



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_PHHO2008CH13360

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: Nov 19, 2008

Re: Investigator Notification for RAD001
Ostenoradionecrosis/ PHHO2008CH13360&PHHO2008CH13379

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 ostenoradionecrosis that occurred in a two female patients who received RAD001 in the study CRAD001C24118, a multicenter, open label, uncontrolled, phase Ib pharmacokinetic trial to determine the dose level of the combination of RAD001 and Caelyx with an escalating daily dose of RAD001 and fixed dose of Caelyx, in patients with advanced solid tumors.

Details of the adverse event as reported to Novartis are provided in the attached CIOMS I forms.

A search of the Novartis Clinical Safety Database for RAD001 for similar cases was performed using MedDRA 11.0 Preferred Terms of ostenoradionecrosis and ostenonecrosis. Six cases were identified from the search including the current two cases. Four additional cases were not suspected.

The case PHHO2008CH13379 involved a 65-year-old female patient with advanced endometrial cancer. The patient received three courses of radiotherapy from September 2006 to Nov 2007. Study medications were started on 24 Jul 2008. Radio-osteonecrosis was diagnosed approximately three months after the study medication initiation. Study medication was discontinued due to the event.

The case PHHO2008CH13360 involved a 61-year-old female patient with advanced endometrial cancer. Prior to taking the study medications, the patient received radiotherapy (dates unknown) and experienced lumbosciatalgia at baseline. The event was diagnosed approximately two months after study medication discontinuation.

The radiotherapy utilized to treat advanced stage gynecologic cancer can cause intestinal, vaginal, and urologic complications from micro-vascular damage to the organs. Pelvic bone osteonecrosis is a rare but disabling complication of pelvic radiation. (*REFERENCE: John P. et al, Pelvic radiation necrosis and osteomyelitis following chemoradiation for*

advanced stage vulvar and cervical carcinoma, Gynecologic Oncology 101 (2006) 349–352).

Both patients received radiotherapy, in one patient (PHHO2008CH13360) the symptoms were already present at the baseline. Patient (PHHO2008CH13379) received radiotherapy approximately eight months before the study medication initiation. Considering the patient's history of radiotherapy, it is unlikely that the study drug interfered with the repairing process of osteoradionecrosis or the event was caused by the study drug. However, a contribution by the study drug cannot be 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
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 (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	61	Female	83.00	Day	Month	Year	
		24	SEP	1947	Years		kg	03	NOV	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 Radio-osteonecrosis of the sacrum [Osteoradionecrosis] ([Back pain], [Fractured sacrum]) Worsening of clinical condition [Malignant neoplasm progression]											
Case Description: Initial report received on 07 Nov 2008: This patient (patient no. xxx) was enrolled in multicentre, open label, uncontrolled, phase Ib pharmacokinetic trial to determine the dose level of the combination of RAD001 and Caelyx with an escalating daily dose of RAD001 and fixed dose of Caelyx, in patients with advanced solid tumours.											
(Continued on Additional Information Page)											

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name) #1) RAD001 + Caelyx (RAD001 + Caelyx) Tablet		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) 5 mg	16. ROUTE(S) OF ADMINISTRATION #1) Oral	
17. INDICATION(S) FOR USE #1) Endometrial cancer (Endometrial 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) 18-FEB-2008 / 25-JUN-2008	19. THERAPY DURATION #1) 129 days	

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction) #1) CAELYX (DOXORUBICIN HYDROCHLORIDE) ; 18-FEB-2008 / 16-JUL-2008 #2) FRAXIPARINA (NADROPARIN CALCIUM) ; Unknown #3) LYRICA (PREGABALIN) ; Unknown #4) PANTOZOL (PANTOPRAZOLE SODIUM) ; Unknown #5) HEPARIN (HEPARIN) ; Unknown										
23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.) <table style="width:100%; border-collapse: collapse;"> <tr> <th style="width:30%;">From/To Dates</th> <th style="width:40%;">Type of History / Notes</th> <th style="width:30%;">Description</th> </tr> <tr> <td>NOV-2007 to JAN-2008</td> <td>Historical Drug</td> <td></td> </tr> <tr> <td>MAR-2007 to DEC-2007</td> <td>Historical Drug</td> <td></td> </tr> </table>		From/To Dates	Type of History / Notes	Description	NOV-2007 to JAN-2008	Historical Drug		MAR-2007 to DEC-2007	Historical Drug	
From/To Dates	Type of History / Notes	Description								
NOV-2007 to JAN-2008	Historical Drug									
MAR-2007 to DEC-2007	Historical Drug									
(Continued on Additional Information Page)										

