



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_PHHO2008US13880

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
Cholelithiasis/PHHO2008US13880

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 cholelithiasis that occurred in 47-year-old female patient who enrolled in the study CRAD001C2325, 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 forms.

A search of the Novartis Clinical Safety Database for RAD001 for similar cases was performed using MedDRA 11.0 Preferred Term of Cholelithiasis. Fourteen cases were identified from the search including the current one. Only the current case is reported as suspected to be related to the study medication.

In the current case, the 47-year-old female patient received Sandostatin concomitantly. Cholelithiasis is a very common adverse event associated with Sandostatin use. Given the available information, it is difficult to assess the causal relationship between RAD001 administration and the event occurrence. 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
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	47 Years	Female	Unk	Day	Month	Year	
		19	DEC	1960				18	OCT	2008	
7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data) Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas) Cholelithiasis [Cholelithiasis] ([Cholecystectomy]) Acute cholecystitis [Cholecystitis acute] ([Hyperhidrosis], [Abdominal pain], [Vomiting], [Nausea]) Case Description: Initial report received on 20 Nov 2008: This patient (centre no. xxx, patient no. xxx) was enrolled in the study CRAD001C2325, a randomized, 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.											<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
(Continued on Additional Information Page)											

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)		20. DID REACTION ABATE AFTER STOPPING DRUG?
#1) RAD001 Vs Placebo (RAD 666 RAD+TAB) Tablet #2) SANDOSTATIN LAR (Patient basis) (OCTREOTIDE WITH POLY(D) (Continued on Additional Information Page)		
15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION	<input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> NA Unknown
#1) 10 mg, QD #2) depot	#1) Oral #2) Subcutaneous	
17. INDICATION(S) FOR USE		21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
#1) Carcinoid tumour (Carcinoid tumour) #2) Carcinoid tumour (Carcinoid tumour)		
18. THERAPY DATES(from/to)	19. THERAPY DURATION	<input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> NA Unknown
#1) 16-OCT-2007 / 17-OCT-2008 #2) 16-OCT-2007 / 17-OCT-2008	#1) 368 days #2) 368 days	

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)		
#1) DIOVAN (VALSARTAN) ; 28-SEP-2008 / Ongoing #2) PHENERGAN (PROMETHAZINE HYDROCHLORIDE) ; 27-SEP-2007 / Ongoing #3) GLUCOPHAGE (METFORMIN) ; 23-JAN-2008 / Ongoing		
23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)		
From/To Dates	Type of History / Notes	Description
Unknown	Current Condition	Hyperglycemia (Hyperglycaemia)
Unknown	Current Condition	Knee pain (Arthralgia)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER		26. REMARKS
Investigator's Notification Copy Novartis Pharma Headquarter		
	24b. MFR CONTROL NO.	25b. NAME AND ADDRESS OF REPORTER
	PHHO2008US13880	
24c. DATE RECEIVED BY MANUFACTURER	24d. REPORT SOURCE	
20-NOV-2008	<input checked="" type="checkbox"/> STUDY <input type="checkbox"/> LITERATURE <input checked="" type="checkbox"/> HEALTH PROFESSIONAL <input type="checkbox"/> OTHER:	
DATE OF THIS REPORT	25a. REPORT TYPE	
02-DEC-2008	<input checked="" type="checkbox"/> INITIAL <input type="checkbox"/> FOLLOWUP:	

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

The patient's medical history included hypertension, nausea, vomiting, UTI, pain in knees, elevated 5H1AA (serotonin) and hyperglycemia. The patient received her first dose of study medication on 16 Oct 2007. On 18 Oct 2008, the patient presented with N/V (nausea/vomiting), abdominal pain and sweats, which resulted in hospitalisation. Final diagnosis was acute cholecystitis and cholelithiasis. The gallbladder was removed. The study medication was temporarily interrupted due to the event. On 22 Oct 2008, the patient was discharged and considered completely recovered. The investigator suspected a relationship between this event and the study medication.

Novartis Comment: For RAD001C: Serious adverse drug reaction, cholelithiasis (hospitalisation), assessed as unexpected according to the Investigator Brochure for RAD001. The information provided in this individual case does not warrant a change to the Investigator Brochure text. The topic will be monitored closely. Investigator causality is suspected.

For RAD001C: Serious adverse drug reaction, cholecystitis (hospitalisation), assessed as expected according to the Investigator Brochure for RAD001. Investigator causality is suspected.

For Sandostatin LAR: Serious adverse drug reaction (hospitalisation), assessed as listed according to the Core data Sheet text for Sandostatin LAR. Investigator causality is suspected.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	20-OCT-2008	Bacterial culture	No growth	
2	19-OCT-2008	Nuclear magnetic resonance imaging	Results pending	

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) Tablet; Regimen #2	Double blind; Oral	Carcinoid tumour (Carcinoid tumour)	23-OCT-2008 / Ongoing; Unknown
#2) SANDOSTATIN LAR (Patient basis) (OCTREOTIDE WITH POLY(D L-LACTIDE-CO-GLYCOLIDE)) Unknown; Regimen #1	depot; Subcutaneous	Carcinoid tumour (Carcinoid tumour)	16-OCT-2007 / 17-OCT-2008; 368 days
#2) SANDOSTATIN LAR (Patient basis) (OCTREOTIDE WITH POLY(D L-LACTIDE-CO-GLYCOLIDE)) Unknown; Regimen #2	Double blind; Subcutaneous	Carcinoid tumour (Carcinoid tumour)	23-OCT-2008 / Ongoing; Unknown

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown	Current Condition	Nausea (Nausea);
Unknown	Current Condition	Hypertension (Hypertension);
Unknown		Serum serotonin increased (Serum serotonin increased);
Unknown		UTI (Urinary tract infection);
Unknown		Vomiting (Vomiting);