



NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

Date: December 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_PHHO2008IT01481_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: Dec 2, 2008

Re: Investigator Notification for RAD001
Hematuria /PHHO2008IT01481 follow-up (Downgraded to Not suspected)

Dear Doctors,

In accordance with the Good Clinical Practice and specific national regulatory requirements, we would like to inform you of medical significant information for a serious, unexpected, possibly related adverse event of hematuria that occurred in a 66 year-old male patient being treated with RAD001 during the course of the clinical trial entitled "A randomised double-blind phase III study of RAD001 plus best supportive care versus placebo plus best supportive care in the treatment of patients with advanced pancreatic neuroendocrine tumor (NET)".

Follow-up information received indicates that the event was not suspected to be related to the study drug. The use of Ugurol may have contributed to hematuria. Details of the adverse event as reported to Novartis are provided in the attached CIOMS I form.

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
		Day	Month	Year	66 Years	Male	57.00 kg	Day	Month	Year	
		15	DEC	1941				14	JAN	2008	
7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data) Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas) Hematuria / worsening [Haematuria] Fever [Pyrexia] Gastroenteritis [Gastroenteritis] ([Vomiting], [Diarrhoea], [Dehydration]) Hb lower than normal ranges (8.7) (non-serious) [Haemoglobin decreased]											<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 22 Jan 2008: This patient (centre no. xxx, patient no. xxx) was enrolled in the study CRAD001C2324, a randomised double-blind phase III study of RAD001 plus best supportive care versus placebo plus best supportive care in the treatment of patients with advanced pancreatic neuroendocrine tumor (NET).											
(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+CMAS) Tablet #2) UGUROL (TRANEXAMIC ACID) <div style="text-align: right;">(Continued on Additional Information Page)</div>		20. DID REACTION ABATE AFTER STOPPING DRUG? <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> NA <input type="checkbox"/> Unknown
15. DAILY DOSE(S) #1) UNK #2) Unknown	16. ROUTE(S) OF ADMINISTRATION #1) Oral #2) Unknown	
17. INDICATION(S) FOR USE #1) pancreatic neuroendocrine (Pancreatic neuroendocrine tumour) #2) Haematuria (Haematuria)		21. DID REACTION REAPPEAR AFTER REINTRODUCTION? <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> NA <input type="checkbox"/> Unknown
18. THERAPY DATES(from/to) #1) 21-NOV-2007 / Ongoing #2) Unknown	19. THERAPY DURATION #1) Unknown #2) Unknown	

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction) #1) MADOPAR (BENSERAZIDE HYDROCHLORIDE, LEVODOPA) ; Unknown #2) MIRAPEXIN (PRAMIPEXOLE DIHYDROCHLORIDE) ; Unknown #3) ARTANE (TRIHENXYPHENIDYL HYDROCHLORIDE) ; Unknown #4) FINASTID "NEOPHARMED" (FINASTERIDE) ; Unknown #5) KINERET (ANAKINRA) ; Unknown	
23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.) From/To Dates 2001 to Unknown	Description Prostatic hypertrophy (Benign prostatic hyperplasia)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER Investigator's Notification Copy Novartis Pharma Headquarter		26. REMARKS	
	24b. MFR CONTROL NO. PHHO2008IT01481	25b. NAME AND ADDRESS OF REPORTER	
24c. DATE RECEIVED BY MANUFACTURER 20-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 02-DEC-2008	25a. REPORT TYPE <input type="checkbox"/> INITIAL <input checked="" type="checkbox"/> FOLLOWUP:		

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

The patient received his first dose of study medication on 21 Nov 2007. On 14 Jan 2008, the patient presented with hematuria, which resulted in hospitalisation on 19 Jan 2008 because vomit deteriorated the patient's clinical condition. Treatment included antibiotic therapy. At the time of this report the patient's condition was improving. The investigator did not suspect a relationship between this event and the study medication.

