



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_PHHY2008DE25330_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 the RAD001, everolimus studies*

Date: 5 February 2009

Re: Investigator Notification for everolimus (Follow-up from previous report of 28-Oct-08)

Reported event: **Anaemia haemolytic autoimmune** (Case ID: PHHY2008DE25330)

Dear Doctor,

In accordance with the Good Clinical Practices and specific national regulatory requirements, we are providing you with an update to information previously provided regarding a serious adverse event report that occurred in a patient being treated with everolimus in a non-clinical trial setting.

The information reported to Novartis is detailed in the attached CIOMS report. The following is a brief summary of the case.

Case summary

This 54 year-old, caucasian lady with lymphangiomyomatosis had undergone bilateral lung transplant in May 2006 since when she had received everolimus, cyclosporin and prednisolone for anti-rejection immunosuppression. She is reported to have developed chronic renal insufficiency attributed to calcineurin inhibitor nephrotoxicity.

The patient was mildly anaemic (Hb values varying between 9.3- 10.6 g/dL between 2006 and April 2008) but without evidence for haemolysis (serum bilirubin within normal range).

On 23-Sep-08, she was found to be severely anaemic (Hb 5.4 g/dL) with accompanying reduced haptoglobin (value not given), raised reticulocyte count and a positive Coombs test. Other blood cell lines were not decreased. There was no sign of thrombotic microangiopathy. Autoimmune haemolytic anemia was diagnosed.

The patient received red cell transfusion on 25 and 26 Sept.

Everolimus was discontinued on 23-Oct-08. The reporter suspected a probable relationship with everolimus because of an increase in haemoglobin and decrease in LDH thereafter.

No specific diagnostic work-up was carried out to investigate further the potential antigen responsible.

There was no search for a possible underlying auto-immune disorder.

Virology studies conclude: EBV-DNA positive since transplantation but without recent increase in copy concentration; CMV negative; Parvovirus Ig-G positive but IG-M negative.

Glucose 6 phosphate dehydrogenase (G6PD) deficiency not investigated considering origin of patient.

In addition to immunosuppressants, comedication is reported as including cotrimoxazole, pantoprazol and itraconazole. Aciclovir, metoprolol, enalapril, diltiazem are also known to have been administered but the dates are unclear.

Current blood values are unknown to the reporter, the patient being cared for elsewhere.

Novartis comment

There remains reasonable doubt as to the responsibility of everolimus as the cause of this episode. Non-drug causes (notably an underlying autoimmune condition) are possible, and there is imprecision on the timing of the numerous comedication.

This is currently the only report of autoimmune haemolytic anaemia in an everolimus-treated patient out of the estimated 11,000 patients who have received the drug in clinical trials (transplant and oncology indications) and the cumulative exposure to commercialized everolimus estimated at 29,000 patient-years..

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, for such; Novartis will submit the Investigator Notification on your behalf to the central IRB.

Sincerely,

N. Shand

Nicholas Shand MD

Drug Safety & Epidemiology (WSJ 157: 3.10.2)

Novartis Pharma, 4002. Basel, Switzerland

Tel: 41/61.324 7531

Fax: 41/61.324 0815

e-mail: nicholas.shand@novartis.com

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 Germany	2. DATE OF BIRTH			2a. AGE 54 Years	3. SEX Female	3a. WEIGHT 51.00 kg	4-6 REACTION ONSET			8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
		Day 16	Month JUL	Year 1954			Day 23	Month SEP	Year 2008	<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	
7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data) Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas) Autoimmune-hemolytic anemia [Anaemia haemolytic autoimmune] platelet count increased [Platelet count increased] Case Description: Initial report received from a physician (nephrology) on 17 Oct 2008. This patient was being treated with Certican (everolimus) for an unknown indication since May 2006. In Sep 2008, the diagnosis of autoimmune hemolytic anemia was made. The outcome of the event was not reported. <p style="text-align: right;">(Continued on Additional Information Page)</p>											