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER Investigator's Notification Copy Novartis Pharma Headquarter		26. REMARKS
	24b. MFR CONTROL NO. PHHO2008CH13360	25b. NAME AND ADDRESS OF REPORTER
24c. DATE RECEIVED BY MANUFACTURER 18-NOV-2008	24d. REPORT SOURCE <input checked="" type="checkbox"/> STUDY <input type="checkbox"/> LITERATURE <input type="checkbox"/> HEALTH PROFESSIONAL <input type="checkbox"/> OTHER:	
DATE OF THIS REPORT 19-NOV-2008	25a. REPORT TYPE <input checked="" type="checkbox"/> INITIAL <input type="checkbox"/> FOLLOWUP:	

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

The patient's medical history included: asymptomatic pulmonary embolism, deep vein thrombosis of right leg and radiotherapy. She received the first dose of study medication on 18 Feb 2008. The study medication was stopped on 25 Jun 2008 due to worsening of clinical condition. Lumbosciatalgia pain, present at baseline, worsened during treatment with RAD001 and Caelyx, requiring hospitalisation on 28th Aug 2008. A diagnosis of radio-osteonecrosis of the sacrum was made confirmed histologically and radiologically. A subcutaneous pump for pain relief was placed and the patient was discharged from hospital. On 13th Oct 2008 a CT scan was performed with evidence of fracture of the sacrum. Due to pain grade 3 the patient was hospitalised on 03 Nov 2008. At the time of this report the patient's condition was still present and unchanged. The investigator did not suspect a relationship between this event and Caelyx but suspected a possible relationship to RAD001.

Follow up received on 18 Nov 2008: The patient was on low-weight heparin for the historical deep vein thrombosis. She had received radiotherapy to the pelvis and had three courses of Taxotere, Adriamycin and cisplatin from Jan 2006 to Apr 2006. From Mar 2007 to Dec 2007 she received Megestrol Acetate and from Nov 2007 to Jan 2008 she received Letrozole. The patient had not had any trauma to the sacral area and had no other relevant medical history. The worsening of the clinical condition was considered to be medically significant. At the time of this report the patient's condition was still present and unchanged. The investigator did not suspect a relationship between the worsening clinical condition and Caelyx but suspected a relationship to RAD001.

Novartis Comment: Serious adverse drug reaction osteoradionecrosis, (hospitalisation), assessed as unexpected according to the Investigator's Brochure. The information provided in this individual case does not warrant a change to the Investigator's Brochure. The topic will be monitored closely. Investigator causality is suspected.

Serious adverse drug reaction, disease progression (medically significant), assessed as expected according to the Investigator's Brochure. Investigator causality is suspected.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	03-NOV-2008	Blood creatinine UMOL/L	90	
2	03-NOV-2008	Computerised tomogram Evidence of fracture of the sacrum		
3	03-NOV-2008	Haemoglobin G/DL	11.8	
4		Histology Radio-osteonecrosis of the sacrum confirmed		
5	03-NOV-2008	Platelet count G/DL	357	
6	03-NOV-2008	White blood cell count G/DL	7.6	

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
NOV-2007 to JAN-2008	Historical Drug	(LETROZOLE); Drug Indication: (), Drug Reaction: ()
MAR-2007 to DEC-2007	Historical Drug	(MEGESTROL ACETATE); Drug Indication: (), Drug Reaction: ()
JAN-2006 to APR-2006	Historical Drug	(CISPLATIN); Drug Indication: (), Drug Reaction: ()

ADDITIONAL INFORMATION**23. OTHER RELEVANT HISTORY continued**

From/To Dates	Type of History / Notes	Description
JAN-2006 to APR-2006	Historical Drug	(ADRIAMYCIN); Drug Indication: (), Drug Reaction: ()
JAN-2006 to APR-2006	Historical Drug	(TAXOTERE); Drug Indication: (), Drug Reaction: ()
2006 to Unknown	Historical Drug Pelvis	(RADIOTHERAPY); Drug Indication: (), Drug Reaction: ()
Unknown		DVT (Deep vein thrombosis);
Unknown		Pulmonary embolism (Pulmonary embolism);
Unknown		Lumbo-sacral pain (Back pain);

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 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	65 Years	Female	56.00 kg	Day	Month	Year	
		21	JUL	1943				31	OCT	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 Radio-osteonecrosis of sacrum [Osteoradionecrosis] ([Back pain], [Back injury]) Fall [Fall]											
Case Description: Initial report received on 07 Nov 2008: This patient (patient no. xxx, centre xx) was enrolled in CRAD001C24118, a multicentre, open label, uncontrolled, phase Ib pharmacokinetic trial to determine the dose level of the combination of RAD001 and Caelyx with an escalating daily dose of RAD001 and fixed dose of Caelyx, in patients with advanced solid tumours.											
(Continued on Additional Information Page)											

