

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: Aug 29, 2008

Re: Investigator Notification for RAD001
PHHO2007US21124/ **Diarrhea, cold sweat and restlessness associated with fatal outcome- follow-up (downgraded to not suspected)**
Study number: CRAD001C2476

Dear Doctors,

In accordance with the Good Clinical Practice and specific national regulatory requirements, we would like to inform you of medical significant information received for the previous report of a serious, unexpected, possibly related adverse events of diarrhea, cold sweat and restlessness associated with fatal outcome that occurred in a 74-year-old female patient being treated with RAD001 during the course of the clinical trial.

Details of the adverse event are provided in the attached CIOMS I form, which contains the available information as reported to Novartis.

Follow-up information indicated that investigator considered that the patient had sudden cardiac death that was suspected to be related to patient's underlying condition of hypertension and was not suspected to be related to the RAD001.

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) XX	1a. COUNTRY XXX	2. DATE OF BIRTH			2a. AGE 74 Years	3. SEX Female	3a. WEIGHT 85.26 kg	4-6 REACTION ONSET			8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION <input checked="" type="checkbox"/> PATIENT DIED Date: 20-DEC-2007 <input type="checkbox"/> INVOLVED OR PROLONGED INPATIENT HOSPITALISATION <input type="checkbox"/> INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY <input type="checkbox"/> LIFE THREATENING
		Day 08	Month DEC	Year 1933				Day 20	Month DEC	Year 2007	
7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data) Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas) Other Serious Criteria: Medically Significant Sudden cardiac death [Sudden cardiac death] ([Cold sweat], [Restlessness], [Diarrhoea]) Case Description: Initial report received on 27 Dec 2007: This patient (patient no. XXX) was enrolled in the investigator initiated trial XXXX, a phase X, single centre, open-label study of low dose weekly cisplatin (20 mg/m ² intravenously on Days 1, 8, and 15) plus escalating doses of daily RAD001 tablets (per oral or via percutaneous gastrostomy tube, Days 1 -21 of a 28-Day Cycle) for patients with advanced solid tumors. <p style="text-align: right;">(Continued on Additional Information Page)</p>											

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name) #1) RAD001 + sorafenib (RAD001 + sorafenib) Tablet #2) SORAFENIB (SORAFENIB)		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) 35 mg/week #2) 400 mg/day	16. ROUTE(S) OF ADMINISTRATION #1) Oral #2) Intravenous	
17. INDICATION(S) FOR USE #1) Solid tumour (Renal cell carcinoma) #2) solid tumour (Neoplasm)		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) 26-OCT-2007 / 16-DEC-2007 #2) 26-OCT-2007 / Ongoing	19. THERAPY DURATION #1) 52 days #2) Unknown	

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction) #1) NORVASC (AMLODIPINE BESILATE) ; Unknown #2) TAGAMET (CIMETIDINE) ; Unknown #3) FLONASE (FLUTICASON PROPIONATE) ; Unknown #4) VITAMINS (NO INGREDIENTS/SUBSTANCES) ; Unknown		
23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)		
From/To Dates Unknown 1973 to Unknown	Type of History / Notes Historical Condition	Description Heavy smoker (Smoker) Thyroidectomy (Thyroidectomy)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER Investigator's Notification Copy Novartis Pharma Headquarter		26. REMARKS
	24b. MFR CONTROL NO. PHHO2007US21124	
24c. DATE RECEIVED BY MANUFACTURER 28-AUG-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 XXXX XXXX XXXX XXXX XXXX
DATE OF THIS REPORT 29-AUG-2008	25a. REPORT TYPE <input type="checkbox"/> INITIAL <input checked="" type="checkbox"/> FOLLOWUP: X	

(Continued on Additional Information Page)

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

The patient's medical history was not reported. She received the first dose of study medication on 28 Oct 2007. On 20 Dec 2007, the patient experienced the onset of several episodes of diarrhoea with clammy skin and restlessness. An ambulance was called to take the patient to hospital; however the patient died before she arrived. Prior to this event, the patient received her last dose of RAD001 on 16 Dec 2007. The investigator suspected there was a relationship between this event and the study medication.

