



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_PHHO2009JP01756

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: February 20, 2009

Re: Investigator Notification for RAD001
Hypothyroidism /PHHO2009JP01756

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 Hypothyroidism that occurred in 58-year-old male patient who enrolled in a study CRAD001C2240, entitled "A randomized, double-blind, placebo-controlled, multi-centre phase III study to compare the safety and efficacy of RAD001 plus Best Supportive Care (BSC) versus BSC plus placebo in patients with metastatic carcinoma of the kidney which has progressed on VEGF receptor tyrosine kinase inhibitor therapy".

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 Hypothyroidism. Four cases were identified, and only the current case is suspected.

Given the available information, it is difficult to assess the causal relationship. 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) XXX	1a. COUNTRY XXX	2. DATE OF BIRTH			2a. AGE 58 Years	3. SEX Male	3a. WEIGHT 73.00 kg	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 24	Month FEB	Year 1949			Day 15	Month NOV	Year 2007		
7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data) Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas) Decreased thyroid function [Hypothyroidism] ([Blood creatine phosphokinase increased], [Hyperlipidaemia], [Hypercholesterolaemia]) Renal impairment [Renal impairment] Toothache [Toothache] Tooth extraction of the fractured second molar on lower left [Tooth extraction] Swelling of face and weight gain (non-serious) [Swelling face] Case Description: Initial report received on 02 Feb 2009: This patient (centre no. XXX, patient no.											

(Continued on Additional Information Page)

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name) #1) RAD001 Vs Placebo (Code not broken) Tablet	20. DID REACTION ABATE AFTER STOPPING DRUG? <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> NA
15. DAILY DOSE(S) #1) Code not broken	16. ROUTE(S) OF ADMINISTRATION #1) Oral
17. INDICATION(S) FOR USE #1) Metastatic renal carcinoma (Renal cancer metastatic)	21. DID REACTION REAPPEAR AFTER REINTRODUCTION? <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> NA
18. THERAPY DATES(from/to) #1) 05-NOV-2007 / 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) #1) ALLOZYM (ALLOPURINOL) ; 12-APR-2005 / 04-FEB-2009 #2) LIDOMEX (PREDNISOLONE VALEREOACETATE) ; 17-JUN-2008 / Unknown #3) CINAL (ASCORBIC ACID, CALCIUM PANTOTHENATE) ; 19-MAY-2008 / Unknown #4) LOCOID (HYDROCORTISONE BUTYRATE) ; 19-MAY-2008 / Unknown #5) KENALOG (TRIAMCINOLONE ACETONIDE) ; 28-FEB-2008 / Unknown #6) ALOSITOL (ALLOPURINOL) ; 04-FEB-2009 / Unknown		
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	Cholelithiasis (Cholelithiasis)
Unknown	Current Condition	Hyperuricaemia (Hyperuricaemia)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER Investigator's Notification Copy Novartis Pharma Headquarter	26. REMARKS
24b. MFR CONTROL NO. PHHO2009JP01756	25b. NAME AND ADDRESS OF REPORTER XXX XXX
24c. DATE RECEIVED BY MANUFACTURER 09-FEB-2009	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 19-FEB-2009	25a. REPORT TYPE <input checked="" type="checkbox"/> INITIAL <input type="checkbox"/> FOLLOWUP:

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

XXX) was enrolled in study CRAD001C2240 a randomised, double-blind, placebo-controlled, multi-centre phase III study to compare the safety and efficacy of RAD001 plus Best Supportive Care (BSC) versus BSC plus placebo in patients with metastatic carcinoma of the kidney which has progressed on VEGF receptor tyrosine kinase inhibitor therapy. The patient's medical history was not reported. The patient received the first dose of study medication on 05 Nov 2007. The study medication action was not reported. On 30 Dec 2008 the patient had toothache. From 14 Jan 2009 to 20 Jan 2009 the patient took over the counter (OTC) medication for the cold symptoms of headache and runny nose. Around this period the patient experienced swelling of the face and weight gain. On 26 Jan 2009 during a visit to the investigators hospital, creatine kinase increased to 1001 IU/L and the patient was put under observation. The patient underwent a tooth extraction of the fractured second molar on the lower left at the dentist on 29 Jan 2009. On 02 Feb 2009 during a visit to the investigators hospital, creatine kinase increased to 1450 IU/L and creatinine to 1.5mg/dL. The patient was hospitalized due to aggravation of creatine kinase increased and renal impairment and put under observation. The patient's outcome was not reported. The investigator suspected a relationship between renal impairment and creatine kinase increased and the study medication. The Novartis Medical Safety physician did not suspect study medication to be related to the tooth fracture and extraction based on the available information.