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name) #1) RAD001 + Caelyx (RAD001 + Caelyx) Tablet #2) CAELYX (DOXORUBICIN HYDROCHLORIDE)		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) 7.5 mg / day #2) 60 mg / day	16. ROUTE(S) OF ADMINISTRATION #1) Oral #2) Oral	
17. INDICATION(S) FOR USE #1) Endometrial cancer (Endometrial cancer) #2) Endometrial cancer (Endometrial 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) 24-JUL-2008 / 31-OCT-2008 #2) 24-JUL-2008 / 24-OCT-2008	19. THERAPY DURATION #1) 100 days #2) 93 days	

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction) #1) SINTROM (ACENOCOUMAROL) ; 26-MAY-2008 / Ongoing #2) DAFALGAN (PARACETAMOL) ; 28-AUG-2008 / Unknown #3) CRESTOR (ROSUVASTATIN CALCIUM) ; 24-JUL-2008 / Ongoing #4) WARFARIN (WARFARIN) ; 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	Historical Condition	Deep vein thrombosis leg (Deep vein thrombosis)
24-OCT-2007 to NOV-2007	Historical Condition	Brachytherapy to vagina (Brachytherapy to vagina)
	60.4 GY	

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER Investigator's Notification Copy Novartis Pharma Headquarter		26. REMARKS
	24b. MFR CONTROL NO. PHHO2008CH13379	25b. NAME AND ADDRESS OF REPORTER
24c. DATE RECEIVED BY MANUFACTURER 18-NOV-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 19-NOV-2008	25a. REPORT TYPE <input checked="" type="checkbox"/> INITIAL <input type="checkbox"/> FOLLOWUP:	

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

The patient's medical history included: endometrial cancer in advanced state and DVT (deep vein thrombosis) of the leg. The patient received radiotherapy for endometrial cancer from Sep to Nov 2006. She received the first dose of study medication on 24 Jul 2008. From the start of the second cycle, after a "fault", lumbar pain started, worsening over time. On 29 Oct 2008, an MRI (magnetic resonance imaging) of the sacrum was performed with a diagnosis of radio-osteonecrosis of the sacrum considered medically significant. The patient was discontinued from the study, due to the event. At the time of reporting, the patient's condition was unresolved/ongoing. The investigator suspected a possible relationship between this event and the study medication (RAD001 and Caelyx).

Follow-up received on 18 Nov 2008: The patient was having ongoing treatment with Warfarin for the historical DVT. She had previous history of radiotherapy of the pelvis (external) total 50 GY from 13 Sep 2007 to 22 Oct 2007 and BR endovaginal brachithery 60.4 GY from 24 Oct 2007 until Nov 2007. The patient had also received previous chemotherapy treatment with cisplatin, Adriamycin and Taxole from Feb 2007 until Jun 2007 and hormone therapy with megestrol acetate from Dec 2006 until Jan 2007. The investigator clarified that the "fault" should have been reported as a "fall", which was not suspected to be related to the study medication (RAD001 and Caelyx). In the fall she hurt the sacral region. There was no evidence of metastasis in the sacrum before, during or after the event. The patient's condition was unchanged.

Novartis Comment: Serious adverse drug reaction report "Osteoradionecrosis", (Medically significant), assessed as unexpected according to the Investigator's Brochure. The information provided in this individual case does not warrant a change to the Investigator's Brochure text. The topic will be monitored closely. Investigator causality is suspected.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	31-OCT-2008	Blood creatinine	35 umol/l	
2	31-OCT-2008	Haemoglobin	11.5 g/dl	
3	31-OCT-2008	Neutrophil count	1.81 g/l	
4	29-OCT-2008	Nuclear magnetic resonance imaging Diagnosis of radio-osteonecrosis of the sacrum		
5	31-OCT-2008	Platelet count	192 g/l	
6	31-OCT-2008	White blood cell count	2.6 g/l	

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
13-SEP-2007 to 22-OCT-2007	Historical Condition	Radiotherapy to pelvis (Radiotherapy); Radiotherapy of the pelvis (external) total 50 GY
FEB-2007 to JUN-2007	Historical Drug	(TAXOL); Drug Indication: (), Drug Reaction: ()
FEB-2007 to JUN-2007	Historical Drug	(ADRIAMYCIN); Drug Indication: (), Drug Reaction: ()
FEB-2007 to JUN-2007	Historical Drug	(CISPLATIN); Drug Indication: (), Drug Reaction: ()
DEC-2006 to JAN-2007	Historical Drug	(MEGESTROL ACETATE); Drug Indication: (), Drug Reaction: ()