Follow up received on 28 Feb 2008: The patient was without significant past medical history. Initial consultation was for abnormal chest wall lesion after being scratched by a dog 4 months prior. While evaluating this lesion, the patient had a CT scan that showed a large renal mass with a few scattered small lymph nodes in the porta hepatis. She also had bilateral adrenal enlargement and axillary adenopathy. She received 15 minutes of CPR, per the family, prior to their arrival. She was intubated and CPR was continued. Treatment included three doses of epinephrine, two doses of atropine, one dose of D50 (dextrose) and a dose of bicarbonate as well as normal saline and oxygen. Her rhythm changed after getting medication from asystole to an idioventricular rhythm but back to asystole. Physical exam on arrival to the emergency room was no pulse, no respirations, no gag reflex and no cough. Pupils were non-reactive. Skin pale and mottled. Patient continued in asystole. CPR was stopped and she was declared deceased. No lab work was done. An autopsy was not carried out and there was no death certificate available but the event term was changed to sudden death.

Follow-up received on 07 Mar 2008: The patient was enrolled in study CRAD001C2480, not CRAD001C2476 as previously reported. CRAD001C2480 is an investigator initiated trial, a phase I/II study of RAD001 + sorafenib in the treatment of patients with advanced clear cell renal carcinoma.

Follow-up received on 13 Mar 2008: The patient's medical history included hypertension and thyroidectomy. The patient's renal cancer status at baseline was BUN 12 and Creatinine 0.7 on 24 Oct 2007. The patient's final cancer status during the study drug treatment was: 'The patient had plaque-like lesions improving on 09 Nov 2007, C1D15, then growing again. On 16 Nov 2007 the lesion on the chest seemed to be decreasing as well as facial and forehead lesions. Neck lesion almost resolved. On 07 Dec 2007 the patient continued to take pills without consequence C2, D15'. The cause of death was unknown. Death certificate and autopsy reports were not available. The investigator provided a rationale for the suspected causality, stating that the patient was old, had cancer and that the study medication could have caused problems.

Follow-up received on 04 Jun 2006: The cause of death was unknown and the death was not suspected to be related to study medication. The serious criteria for the events clammy, restlessness and diarrhea was 'medically significant'.

Follow-up received on 20 Aug 2008: The investigator reassessed the causality assessment and did not suspect a relationship between the events clammy skin, restlessness and diarrhea and the study medication.

Follow-up received on 28 Aug 2008: The cause of death remained unknown. No tests or autopsy were performed and the causality was considered to be unknown regarding study medication.

Follow-up received on 28 Aug 2008 (prior to circulation of previous follow-up): The investigator further clarified that the patient had hard to control hypertension and heavy smoking history. The investigator suspected that she died of a sudden cardiac death.

Novartis Comment: New information received on 20 Aug 2008 reported that the events clammy, restlessness and diarrhoea was reassessed as not suspected by the investigator.

All remaining reported leading events and associated symptoms were already assessed as not suspected by the investigator.

13. Relevant Tests

(24 Oct 2007) BUN: 12
(07 Dec 2007) BUN: 6

(24 Oct 2007) Creatinine: 0.7

(24 Oct 2007) LDH: 489
(07 Dec 2007) LDH: 5428

(24 Oct 2007) ALT: 48
(07 Dec 2007) ALT: 113

(24 Oct 2007) AST: 34
(07 Dec 2007) AST: 114

(24 Oct 2007) Uric Acid: 5.7
(12 Jul 2007) Uric acid: 10.5

ADDITIONAL INFORMATION

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown	Hard to control	Hypertension (Hypertension);
Unknown		Axillary adenopathy (Lymphadenopathy);
Unknown	Enlargement	Adrenal disorder (Adrenal disorder);
Unknown	Porta hepatis	Lymph node metastases (Metastases to lymph nodes);
Unknown	Lesion	Chest wall mass (Chest wall mass);

25b. Name And Address of Reporters continued

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