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name) #1) CERTICAN (RAD) Unknown		20. DID REACTION ABATE AFTER STOPPING DRUG? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> NA
15. DAILY DOSE(S) #1) 0.25 mg, BID	16. ROUTE(S) OF ADMINISTRATION #1) Oral	
17. INDICATION(S) FOR USE #1) Double lung transplant in 2006 (Lung 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) MAY-2006 / 23-OCT-2008	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) SANDIMMUN OPTORAL (CICLOSPORIN) ; MAY-2006 / Unknown #2) DECORTIN-H (PREDNISOLONE) ; MAY-2006 / Unknown #3) COTRIM FORTE (SULFAMETHOXAZOLE, TRIMETHOPRIM) ; MAY-2006 / Unknown #4) SEMPERA (ITRACONAZOLE) ; Unknown #5) ACIC (ACICLOVIR) ; Unknown #6) BELOC-ZOC MITE (METOPROLOL SUCCINATE) ; Unknown (Continued on Additional Information Page)		
23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)		
From/To Dates Unknown 2006 to Unknown	Type of History / Notes Historical Condition Current Condition chronic reactivation	Description Parvovirus infection (Parvovirus infection) EBV antigen positive (Epstein-Barr virus antigen positive)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER Investigator's Notification Copy Novartis Pharma Headquarter		26. REMARKS
	24b. MFR CONTROL NO. PHHY2008DE25330	
24c. DATE RECEIVED BY MANUFACTURER 30-JAN-2009	24d. REPORT SOURCE <input type="checkbox"/> STUDY <input type="checkbox"/> LITERATURE <input checked="" type="checkbox"/> HEALTH PROFESSIONAL <input checked="" type="checkbox"/> OTHER: Spontaneous Report	25b. NAME AND ADDRESS OF REPORTER
DATE OF THIS REPORT 06-FEB-2009	25a. REPORT TYPE <input type="checkbox"/> INITIAL <input checked="" type="checkbox"/> FOLLOWUP:	

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

No causality assessment was provided.

Follow up received from a physician on 30 Oct 2008: The patient was on immunosuppression after double lung transplantation in Apr 2006 (underlying disease: lymphangioleiomyomatosis). The patient's history included chronic renal insufficiency (calcineurin inhibitor toxicity), cholecystolithiasis, osteoporosis, and arterial hypertension. Certican 0.5mg/d, Sandimmun Optoral (cyclosporin microemulsion) 70mg/d and Decortin H (prednisolon) 5mg/d were used since May 2006. The patient was also set on continuous treatment with Cotrim forte (co-trimoxazol) and Sempira (itraconazol) from May 2006. From May 2006 until April 2008, hemoglobin levels had ranged between 9.3g/dl and 11.6g/dl. On 23 Sep 2008, hemoglobin dropped to 5.4g/dl (nadir), and on that day, the diagnosis of autoimmune hemolytic anemia was made (Coombs test positive). As hemolysis parameters, an increase of LDH (lactate dehydrogenase), a decrease of haptoglobin, and increased reticulocytes were mentioned (no date and no exact levels provided). The patient was hospitalized due to the event, and she required transfusion (not further specified). The reporter indicated that no explanatory event occurred prior to autoimmune anemia diagnosis, especially no change in medication. Certican was stopped on 23 Oct 2008, and no rechallenge was done. Seven days after Certican withdrawal, hemoglobin increased and LDH decreased. Outcome was reported as improving, but the reporter stated that no final evaluation can be made at this point in time. The reporter assessed causality with respect to Certican as probable.

Non-significant follow-up information received via phone on 09 Jan 2009: In a third attempt to receive further medical information, the physician stated briefly that she would try to screen the patient's file and provide more information if available.

