



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_PHHO2008DE03857

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*

DATE: 31 March 2008

Re: Investigator Notification for RAD001 (everolimus):
Fatal Rhabdomyolysis (PHHO2008DE03857)

Dear Doctor,

In accordance with the Good Clinical Practice and specific national regulatory requirements we wish to inform you of a serious, unexpected, possibly-related, fatal adverse report of fatal rhabdomyolysis which occurred in a transplant patient being treated with RAD001 (everolimus).

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.

Brief case summary

The 65 year-old man was admitted into a Novartis-sponsored clinical trial (CRAD001DE06) evaluating the effectiveness of an everolimus regimen in *de-novo* lung transplant patients. The study is open-label with immunosuppressive medication immediately after transplantation comprising cyclosporine (Neoral®), mycophenolic mofetil (MMF) and steroids followed by randomization of patients one month later to one of two parallel groups: either maintenance of MMF, or substitution of everolimus for MMF, the other immunosuppressive drugs remaining unchanged.

Medical history included idiopathic lymphocytic alveolitis and pulmonary hypertension.

Transplantation was on 14-Sep-07. The patient was randomized to the everolimus group.

The starting date for everolimus treatment has not been provided but by protocol can be expected to have occurred in mid-October. Everolimus was interrupted on 17-Jan-08 to facilitate healing after a hernioplasty.

On 2 February, the patient was hospitalized for respiratory infection, identified as atypical E.coli pneumonia which responded well to a change of antibiotherapy from moxifloxacin to ceftazidim and clarithromycin.

On 5 February, treatment with ganciclovir was started for CMV infection and MMF (presumably reintroduced at the time of interruption of everolimus) was withdrawn. On 15 February, foscavir was substituted for ganciclovir. On 28 February, CMV PCR was below detection level.

On 28 February, foscavir was discontinued because of raised serum CK levels. Rhabdomyolysis was diagnosed. The patient was transferred into intensive care, initially doing well with forced volume substitution and diuresis.

On 5 March, a new increase in CK was accompanied by increased serum potassium and acute renal failure leading to cardiac arrhythmia which proved fatal despite haemodialysis and cardio-pulmonary resuscitation.

The investigator suspects everolimus treatment to have contributed to these events.

It is unknown whether an autopsy was performed.

The investigator suspects a relationship between these events and the study medication.

Novartis Comment

Depending on published series, between 10-50% of patients with rhabdomyolysis develop acute renal failure (ARF) with an attendant mortality rate of 7-80% (Huerta-Alardin, 2005). Muscle destruction leads to renal tubular obstruction as well as hyperkalemia and the risk of cardiac dysrhythmias and cardiac arrest.

Treatment with everolimus has been associated with rhabdomyolysis but with the majority of cases an apparent extension of the known adverse reaction to statins, frequently coadministered with everolimus and frequently with their blood levels increased by the 3A4-inhibitory effect of cyclosporine. A recent Novartis review revealed 24 cases of clinically-manifest rhabdomyolysis or raised CK reported in everolimus-treated transplant recipients. Of these, 16 were known to be receiving concomitant statins, a further three (including the only previously-reported fatality) being inadequately documented to allow a meaningful assessment (Shand, 2007).

In the currently reported episode, the initial signs of rhabdomyolysis occurred five weeks after interruption of everolimus but two weeks after the introduction of foscavir for which rare cases of rhabdomyolysis have been reported in post-marketing studies (Foscavir label, 2007) while herpes virus infections have also been identified as a cause of rhabdomyolysis (Huerta-Alardin, 2005).

In conclusion, although the current information does not allow the responsibility of everolimus to be disregarded, the data suggests other causes to be more probable.

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
Integrated Medical Safety
Novartis Pharma Basel, Switzerland
Attachment: CIOMS case report

US ICRO Investigator
Local Trial Leader
Field Monitor

Central IRB (if applicable)
mDOC

References.

Huerta-Alardin AL, Varon J, Maril PE. Bench to bedside: rhabdomyolysis – an overview for clinicians. *Critical Care* 2005,9(2)158-169.

Shand N, Habersetzer A et al. Periodic Safety Update Report #6 for Certican (everolimus). 18-Sep-07. Novartis Pharma.

* 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	65 Years	Male	79.00 kg	Day	Month	Year	
		06	AUG	1942				17	JAN	2008	
7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data) Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas) Rhabdomyolysis [Rhabdomyolysis] ([Renal failure acute], [Blood creatine phosphokinase increased], [Hyperkalaemia], [Arrhythmia]) Atypical pneumonia with E coli [Pneumonia escherichia] ([Pyrexia], [Malaise], [Pharyngolaryngeal pain], [Cough]) CMV [Cytomegalovirus infection] Thoracic wall hernia [Hernia] ([Hernia repair]) Case Description: Initial report received on 19 Mar 2008: This patient (no. (continue))											<input checked="" type="checkbox"/> PATIENT DIED Date: 05-MAR-2008 <input checked="" type="checkbox"/> INVOLVED OR PROLONGED INPATIENT HOSPITALISATION <input type="checkbox"/> INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY <input type="checkbox"/> LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)		20. DID REACTION ABATE AFTER STOPPING DRUG?
#1 CERTICAN (RAD) Unknown #2 Certican vs MMF(MYCOPHENOLATE MOFETIL COMP-MYC+)Unknown		
15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION	Unknown
#1 UNK, UNK #2 Unknown	#1 Oral #2 Oral	<input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> NA
17. INDICATION(S) FOR USE		21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
#1 Lung transplant #2 Lung transplant		
18. THERAPY DATES(from/to)	19. THERAPY DURATION	Unknown
#1 Unknown / 17-JAN-2008 00:00 #2 Unknown	#1 Unknown #2 Unknown	<input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> NA