Follow up received on 30 Jan 2008: An abdominal ultrasound was performed on 16 Jan 2008 which was negative. PSA on 16 Jan 2008 was 0.65 ug/ml (normal range). The patient was hospitalised from 18 Jan 2008 to 23 Jan 2008 for hematuria and because vomit deteriorated the patient's clinical condition. The patient also had dehydration due to diarrhea. The dose of study medication was reduced to 50% of total dose for a week. At the time of this report the patient's condition was improving. The investigator changed the causality and suspected a relationship between this event and the study medication.

Follow up received on 05 Feb 2008 prior to circulation of previous follow up: The patient had hematuria since 14 Jan 2008. The patient was hospitalised for increased hematuria the severity was 2. The patient also had a fever. Microbiological examination was not done. Treatment included antibiotics. Ultrasound scan on 16 Jan 2008 did not reveal any lesions of prostatic origin and Urologist examination on 18 Jan 2008 did not find any lesion to treat during hospitalisation. On 16 Jan 2008 PSA was 0.65 [0-4] in the normal range. Abdomen x-ray showed levels of bowel. On 30 Jan 2008 the hematuria was still persistent but improving (with reduced study medication dose of 50%). The investigator did not suspect a relationship between the vomiting, diarrhoea and dehydration and the study medication but suspected a relationship between the haematuria and the study medication. In the absence of an investigator causality, the Novartis Medical Safety Physician has provisionally assessed fever as suspected based on the current available information.

Follow up received 18 Feb 2008: The investigator confirmed that the patient made a complete recovery from the haematuria from the 14 Feb 2008.

Follow-up received on 26 Mar 2008: The patient experienced vomiting that deteriorated his clinical condition, resulting in hospitalisation on 18 Jan 2008, and haematuria was still present. The patient was subsequently diagnosed with gastroenteritis (vomiting, dehydration and diarrhea). The patient completely recovered from the gastroenteritis. At the time of reporting hematuria was improving, but was still present intermittently and hemoglobin was lower than normal ranges (8.7 g/dl). The study medication was still being administered at 50% of the total dose. In the absence of an investigator causality for the gastroenteritis the Novartis medical safety physician has provisionally assessed the event as not suspected to be related to RAD001 based on the current available information.

Follow-up received on 09 Apr 2008 (prior to circulation of no-new information follow-up received on 4 Apr 2008): The patient recovered from the gastroenteritis by 23 Jan 2008. The haematuria was considered to be improving at the time of this report. The investigator did not suspect a relationship between the fever or gastroenteritis and RAD001 but did suspect a relationship between the haematuria and RAD001.

Follow up received on 14 Nov 2008: The investigator reported that on 09 Nov 2008 the patient experienced worsening haematuria (onset date 14 Jan 2008 grade 1) which involved hospitalization. At the time of this report the patient's condition was improving. The investigator suspected a relationship between this event and the study medication.

Follow up received on 20 Nov 2008: The patient was hospitalized on 13 Nov 2008 for haematuria. Haemoglobin was 7/1 g/d. Treatment included hemotransfusion (2 units); endoscopy examination and antibiotics. Ugurol was discontinued because it was suspected for haematuria on 13 Nov 2008. The patient made a complete recovery from the worsening haematuria on 19 Nov 2008 and was discharged from hospital. The investigator did not suspect a relationship between the study medication and this event but did suspect a relationship to the comedication Ugurol.

Novartis Comment: New information received on 20 Nov 2008 reported that the haematuria has been reassessed as not suspected to be related to RAD001 by the investigator.

New information received on 9 Apr 2008 reported that the fever and gastroenteritis has been reassessed as not suspected by the investigator.

All remaining reported leading events and associated symptoms were assessed as non-serious by the investigator.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	13-NOV-2008	Haemoglobin	7.1	
		g/dl		

ADDITIONAL INFORMATION**13. Relevant Tests**

(16 Jan 2008) Abdominal ultrasound - negative

(16 Jan 2008) PSA was 0.65 ug/ml (range 0-4)

(Unknown date) Abomen x-ray: levels of bowel

(Date unknown) Hb (hemoglobin) : 8.7 g/dl

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
#1) RAD001 Vs Placebo (RAD 666 RAD+TAB+CMAS) Tablet; Regimen #2	5mg daily; Oral	pancreatic neuroendocrine (Pancreatic neuroendocrine tumour)	Ongoing; Unknown