Follow up report received from treating physician on 30 Jan 2009. The reporter confirmed that Certican was used also from 23 Sep until 23 Oct 2008, and the drug was only stopped on 23 Oct 2008. It was confirmed that, after transplantation, mild anemia had been present but no evidence of hemolysis had been found (S-bilirubin and S-LDH were always within normal range; reticulocytes were 25/nl in Nov 2006 and 86/nl in Dec 2006, both normal, and no other recordings were done for this parameter). The blood drawing on 23 Sep 2008 was done as an emergency diagnostics in the hospital, after progressively decreasing hemoglobin had been seen before. At that point in time, the patient required transfusion (hemoglobin being 5.4g/dl). Patient had been EBV-DNA positive since transplantation (always in the range between 30.000 and 150.000 copies, and no change of this parameter occurred at the time of the event / diagnosis). CMV was also negative; Parvovirus IgG was positive, but IgM negative. As for comedication, the reporter stated that she did not have access to the patient file, currently. She added that Pantozol (pantoprazole) and cotrimoxazole were definitely used. G6PD deficiency tests were not done because the patient was female and Caucasian. Two erythrocyte concentrates were given on 25 Sep 2008, and one further erythrocyte concentrate was given on 26 Sep 2008. The Coombs test was done on 23 Sep 2008. When asked for further blood cell lines, the leukocyte counts (7.6 thousands/microl) and thrombocyte counts (540 thousands/microl) were repeated (see previous report). There was no evidence of thrombocytopenia or thrombotic microangiopathy. No further specific diagnostics (autoimmune disorder etc.) were done. The reporter stated that patient was currently under monitoring by the family physician and that no current blood values were available.

Novartis Comment: Serious spontaneous report, autoimmune hemolytic anemia [hospitalization], assessed as unlisted according to the Core Data Sheet due to greater specificity.

The following terms "anemia; hemolysis" are already included in the Core Data Sheet. All spontaneous reports are considered suspected for reporting purposes or in accordance with national regulatory requirements

Thrombocyte counts (540 thousands/microl) was assessed as non-serious by the reporting health care professional/Novartis Medical Safety Physician.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	23-SEP-2008	Blood lactate dehydrogenase High		
2	23-SEP-2008	Coombs test	positive	
3	14-MAY-2006	Haemoglobin Low	9.9 g/dl	
4	29-AUG-2006	Haemoglobin Low	10.6 g/dl	
5	08-DEC-2006	Haemoglobin Low	9.4 g/dl	
6	08-JAN-2007	Haemoglobin Low	9.7 g/dl	
7	17-APR-2007	Haemoglobin Low	10.4 g/dl	
8	21-JUN-2007	Haemoglobin	9.3 g/dl	

ADDITIONAL INFORMATION**13. Lab Data**

#	Date	Test / Assessment / Notes	Results	Normal High / Low
9	07-APR-2008	Haemoglobin Low	9.7 g/dl	
10	23-SEP-2008	Haemoglobin Low	5.4 g/dl	
11	09-OCT-2008	Haemoglobin Low	10.4	
12	23-SEP-2008	Haptoglobin Low		
13		Platelet count	540 thousands/microl	
14	NOV-2006	Reticulocyte count	25 nl	
15	DEC-2006	Reticulocyte count	86 nl	
16	23-SEP-2008	Reticulocyte count High		
17	09-OCT-2008	Viral DNA test positive 30,000-150,000 copies		

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

#7) ENALAPRIL (ENALAPRIL) ; Unknown

#8) PRAVASIN (PRAVASTATIN SODIUM) ; Unknown

#9) PANTOZOL (PANTOPRAZOLE SODIUM) ; Unknown

#10) DILZEM (DILTIAZEM HYDROCHLORIDE) ; Unknown

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown	Current Condition	Hypertension arterial (Hypertension);
Unknown	Current Condition	Osteoporosis (Osteoporosis);
Unknown	Current Condition	Cholecystolithiasis (Cholelithiasis);
Unknown	Current Condition	Lymphangioliomyomatosis (Lymphangioliomyomatosis);
Unknown	Current Condition CNI toxicity	Chronic renal insufficiency (Renal failure chronic);