



NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

Date: December 5, 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_PHHO2008US14020

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: Dec 5, 2008

Re: Investigator Notification for RAD001
Pneumothorax / PHHO2008US14020

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 pneumothorax that occurred in 62-year-old male patient who enrolled in study CRAD001C2114, a two-step, phase 1 study investigating the combination of RAD001 with carboplatin, paclitaxel and bevacizumab in non-small-cell lung cancer (NSCLC) patients not treated previously with systemic therapy. The two steps include: Step 1 - RAD001, carboplatin and paclitaxel (CP) and step 2 - RAD001, carboplatin, paclitaxel and bevacizumab (CPB).

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 Term of Pneumothorax. Eleven cases were identified from the search including the current one. Two cases were suspected. The additional suspected case was reported as a complication of esophageal perforation which has been communicated to you.

In the current case, the patient had stage IV NSCLC with consolidation, cavity and emphysematous changes at baseline. Increased cavity was noted during the study treatment. Pneumothorax occurred in approximately two months after the study drug initiation. Considering the patient's base line condition, the event is likely to be the complication of underlying disease; however, a contribution by the study drug cannot be excluded. Bevacizumab is an other confounder.

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

* 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 <small>(first, last)</small> | 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 | 62 Years | Male | 83.00 kg | Day | Month | Year | |
| | | 26 | SEP | 1946 | | | | 22 | NOV | 2008 | |
| 7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data) Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas) Pneumothorax [Pneumothorax] ([Pain], [Dyspnoea], [Chest tube insertion]) | | | | | | | | | | | <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 |
| Case Description: Initial report received on 24 Nov 2008: Patient xxx from centre xxx was enrolled in study CRAD001C2114, a two-step, phase 1 study investigating the combination of RAD001 with carboplatin, paclitaxel and bevacizumab in non-small-cell lung cancer (NSCLC) patients not treated previously with systemic therapy. The two steps include: Step 1 - RAD001, carboplatin and paclitaxel (CP) and step 2 - RAD001, carboplatin, paclitaxel and bevacizumab (CPB). The patient's medical history included generalized pain, type 2 diabetes, GERD and hypercholesterolemia. | | | | | | | | | | | |
| (Continued on Additional Information Page) | | | | | | | | | | | |

II. SUSPECT DRUG(S) INFORMATION

| | | |
|---|---|--|
| 14. SUSPECT DRUG(S) (include generic name) #1) RAD001 (RAD001) Tablet #2) BEVACIZUMAB (BEVACIZUMAB) | | 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) 30 mg weekly #2) UNK | 16. ROUTE(S) OF ADMINISTRATION #1) Oral #2) Unknown | |
| 17. INDICATION(S) FOR USE #1) Non-small cell lung cancer (Non-small cell lung cancer) #2) Non-small cell lung cancer (Non-small cell lung 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) 10-SEP-2008 / 17-NOV-2008 #2) 09-SEP-2008 / Unknown | 19. THERAPY DURATION #1) 69 days #2) Unknown | |

III. CONCOMITANT DRUG(S) AND HISTORY

| | |
|---|---|
| 22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction) #1) CARBOPLATIN (CARBOPLATIN) ; 09-SEP-2008 / Unknown #2) PACLITAXEL (PACLITAXEL) ; 09-SEP-2008 / Unknown #3) PREVACID (LANSOPRAZOLE) ; Unknown #4) ADVIL (IBUPROFEN) ; Unknown #5) VITAMIN B12 (CYANOCOBALAMIN) ; Unknown #6) MULTIVITAMINS (ASCORBIC ACID, ERGOCALCIFEROL, FOLIC (Continued on Additional Information Page) | |
| 23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.) From/To Dates Unknown Unknown | Description Type of History / Notes Hyperglycemia (Hyperglycaemia) Dry skin (Dry skin) |

