



To: All Investigators in RAD001 Studies\*

Date: March 10, 2009

Re: Investigator Notification for RAD001  
Multi-organ failure (fatal) /PHHO2009US02442

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 Multi-organ failure (fatal) that occurred in 58-year-old female patient who enrolled in a study CRAD001C2464 entitled "A phase II study of RAD001 (everolimus) and bevacizumab in the treatment of 2 groups of patient's with advanced clear cell renal carcinoma."

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 was performed using MedDRA 11.0 Preferred Term of Multi-organ failure for the event that is associated with fatal outcome. Nineteen cases were identified. Four cases were suspected including the current case. For the three previously reported cases, multi-organ failures are secondary to the severe infection and/ or sepsis and no fulminant hepatic failure with hepatorenal syndrome was reported in these cases.

In the current case, the patient had advanced malignancy with pulmonary metastasis. The event occurred approximately seven days after the RAD001 discontinuation when liver metastasis and pulmonary embolism were highly suspected. Given the available information, it is difficult to assess the causal relationship. Multi-organ failure is listed in the current IB, but fatal outcome is not specified. 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,

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

Attachment: CIOMS case report

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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.



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

Case Description: Initial report received on 13 Feb 2009: This patient (patient no. xxxx) was enrolled in the investigator initiated trial CRAD001C2464, a phase II study of RAD001 (everolimus) and bevacizumab in the treatment of 2 groups of patient's with advanced clear cell renal carcinoma. The patient's medical history included hypertension, anxiety, hyperlipidemia and anemia. She received the first dose of study medication on 11 Sep 2008. On an unspecified date the patient developed an upper respiratory infection. Despite 2 different oral antibiotics, on 09 Feb 2009 the patient experienced worsening of fever, SOB (shortness of breath), malaise and cough. She went to the ER (emergency room) and was admitted to hospital. The patient was not recovered at the time of reporting. The investigator did not provide a causality assessment, however, the Novartis medical safety physician assessed this event as suspected, based on current available information.

Follow up received on 26 Feb 2009: Avastin was last administered on 30 Jan 2009 and RAD001 on 09 Feb 2009. The patient was admitted to hospital on 09 Feb 2009 with productive cough of yellow sputum, fevers, chills and weakness secondary to pneumonia grade 3. CXR on 15 Feb 2009 showed bilateral atelectasis. The patient was removed from the study on 10 Feb 2009. Labs on 17 Feb 2009 showed: WBC 17.8, creatinine 2.3, BUN 79, AST 1119, ALT 120 and total bilirubin 8.3. She began to worsen with kidney function deteriorated and high suspicion of metastatic liver disease and high anion gap metabolic acidosis. Treatment included intravenous broad spectrum antibiotics and bicarb. Respiratory failure and high probability of pulmonary embolism developed. Liver function tests and total bilirubin continued to increase. The patient rapidly deteriorated with worsening of hepatorenal syndrome, multiorgan failure and hepatic encephalopathy secondary to fulminant liver failure. She was transferred to Hospice care and expired on 18 Feb 2009 from multi-organ failure. It was not reported whether an autopsy was performed. The investigator did not suspect a relationship between the pneumonia and the study medication. The investigator suspected possible a relationship between the pulmonary embolism, elevated liver enzymes, acute on chronic renal insufficiency, multiorgan failure and the study medication. The investigator did not provide a causality assessment for the suspicion of metastatic liver disease. However, the Novartis Medical Safety Physician provided a provisional causality and did not suspect a relationship between this event and the study medication, based on currently available information.

Follow-up received on 02 Mar 2009: The patient's medical history also included left nephrectomy for metastatic renal cell ca (clear cell type with extensive necrosis) with pulmonary mets. (metastases).

Novartis Comment: Serious adverse drug reaction report, fatal multi-organ failure, assessed as unexpected according to the Investigator's Brochure. However, other alternative causes (concurrent pneumonia) provide a possible explanation for the reported adverse event. Investigator causality is suspected.

Serious adverse drug reactionm pulmonary embolism (hospitalisation), assessed as expected according to the Investigator's Brochure. Investigator causality is suspected.

All remaining reported leading events and associated symptoms were assessed as not suspected by the investigator (pneumonia) and Novartis Medical Safety Physician (malignant neoplasm progression).

**13. Lab Data**

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	17-FEB-2009	Alanine aminotransferase	120	
2	17-FEB-2009	Anion gap	23	
3	17-FEB-2009	Aspartate aminotransferase	1119	
4	17-FEB-2009	Blood bilirubin	8.3	
5	17-FEB-2009	Blood creatinine	2.3	
6	17-FEB-2009	Blood urea	79	
7	10-FEB-2009	Bone scan No metastases		
8	17-FEB-2009	Carbon dioxide abnormal	18	
9	15-FEB-2009	Chest X-ray		

**ADDITIONAL INFORMATION****13. Lab Data**

#	Date	Test / Assessment / Notes	Results	Normal High / Low
		Poor inspiration and bilateral atelectasis		
10	17-FEB-2009	Chest X-ray		
11	13-FEB-2009	Computerised tomogram		
		SM left effusion, left lower lobe pneumonia, indeterminate soft tissue densities, patchy interstitial infiltrates within the upper lobes		
12	14-FEB-2009	Ejection fraction		
		Depressed GB ejection fraction with GB wall thickening		
13	14-FEB-2009	Hepatobiliary scan		
		No obstruction		
14	12-FEB-2009	Scan		
		High probability of embolis in left upper lobe		
15	10-FEB-2009	Spinal X-ray		
		Mild-moderate degenerative changes		
16	13-FEB-2009	Ultrasound abdomen		
		GB wall thickening		
17	17-FEB-2009	White blood cell count	17.8	

**23. OTHER RELEVANT HISTORY continued**

From/To Dates	Type of History / Notes	Description
Unknown		Anemia (Anaemia);
Unknown		Hyperlipidemia (Hyperlipidaemia);
Unknown		Anxiety (Anxiety);
Unknown		Hypertension (Hypertension);

**25b. Name And Address of Reporters continued**

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**ADDITIONAL INFORMATION**

**23. OTHER RELEVANT HISTORY continued**

From/To Dates	Type of History / Notes	Description
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