



NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

Date: March 6, 2009

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 report of an adverse event that has occurred in association with RAD001 for a study where the Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI) is distributing this agent. You may have also received this communication directly from DCTD.

AE_PHHO2008DE11982

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: Dec 10, 2008

Re: Investigator Notification for RAD001
Capillary leak syndrome _PHHO2008DE11982

Dear Doctor,

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 Capillary leak syndrome that occurred in 64-year-old female patient who enrolled in in study enrolled in CRAD001C24114, Multicenter, single-arm, single-stage, phase II trial to determine the preliminary efficacy and safety of RAD001 in patients with histological evidence of progressive or metastatic bone or soft tissue sarcomas and patient's with gastrointestinal stromal tumor (GIST) after failure or intolerance of treatment with imatinib or sunitinib in 1st and 2nd line.

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 11.0 Preferred Term of Capillary leak syndrome. No additional case was identified from the search.

Given the available information, study drug contribution to the event occurrence cannot be established or 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

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)	1a. COUNTRY	2. DATE OF BIRTH			2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET			8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION <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
		Day	Month	Year	64 Years	Female	Unk	Day	Month	Year	
		11	NOV	1943				03	OCT	2008	
7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data) Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas) Capillary leakage [Capillary leak syndrome] ([Dehydration]) Pancytopenia [Pancytopenia]											
Case Description: Initial report received on 07 Oct 2008: This patient (patient no. x, centre no.x) was enrolled in CRAD001C24114, Multicenter, single-arm, single-stage, phase II trial to determine the preliminary efficacy and safety of RAD001 in patients with histological evidence of progressive or metastatic bone or soft tissue sarcomas and patient's with gastrointestinal stromal tumor (GIST) after failure or intolerance of treatment with imatinib or sunitinib in 1st and 2nd line. The patient's medical history was not reported.											
(Continued on Additional Information Page)											

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name) #1) RAD001 (RAD001) Tablet		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) 10mg	16. ROUTE(S) OF ADMINISTRATION #1) Oral	
17. INDICATION(S) FOR USE #1) Liposarcoma right under abdominal (Liposarcoma)		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) 15-SEP-2008 / Unknown	19. THERAPY DURATION #1) 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. PHHO2008DE11982			25b. NAME AND ADDRESS OF REPORTER	
24c. DATE RECEIVED BY MANUFACTURER 28-NOV-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 10-DEC-2008	25a. REPORT TYPE <input checked="" type="checkbox"/> INITIAL <input type="checkbox"/> FOLLOWUP:				

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

She received the first dose of study medication on 15 Sep 2008. On 03 Oct 2008, the patient experienced pancytopenia and exsiccation which resulted in hospitalisation. Treatment or outcome was not specified. The investigator did not provide an assessment of causality, but the Novartis medical safety physician provided a provisional assessment and suspected a relationship between this event and the study medication.

Follow-up received on 28 Nov 2008: The indication for which the patient was entered into the study was liposarcoma right, under abdomen. She received treatment with 4 units of RBC (red blood cells) for the event. Capillary leakage was considered to have caused the exsiccation. The investigator suspected a relationship between the events and the study medication.

Novartis Comment: Serious adverse drug reaction, capillary leakage, (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, pancytopenia, (hospitalisation), assessed as expected according to the Investigator's Brochure. Investigator causality is suspected.