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 CLARITHROMYCIN (CLARITHROMYCIN) ; ; 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	Historical Condition	Alveolitis
	idiopathic lymphocytic alveolitis	
Unknown	Current Condition	Pulmonary hypertension

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
	PHHO2008DE03857	
24c. DATE RECEIVED BY MANUFACTURER	24d. REPORT SOURCE	
19-MAR-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	
31-MAR-2008	<input checked="" type="checkbox"/> INITIAL <input type="checkbox"/> FOLLOWUP:	

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

XXX) from centre X was enrolled in study CRAD001ADE06, a two-year, multicenter, prospective, open-label, clinical study to evaluate the incidence and severity of chronic allograft impairment (Bronchiolitis Obliterans Syndrome > 1) two years after lung transplantation; death and study discontinuation due to switch of immunosuppression and also to evaluate the safety and tolerability of Certican, especially with respect to the incidence and severity of nephrotoxicity and infections (lower airway and CMV-infections). All patients received initial postoperative immunosuppression (cyclosporine A (Neoral), MMF (mycophenolate mofetil) and steroids). After four weeks the study population was randomized into two groups. Patients randomized into the treatment group will be switched from MMF to Certican. Patients within the control group will continue with initial immunosuppressive therapy. The patient underwent transplantation on 14 Sep 2007 and he received the first dose of mycophenolate mofetil on an unspecified date. The patient was randomised on an unspecified date was switched to Certican (everolimus). The patient's medical history includes idiopathic lymphocytic alveolitis, pulmonary hypertension ('hypertonus'), axial sliding hernia, diverticulosis and bronchopulmonary infection with pleuritis in Oct 2007. The patient had thoracic wall hernia during Jan 2008. Certican was interrupted on 17 Jan 2008 to improve wound healing after hernioplasty. On 02 Feb 2008, the patient was hospitalised with suspected pneumonia of the left inferior lobe. The patient had fever, heavy illness feeling with sore throat and chronic cough which had been treated with Avelox. CT morphology and bronchoscopy showed an atypical pneumonia with detection of E. coli, which was successfully treated with ceftazidim and clarithromycin. CMV pp65 was positive and the patient was treated with Cymeven from 05 Feb 2008. Cellcept was stopped. Due to failed response (positive CMV in serum), the treatment was switched from Cymeven to Foscavir on 15 Feb 2008. On 28 Feb 2008, Foscavir was stopped after CK increase was detected in serum followed by rhabdomyolysis. CMV PCR had fallen below detection on 28 Feb 2008. The patient was transferred to intensive care. Initially his cardiorespiratory situation was stable. He had forced volume substitution and diuresis, with good renal excretion. On 05 Mar 2008 there was further CK increase, with significant increase of serum potassium caused by acute renal failure. He developed haemodynamically relevant cardiac dysarrhythmia. The patient was intubated and received CPR (cardiopulmonary resuscitation). In spite of emergency haemodialysis and 2.5 hours CPR, the patient died from a hyperkalaemia by acute renal failure by rhabdomyolysis on 05 Mar 2008. It was not known whether an autopsy was performed. The investigator suspected a relationship between these events and the study medication. In the absence of an investigator causality assessment, the Novartis medical safety physician has assessed the hernia with hernioplasty as not suspected to be related to study medication (Certican or Cellcept), based on available information).

Novartis Comment: Serious adverse drug reaction, rhabdomyolysis (death), assessed as unexpected according to the Investigator's Brochure.

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.

Serious adverse drug reaction, bacterial pneumonia and CMV infection (hospitalisation), assessed as expected according to the Investigator's Brochure. Investigator causality is suspected.

13. Relevant Tests

(05 Feb 2008) CMV-DNA: 4800 copies/mL
 (06 Feb 2008) CMV-DNA: 2700
 (11 Feb 2008) CMV-DNA: 2900
 (12 Feb 2008) CMV-DNA: 5400
 (14 Feb 2008) CMV-DNA: 120,000
 (20 Feb 2008) CMV-DNA: 710
 (21 Feb 2008) CMV-DNA: 870
 (26 Feb 2008) CMV-DNA: 700
 (28 Feb 2008) CMV-DNA: negative
 (29 Feb 2008) CMV-DNA: negative

(date unknown) CT scan and bronchoscopy: atypical pneumonia with E. coli

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown	Current Condition sliding axial hernia	Hiatus hernia
Unknown	Current Condition	Diverticulum
OCT-2007 to Unknown	Historical Condition bronchopulmonary infection with pleuritis	Bronchopneumonia
OCT-2007 to Unknown	Historical Condition bronchopulmonary infection with pleuritis	Pleurisy