Follow-up received on 09 Feb 2009: The patient's medical history included hyperuricaemia, cholelithiasis and contrast media allergy. On 04 Feb 2009, an endocrinological examination showed TSH (thyroid-stimulating hormone) 119.05u/ml, F-T3 (free thyroxine) 0.50 pg/ml and F-T4 (free tri-iodothyronine) 0.13ng/dl. The patient was diagnosed with hypercholesterolaemia (non-serious) and increased creatine phosphokinase, associated with decreased thyroid function. Hyperlipidemia was also considered to be associated with the decreased thyroid function. The patient also presented with anal erosion, feeling of enlarged abdomen, nasal vestibulitis, gastralgia, anemia, arthritis, photosensitive rash, common cold and stomatitis, which were all considered to be non-serious. The face oedema was also considered to be non-serious. Treatment for the events included ACTIT and Veen-F (raised creatinine phosphokinase), Thyradin S (hypothyroidism), Kenalog (stomatitis), Locoid, Cinal and Lidomex (photosensitivity reaction) and Lasix (renal impairment). As of 06 Feb 2009, the renal impairment and increased creatine phosphokinase were persisting. The investigator stated that a relationship between the increased creatine phosphokinase and renal impairment and RAD001 could not be denied.

Follow-up received on 12 Feb 2009, prior to circulation of previous report: The onset date of the decreased thyroid function was 04 Feb 2009. On 05 Feb 2009 the patient presented with redness and pain of the left first metatarsophalangeal joint caused by a gout attack. The redness later abated. The patient was discharged on an unspecified date with a decrease in weight of 1.3kg and with improved face oedema. At the time of reporting, the decreased thyroid function was improving. The investigator suspected a relationship between the decreased thyroid function and the study medication.

Novartis Comment: Serious adverse drug reaction report, reduced thyroid function (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.

Serious adverse drug reaction report, renal impairment (hospitalisation), assessed as expected according to the Investigator's Brochure for RAD001. Investigator causality is suspected.

All remaining reported leading events and associated symptoms were assessed as non serious by the investigator or not suspected by the Novartis Medical Safety Physician.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	26-JAN-2009	Blood creatine phosphokinase	1001 IU/l	
2	02-FEB-2009	Blood creatine phosphokinase	1450 IU/l	
3	09-FEB-2009	Blood creatine phosphokinase	879 IU/l	
4	12-FEB-2009	Blood creatine phosphokinase	829 IU/l	
5	02-FEB-2009	Blood creatinine	1.5	
		mg/dL		
6	09-FEB-2009	Blood creatinine	1.3 mg/dl	
7	12-FEB-2009	Blood creatinine	1.3 mg/dl	

ADDITIONAL INFORMATION**13. Lab Data**

#	Date	Test / Assessment / Notes	Results	Normal High / Low
8	04-FEB-2009	Blood thyroid stimulating hormone	119.05 u/ml	
9	09-FEB-2009	Blood thyroid stimulating hormone	132.10 u/ml	
10	12-FEB-2009	Blood thyroid stimulating hormone	121.10 u/ml	
11	04-FEB-2009	Thyroxine free	0.13 ng/dl	
12	09-FEB-2009	Thyroxine free	2.64 ug/dl	
13	12-FEB-2009	Thyroxine free	0.32 ng/dl	
14	09-FEB-2009	Tri-iodothyronine	0.43 ng/ml	
15	04-FEB-2009	Tri-iodothyronine free	0.50 pg/ml	
16	12-FEB-2009	Tri-iodothyronine free	1.10 pg/ml	

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown		Contrast media allergy (Contrast media allergy);