



NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

Date: November 28, 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_PHHY2008DE25330

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: 28 October 2008

Re: Initial Investigator Notification for everolimus: **Anaemia haemolytic autoimmune – (PHHY2008DE25330)**

Dear Doctor,

In accordance with the Good Clinical Practices and specific national regulatory requirements, we inform you of a serious adverse event report that occurred in a patient being treated with everolimus (0.25 mg twice daily) since May 2006, as reported by a nephrologist in a non-clinical trial setting.

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 in this initial report.

Hemolytic anemia is a listed event. However, reported as *autoimmune* hemolytic anemia, has added specificity that deems it to be considered unexpected.

An estimated 11,000 patients have received everolimus in clinical trials (transplant and oncology indications) in addition to which cumulative exposure to commercialized everolimus is estimated at 29,000 patient-years. A search of Novartis database did not yield additional cases of autoimmune haemolytic anaemia.

The report is preliminary. Notably no information has yet been received on the severity of the event, results of laboratory investigations and other diagnostic considerations as well as outcome.

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,

Dr. Wasim Khan, MD
Integrated Medical Safety
Novartis Pharma Basel
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	Unk	Female	Unk	Day	Month	Year	
		16	JUL	1954				16	SEP	2008	
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 Autoimmune-hemolytic anemia [Anaemia haemolytic autoimmune] 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.											<input type="checkbox"/> PATIENT DIED <input 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) #1) CERTICAN (RAD) Unknown		20. DID REACTION ABATE AFTER STOPPING DRUG? <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> NA Unknown
15. DAILY DOSE(S) #1) 0.25 mg, BID	16. ROUTE(S) OF ADMINISTRATION #1) Unknown	
17. INDICATION(S) FOR USE #1) Unknown		21. DID REACTION REAPPEAR AFTER REINTRODUCTION? <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> NA Unknown
18. THERAPY DATES(from/to) #1) MAY-2006 / 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)		
23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)		
From/To Dates	Type of History / Notes	Description
Unknown		

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER Investigator's Notification Copy Novartis Pharma Headquarter		26. REMARKS
	24b. MFR CONTROL NO. PHHY2008DE25330	25b. NAME AND ADDRESS OF REPORTER
24c. DATE RECEIVED BY MANUFACTURER 17-OCT-2008	24d. REPORT SOURCE <input type="checkbox"/> STUDY <input type="checkbox"/> LITERATURE <input checked="" type="checkbox"/> HEALTH PROFESSIONAL <input checked="" type="checkbox"/> OTHER: Spontaneous Report	
DATE OF THIS REPORT 28-OCT-2008	25a. REPORT TYPE <input checked="" type="checkbox"/> INITIAL <input type="checkbox"/> FOLLOWUP:	

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

No causality assessment was provided.

Novartis Comment: Serious spontaneous report, autoimmune hemolytic anemia [medically significant], 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