



NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

Date: May 2, 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_PHHO2007NO19319_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/df
enclosure



To: All Investigators in RAD001 (everolimus) Studies*

28 January 2008

Re: Investigator Notification for

RAD001 (everolimus): **Fatal Pulmonary Embolism (PHHO2007NO19319)**

Follow-up to previous notification of Fatal Renal Failure (27-Nov-07)

Dear Doctor,

In accordance with the Good Clinical Practice and specific national regulatory requirements we wish to provide follow-up on an adverse event, previously reported as a serious, unexpected, possibly related adverse report of fatal renal failure during the course of a clinical study.

For the current case, details of the adverse event are provided in the attached CIOMS form, which contains the available information as reported to Novartis.

Previously reported (27-Nov-07):

Brief Summary

A 56-year-old male patient was enrolled in study CRAD001AIC01 (NOCTET = Nordic Certican trial in heart and lung transplantation), an open-label, randomized, controlled study to determine whether switch from calcineurin inhibitor (CNI) to Certican in maintenance heart or lung transplant patients with renal impairment can improve renal function. He developed coronary artery disease and underwent PCI (percutaneous coronary intervention) one year post transplant (reported as medical history). He received the first dose of study medication on an unspecified date. At week 6 visit his renal function had deteriorated, therefore both Certican and Neoral doses were lowered. On 20 Nov 2007, he was found at home, unclean and in "a bad condition". He was admitted to hospital on the same day. Examination showed renal failure and dialysis was started. The patient experienced severe bradycardia. He died later in the evening on 21 Nov 2007. An autopsy was performed but results have not yet been provided.

The investigator suspected a relationship between the event and the study medication (Certican) and Neoral (a Novartis product).

Novartis comment:

The patient had a pre-existing condition of renal impairment as a result of CNI therapy for heart transplant. The severity of renal failure along with any severe hydro-electrolytic abnormalities which might have been associated is not detailed, either before or during dialysis. The results of the autopsy are awaited.

Although renal failure is listed associated with Certican/ CsA in the Investigators' Brochure, it is Novartis policy to assess a fatal case as unexpected if death is not mentioned as possible outcome of the listed risks. Hence this notification.

Follow-up information (28-Jan-08)

After performance of autopsy, the investigator has attributed this death to pulmonary embolism which was associated with deep vein thrombosis.

The investigator has noted a possible relationship between this event and treatment with everolimus. However, the investigator also speculates on the possibility of lack of compliance as the cause of the terminal events.

A heart biopsy carried out on 7 November (13 days before hospitalization) had not shown evidence of rejection. But study medication had been reduced at that time because of high serum creatinine. Dosages at time of event were: everolimus: 1.5mg/d; Neoral: 75mg/d. Blood levels unknown.

Novartis comment

Pulmonary embolism is a not infrequent cause of death in transplant patients. A recent review of autopsies in deceased solid organ transplant recipients at a single hospital (Coruna, Spain) found pulmonary embolism as the cause of death in 4/76 (5.3%) of heart transplant recipients, 1/19 (5.3%) of lung recipients (Sanroman Budino, 2004).

A cumulative search for fatal cases of ‘pulmonary embolism’ (MedDRA preferred term) in everolimus-treated heart transplant recipients in the Novartis Safety Database reveals a total of 4 reports out of an estimated 1000 patients exposed in clinical trials with no reports received outside the context of clinical trials. However, this is the first fatal case of pulmonary embolism which has been assessed as suspected due to Certican. It is Novartis policy to consider fatal disorders unexpected unless explicitly mentioned as potentially fatal in the Investigators’ Brochure.

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,

 Nicholas Shand MD

Brand Safety Leader
Integrated Medical Safety
Novartis Pharma Basel, Switzerland

Reference:

Sanroman Budino BS et al. Autopsy-determined causes of death in solid organ transplant recipients. *Transplantation Proceedings*. 2004;36:787-789.

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	56 Years	Male	124.00 kg	Day	Month	Year	
		16	MAY	1951				Unk			
7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data) Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas) Other Serious Criteria: Medically Significant Pulmonary emboly [Pulmonary embolism] Renal failure [Renal failure] ([Renal impairment], [Blood creatinine increased]) Potassium high [Blood potassium increased] Enlarged failing heart [Cardiac failure] ([Bradycardia]) Deep vein thrombosis [Deep vein thrombosis]											<input checked="" type="checkbox"/> PATIENT DIED Date: 20-NOV-2007 <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 21 Nov 2007: Patient XXXX from centre X was enrolled in study CRAD001AIC01 (NOCTET = Nordic Certican (continue))											

II. SUSPECT DRUG(S) INFORMATION

(Continued on Additional Information Page)

14. SUSPECT DRUG(S) (include generic name) #1 Certican(RAD 666 RAD++PTR)Unknown #2 NEORAL (CICLOSPORIN) Unknown		20. DID REACTION ABATE AFTER STOPPING DRUG? <input type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> NA
15. DAILY DOSE(S) #1 0.75 mg, BID #2 25 mg + 50 mg	16. ROUTE(S) OF ADMINISTRATION #1 Oral #2 Oral	
17. INDICATION(S) FOR USE #1 Heart transplant #2 Heart transplant		21. DID REACTION REAPPEAR AFTER REINTRODUCTION? <input type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> NA
18. THERAPY DATES(from/to) #1 04-OCT-2007 00:00 / Unknown #2 02-SEP-2003 00:00 / Unknown	19. THERAPY DURATION #1 Unknown #2 Unknown	

