



NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

Date: October 24, 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_PHHO2008AU07680

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 RAD001 Studies*

Date: June 30, 2008

Re: Investigator Notification for RAD001
Leukaemoid Reaction / PHHO2008AU07680

=> APLB

LC

AC

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 Leukaemoid Reaction that occurred in a 78-year-old male patient enrolled in study CRAD001C24112; A Phase 1 Dose Finding Study of Everolimus (RAD001) in Elderly Patients With Acute Myeloid Leukemia (AML) Unfit For Intensive Induction Chemotherapy. 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 MedDRA 10.1 for Preferred Terms of Leukaemoid Reaction and Tumor Flare. This is the only case retrieved from the safety database.

Considering the patient's baseline condition, the event Leukaemoid Reaction is likely to be related to the complications of underlying disease, however, a causal relationship to study drug cannot be excluded. The patient made a complete recovery.

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,

Syed Sajjad, MD
SBSL, Integrated Medical Safety
Novartis Pharmaceuticals Corporation
East Hanover, New Jersey, 07936-1080
United States

CRAD001C 2241

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

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) XX	1a. COUNTRY Australia	2. DATE OF BIRTH			2a. AGE XX Years	3. SEX Male	3a. WEIGHT Unk	4-6 REACTION ONSET			8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
		Day XX	Month XXX	Year XXX			Day 03	Month JUN	Year 2008		
7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data) Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas) Moderate flare reaction [Leukaemoid reaction] ([Hypoxia], [Dyspnoea]) G-CSF hyperleukocytosis [Leukocytosis]										<input type="checkbox"/> PATIENT DIED	
Case Description: Initial report received on 18 Jun 2008: This patient (patient no. X, centre no. X) was enrolled in study CRAD001C24112; A Phase 1 Dose Finding Study of Everolimus (RAD001) in Elderly Patients With Acute Myeloid Leukemia (AML) Unfit For Intensive Induction Chemotherapy. The patient's medical history was not reported. He received the first dose of study medication on 23 May 2008.										<input checked="" type="checkbox"/> INVOLVED OR PROLONGED INPATIENT HOSPITALISATION	
										<input type="checkbox"/> INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY	
(Continued on Additional information Page)										<input type="checkbox"/> LIFE THREATENING	

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name) #1) RAD (RAD) Tablet #2) ARA-C (CYTARABINE)		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) 2.5 mg/daily #2) 20 mg, BID	16. ROUTE(S) OF ADMINISTRATION #1) Oral #2) Subcutaneous	
17. INDICATION(S) FOR USE #1) AML (Acute myeloid leukaemia) #2) 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) 23-MAY-2008 / Unknown #2) 23-MAY-2008 / 01-JUN-2008	19. THERAPY DURATION #1) Unknown #2) 10 days	

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. PHHO2008AU07680		
24c. DATE RECEIVED BY MANUFACTURER 18-JUN-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 XXX XXX XXX XXX XXX XXX
DATE OF THIS REPORT 27-JUN-2008	25a. REPORT TYPE <input checked="" type="checkbox"/> INITIAL <input type="checkbox"/> FOLLOWUP:	

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

On 03 Jun 2008, the patient was having his first cycle as an inpatient when he developed a sub acute flare of his leukaemia cell count. Subsequently he became SOB (short of breath) and hypoxic. WBC (white blood count) on 04 Jun 2008 was 25.70 x 10⁹/L. On 06 Jun 2008, WBC was 57.10 x 10⁹/L. The event prolonged hospitalisation. He commenced oral steroids with a good effect. RAD001 was temporarily withheld during this time. Blasts rapidly decreased. His condition improved and the patient was discharged on 10 Jun 2008, having completely recovered. WBC on 10 Jun 2008 was 2.84 x 10⁹/L. The final diagnosis was moderate flare reaction. The investigator suspected a relationship between this event and the study medication.

Follow-up received on 26 Jun 2008 (prior to initial circulation) The investigator assessed that the patient could either have had a G-CSF hyperleukocytosis reaction or a RAD001 flare reaction; but could not distinguish between the two. The investigator reported that the marked blast cell increase was a little unusual for the former, where more neutrophils would have been expected; however the rapid decrease with steroids was consistent with a G-CSF related problem. In the absence of an investigator's causality assessment, the Novartis Medical Safety Expert provisionally assessed the G-CSF hyperleukocytosis as not suspected to be related to study medication.

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

The information provided in this case does not warrant a change to the Investigator's Brochure. The topic will be monitored closely. Investigator causality is suspected.

All remaining reported leading events and associated symptoms were provisionally assessed as not suspected by the Novartis Medical Safety Physician.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	02-JUN-2008	White blood cell count 10 x 9/L	3.08	
2	03-JUN-2008	White blood cell count 10 x 9/L	12.08	
3	04-JUN-2008	White blood cell count 10 x 9/L	25.70	
4	06-JUN-2008	White blood cell count 10 x 9/L	57.10	
5	07-JUN-2008	White blood cell count 10 x 9/L	26.20	
6	10-JUN-2008	White blood cell count 10 x 9/L	2.84	