



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_PHHO2008CY09722

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: Aug 19, 2008

Re: Investigator Notification for RAD001
Grand mal convulsion / PHHO2008CY09722

→ APCR

AG
bc

Dear Doctor,

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 grand mal convulsion that occurred in a 51-year-old female patient that who received RAD001 in as compassionate use program.

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 11.0 Preferred Terms that contain convulsion and seizure. A total of 20 cases were identified. Eighteen cases were not suspected and two suspected including current case. The additional suspected case involved a patient who received RAD001 for recurrent glioblastoma. The case has been communicated to you.

Given the available information in the current case, a causal relationship between study drug and event occurrence cannot be established or excluded. 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

CRADC 2241

East Hanover, New Jersey, 07936-1080

United States

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.

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| SUSPECT ADVERSE REACTION REPORT | |
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I. REACTION INFORMATION

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|---|---------------------------|------------------|---------------------|---------------------|-------------------------------|-------------------------|----------------------------------|--------------------|---------------------|---------------------|---|
| 1. PATIENT INITIALS (first, last) XX | 1a. COUNTRY XXX | 2. DATE OF BIRTH | | | 2a. AGE 51 Years | 3. SEX Female | 3a. WEIGHT 48.00 kg | 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 08 | Month NOV | Year 1956 | | | | Day 03 | Month AUG | Year 2008 | |
| 7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data) Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas) Grand mal - generalised tonic clonic seizure [Grand mal convulsion] ([Loss of consciousness]) Case Description: Initial report received on 07 Aug 2008: This patient received RAD001 as compassionate use for the indication of 2nd line relapsed kidney cancer. She received the first dose of RAD001 on 09 Jul 2008. On 06 Aug 2008 the patient was witnessed having a grand mal generalised tonic clonic seizure with loss of consciousness, and resulted in hospitalisation. A similar episode was reported as having occurred on 03 Aug 2008. The patient was treated with phenytoin after a CT (computerised tomogram) brain scan was negative. (Continued on Additional Information Page) | | | | | | | | | | | |

II. SUSPECT DRUG(S) INFORMATION

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|---|--|--|
| 14. SUSPECT DRUG(S) (include generic name) #1) EVEROLIMUS (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) 10 mg, daily | 16. ROUTE(S) OF ADMINISTRATION #1) Oral | |
| 17. INDICATION(S) FOR USE #1) 2nd line relapsed kidney cancer (Renal cancer) | | 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) 09-JUL-2008 / 07-AUG-2008 | 19. THERAPY DURATION #1) 30 days | |

III. CONCOMITANT DRUG(S) AND HISTORY

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| 22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction) #1) MORPHINE SULFATE (MORPHINE SULFATE) ; Unknown #2) METOCLOPRAMIDE (METOCLOPRAMIDE) ; Unknown #3) CLEXANE (ENOXAPARIN SODIUM, HEPARIN-FRACTION, SODIUM SALT) ; 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 | |

IV. MANUFACTURER INFORMATION

| | | |
|--|--|---|
| 24a. NAME AND ADDRESS OF MANUFACTURER Investigator's Notification Copy Novartis Pharma Headquarter | | 26. REMARKS |
| 24b. MFR CONTROL NO. PHHO2008CY09722 | | 25b. NAME AND ADDRESS OF REPORTER XXX XXX XXX |
| 24c. DATE RECEIVED BY MANUFACTURER 07-AUG-2008 | 24d. REPORT SOURCE <input checked="" type="checkbox"/> STUDY <input type="checkbox"/> LITERATURE <input checked="" type="checkbox"/> HEALTH PROFESSIONAL <input type="checkbox"/> OTHER: | |
| DATE OF THIS REPORT 15-AUG-2008 | 25a. REPORT TYPE <input checked="" type="checkbox"/> INITIAL <input type="checkbox"/> FOLLOWUP: | |

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

She recovered on an unspecified date. The patient had not experienced similar manifestations before and it was unknown if other factors could have contributed to the events. The reporting physician considered the events to be possibly related to RAD001.

Novartis Comment: Serious adverse drug reaction report (hospitalisation), assessed as unexpected according to the Investigators Brochure.

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

13. Lab Data

| # | Date | Test / Assessment / Notes | Results | Normal High / Low |
|---|------|---------------------------|----------|-------------------|
| 1 | | Blood glucose Normal | | |
| 2 | | Blood sodium | 129 | |
| 3 | | Scan brain | Negative | |