III. CONCOMITANT DRUG(S) AND HISTORY

(Continued on Additional Information Page)

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction) #1 CELLCEPT (MYCOPHENOLATE MOFETIL) ; ; Unknown #2 PREDNISOLON (PREDNISOLONE) ; ; Unknown #3 PRAVACHOL (PRAVASTATIN SODIUM) ; ; 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	Coronary artery disease
Unknown	Historical Condition	Percutaneous coronary intervention
	PCI	

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER Investigator's Notification Copy Novartis Pharma Headquarter		26. REMARKS
	24b. MFR CONTROL NO. PHHO2007NO19319	25b. NAME AND ADDRESS OF REPORTER
24c. DATE RECEIVED BY MANUFACTURER 21-JAN-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 25-JAN-2008	25a. REPORT TYPE <input type="checkbox"/> INITIAL <input checked="" type="checkbox"/> FOLLOWUP:	

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

trial in heart and lung transplantation) which is an open-label, randomized, controlled study to determine whether switch from calcineurin inhibitor (CNI) to Certican in maintenance heart or lung transplant patients with renal impairment can improve renal function. He received the first dose of study medication on date not specified. The patient developed coronary artery disease and underwent PCI (percutaneous coronary intervention) one year post transplant. At week 6 visit the patient's renal function had deteriorated, therefore both Certican and Neoral doses were lowered. On 20 Nov 2007, the patient was found at home, unclean and in 'a bad condition'. He was admitted to hospital on the same day. Examination showed renal failure. Dialysis was started. The patient experienced severe bradycardia and died later in the evening on 21 Nov 2007. An autopsy was performed (results not reported).

Follow-up received on 23 Nov 2007, prior to initial circulation: The investigator suspected a relationship between the event and the study medication (Certican) and Neoral (a Novartis product).

Follow-up received on 15 Jan 2008: The investigator reported the first dose of Certican was administered on 4 Oct 2007 and Neoral 2 Sep 2003. An autopsy was not completed. Temporary diagnosis/cause of death was pulmonary embolism, deep venous thrombosis and enlarged failing heart although the investigator provided the final cause of death as pulmonary embolism. On admission creatinine and potassium were elevated. The investigator did not suspect a relationship between these events and Neoral but assessed the causality assessment for Certican as suspected (although the investigator was uncertain).

Follow-up received on 21 Jan 2008: The patient underwent heart and lung transplant on 2 Sep 2003. The patient was diagnosed with underlying coronary artery disease with previous myocardial infarction which required transplantation. The patient underwent PCI (angioplasty) of the right coronary artery at 2 places on 15 Sep 2004. At the 6-week visit (07 Nov 2007) the patient was clinically stable with no evidence of heart failure but serum creatinine was increased to 207 umol/l. Heart biopsy showed no evidence of rejection. Prior to the event the patient was receiving, Certican, Sandimmun Neoral, Cellcept, prednisolon, Pravachol, Furix, Triatec, Selozok, Allyl, allopurinol and Nexium. The patient did not have a history of heart failure post intervention. The pulmonary embolism could be causally related to the deep vein thrombosis. The investigator reported the circumstances around the patient's death were unclear. Auto seponation (lack of compliance) with medication was possible and so a clinical deterioration could be followed by DVT/pulmonary embolism. Alternatively DVT/pulmonary embolism could be triggered by immunosuppressive regimen. The investigator re-confirmed the causality assessment and suspected a relationship between the pulmonary embolism and Certican and a relationship between elevated creatinine and Certican and Neoral. A relationship with Certican and Neoral was not suspected for deep vein thrombosis, enlarged failing heart and elevated potassium and was not suspected for pulmonary embolism and Neoral.

Novartis Comment: Serious adverse event report, pulmonary embolism (death), assessed as unexpected according to the Investigator's Brochure for Certican.

It is Novartis' policy to assess a case with a fatal outcome as unexpected unless the label specifically mentions death as a possible outcome of the listed risks. Investigator causality is suspected to Certican.

Serious adverse event report, renal failure (hospitalisation), assessed as expected according to the Investigator's Brochure for Certican and listed according to the Core Data Sheet for Neoral. Investigator causality is suspected for Certican and Neoral.

New information received on 21 Jan 2008, reported that the other events were reassessed as not suspected to be related to Certican or Neoral by the investigator.

13. Relevant Tests

(07 Nov 2007) Creatinine : 201 umol/l (normal value <120 umol/L)

(20 Nov 2007) Creatinine: 541 umol/L

(07 Nov 2007) Heart biopsy : No evidence of rejection.

(20 Nov 2007) Potassium: 6.4 mmol/L (normal value <5.0)

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 Certican (Certican) Unknown; Regimen #2	0.50 mg + 0.75 mg daily; Oral		Unknown; Unknown

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION continued

#4 FURIX (FUROSEMIDE) , ; Unknown

ADDITIONAL INFORMATION

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION continued

#5 TRIATEC (RAMIPRIL) , ; Unknown

#6 SELO-ZOK (METOPROLOL SUCCINATE) , ; Unknown

#7 ALLOPURINOL (ALLOPURINOL) , ; Unknown

#8 NEXIUM (ESOMEPRAZOLE MAGNESIUM) , ; Unknown