IV. MANUFACTURER INFORMATION

| | | |
|--|--|-----------------------------------|
| 24a. NAME AND ADDRESS OF MANUFACTURER Investigator's Notification Copy Novartis Pharma Headquarter | | 26. REMARKS |
| | 24b. MFR CONTROL NO. PHHO2008US14020 | 25b. NAME AND ADDRESS OF REPORTER |
| 24c. DATE RECEIVED BY MANUFACTURER 02-DEC-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 05-DEC-2008 | 25a. REPORT TYPE <input checked="" type="checkbox"/> INITIAL <input type="checkbox"/> FOLLOWUP: | |

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

He received the first dose of study medication on 10 Sep 2008 and was in an unspecified step of the study. On 22 Nov 2008, the patient experienced shortness of breath and generalized pain. A CT scan on 24 Nov 2008 showed right-sided pneumothorax, and the patient was hospitalised the same day for chest tube insertion. The study medication was temporarily interrupted, with the last dose having been given on 17 Nov 2008. At the time of reporting, the patient's condition was still present and unchanged. The investigator assessed the relationship between the event and study medication as suspected.

Follow-up received on 02 Dec 2008: The patient also received treatment with carboplatin, paclitaxel and bevacizumab, all commencing on 09 Sep 2008. Baseline PFTs (pulmonary function tests) on 09 Apr 2008 showed flow volume loop suggesting poor effort/technique which may have affected results. Mild obstructive airflow defect was observed, DUCO was normal. The patient presented at baseline with consolidation w/in (with in) sup. (superior) segment R (right) lower lobe with central cavitation. Emphysematous changes were also reported. In Oct 2008, the cavity had increased in size. A CT (computerised tomogram) scan performed in Nov 2008 showed collapse of the lesion and a 100% right sided pneumothorax. The patient's condition was improving. In the investigator's opinion, the event was not related to carboplatin and paclitaxel, but a relationship between the event and RAD001 and bevacizumab (non Novartis drug) was suspected. The investigator's rationale for this assessment was 'patient developed an increasing cavity while on treatment and pneumothorax was secondary to cavity and chemotherapy rarely results in the development'.

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 | | Computerised tomogram | | |
| | | | Collapse of lesion and 100% pneumothorax | |
| 2 | 24-NOV-2008 | Computerised tomogram | | |
| | | | Pos for right-sided pneumothorax. | |
| 3 | 09-APR-2008 | Pulmonary function test | | |
| | | | Baseline: Flow volume loop suggests poor effort/technique. May affect results. Mild obstructive airflow defect. DUCO normal. | |

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

#6) MULTIVITAMINS (ASCORBIC ACID, ERGOCALCIFEROL, FOLIC ACID, NICOTINAMIDE, PANTHENOL, RETINOL, RIBOFLAVIN, THIAMINE HYDROCHLORIDE) ; Unknown

#7) SENOKOT-S (DOCUSATE SODIUM, SENNA, SENNA ALEXANDRINA) ; Unknown

#8) HYDROCODONE W/ACETAMINOPHEN (HYDROCODONE BITARTRATE, PARACETAMOL) ; Unknown

#9) GOLD BOND (MENTHOL, ZINC OXIDE) ; Unknown

#10) GLIPIZIDE (GLIPIZIDE) ; Unknown

#11) CORTISONE (CORTISONE) ; Unknown

23. OTHER RELEVANT HISTORY continued

| From/To Dates | Type of History / Notes | Description |
|---------------|-------------------------|------------------------------|
| Unknown | | Constipation (Constipation); |

ADDITIONAL INFORMATION

23. OTHER RELEVANT HISTORY continued

| From/To Dates | Type of History / Notes | Description |
|---------------|-------------------------|--|
| Unknown | | Hypercholesterolemia (Hypercholesterolaemia); |
| Unknown | | GERD (Gastroesophageal reflux disease); |
| Unknown | | Type 2 diabetes mellitus (Type 2 diabetes mellitus); |
| Unknown | | General body pain (Pain); |