



NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

Date: May 9, 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_PHHO2008JP04055

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 Studies*

⇒ KC

4/27/08

Date: April 14, 2008

Re: Investigator Notification for RAD001
Cerebral infarction /PHHO2008JP04055

Handwritten signature

Dear Doctors,

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 cerebral infarction that occurred in 64-year-old male patient being treated with RAD001 during the course of the clinical trial entitled "A single arm multi-centre phase II study of RAD001 in patients with advanced gastric carcinoma whose cancer has progressed despite prior treatment".

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 for similar cases was performed using the following MedDRA 10.1 Preferred Terms: Cerebral infarction, Haemorrhagic cerebral infarction, Lacunar infarction, Pituitary infarction, Spinal cord infarction, Thalamic infarction, Thrombotic cerebral infarction, Ischaemic cerebral infarction, Thromboembolic stroke, Thrombotic stroke, Embolic stroke, Ischaemic stroke, Haemorrhagic transformation stroke, Stroke in evolution, Cerebrovascular accident, Transient ischaemic attack, Cerebral ischaemia, and Spinal cord ischemia.

Four cases were identified from the search including the current one. The additional three cases including two reports of cerebral infarction and one thalamic infarction, which occurred in patients with various advanced cancers, were not suspected to be related to RAD001 by the investigators.

Considering the patient's history of hypertension, smoking and an old infarction in addition to the advanced metastatic disease, it is unlikely that the event was caused by RAD001, but a causal relationship to study drug cannot be excluded. Patients with cancer are at greater risk for development of thromboembolic complications. The thromboembolic events are expected in the current IB, however, cerebral infarction is currently not expected. 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

cc: US ICRO Investigator
Local Trial Leader
Field Monitor
Central IRB (if applicable)
mDOC

* 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 <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	Month	Year	64	Male	Unk	Day	Month	Year	
		03	JUN	1943	Years			21	MAR	2008	
7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data) Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas) Cerebral infarction [Cerebral infarction] ([Dysphagia], [Hemiparesis], [Dizziness], [Dyslalia], [Facial palsy]) Pyrexia 38.0 degrees Celsius [Pyrexia]											
Case Description: Initial report received on 21 Mar 2008: This patient (patient no. XX, centre no. XX) was enrolled in protocol CRAD001C1201, a single arm multi-centre phase II study of RAD001 in patients with advanced gastric carcinoma whose cancer has progressed despite prior treatment. The patient's medical history included: smoking and hypertension. The patient received the first dose of study medication on an unspecified date. (continue)											

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name) #1 RAD001(RAD 666 RAD+TAB+CMAS)Tablet		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 10 mg, QD	16. ROUTE(S) OF ADMINISTRATION #1 Oral	
17. INDICATION(S) FOR USE #1 Gastric cancer		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-MAR-2008 00:00 / 14-MAR-2008 00:00	19. THERAPY DURATION #1 11 days	

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction) #1 CONIEL (BENIDIPINE HYDROCHLORIDE) , ; 04-MAR-2008 00:00 / 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		Smoker
Unknown		Hypertension

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER Investigator's Notification Copy Novartis Pharma Headquarter		26. REMARKS
	24b. MFR CONTROL NO. PHHO2008JP04055	
24c. DATE RECEIVED BY MANUFACTURER 02-APR-2008	24d. REPORT SOURCE <input checked="" type="checkbox"/> STUDY <input type="checkbox"/> LITERATURE <input checked="" type="checkbox"/> HEALTH PROFESSIONAL <input type="checkbox"/> OTHER:	25b. NAME AND ADDRESS OF REPORTER
DATE OF THIS REPORT 14-APR-2008	25a. REPORT TYPE <input checked="" type="checkbox"/> INITIAL <input type="checkbox"/> FOLLOWUP:	