



NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

Date: December 12, 2008

To: NCCTG Primary Clinical Research Associates

From: Sara Braun

Re: N0775, A Randomized Phase II Trial of Temozolomide (TMZ) and Avastin® or ABI-007/Carboplatin (CBDCA) and Avastin® in Patients with Unresectable Stage IV Malignant Melanoma

The purpose of this memorandum is to provide investigators with a recent industry report of an adverse event that has occurred in association with Abraxane (ABI-007) at a non-NCCTG institution. You may have also received this communication directly from the drug manufacturer.

AE_CA031-08-0473

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

U.S. Department of Health and Human Services
Food and Drug Administration

For use by user-facilities,
importers, distributors and manufacturers
for MANDATORY reporting

MEDWATCH

FORM FDA 3500A (10/05)

| |
|--------------------------------|
| Mfr Report # CA031-08-0473 (0) |
| UF/Importer Report # |
| FDA Use Only |

| A. PATIENT INFORMATION | | | |
|---|--|---|--|
| 1. Patient Identifier SGL In confidence | 2. Age at Time of Event: 43 Y or _____ Date of Birth: 02/11/1965 | 3. Sex <input type="checkbox"/> Female <input checked="" type="checkbox"/> Male | 4. Weight _____ lbs or 96 _____ kgs |

| B. ADVERSE EVENT OR PRODUCT PROBLEM | |
|---|---|
| 1. <input checked="" type="checkbox"/> Adverse Event and/or <input type="checkbox"/> Product Problem (e.g., defects/malfunctions) | |
| 2. Outcomes Attributed to Adverse Event (Check all that apply) | |
| <input type="checkbox"/> Death: _____ (mm/dd/yyyy) | <input type="checkbox"/> Disability or Permanent Damage |
| <input type="checkbox"/> Life-threatening | <input type="checkbox"/> Congenital Anomaly/Birth Defect |
| <input checked="" type="checkbox"/> Hospitalization - initial or prolonged | <input type="checkbox"/> Other serious (Important Medical Events) |
| <input type="checkbox"/> Required Intervention to Prevent Permanent Impairment/Damage (Devices) | |
| 3. Date of Event (mm/dd/yyyy) 11/06/2008 | 4. Date of This Report (mm/dd/yyyy) 11/19/2008 |

5. Describe Event or Problem

A 43-year old, Caucasian male subject (655-0005) experienced acute atrial fibrillation while enrolled in A Randomized, Phase III Trial of ABI-007 and Carboplatin Compared with Taxol and Carboplatin as First-line Therapy in Patients with Advanced Non-Small Cell Lung Cancer (NSCLC). The first doses of ABI-007 (100 mg/m²) and carboplatin (6 AUC) were received on 24-Jul-08. The last doses of ABI-007 (50 mg/m²) and carboplatin (3 AUC) received prior to the onset of the event were on 30-Oct-08.

On 06-Nov-08, eight days after the last dose of ABI-007, the subject was hospitalized for acute atrial fibrillation that was noted on an electrocardiogram. Treatment information has not yet been provided. At the time of this report, the event is ongoing.

No action was taken with study therapy due to this event.

The subject's medical history includes acute appendectomy, chronic tonsillitis, chronic erosive gastritis, polyp of sigmoid,

Cont...

| |
|--|
| 6. Relevant Tests/Laboratory Data, Including Dates |
| None reported. |

7. Other Relevant History, Including Preexisting Medical Conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

Past Disease:
Acute appendicitis[10000677] (??/??/1998 -)

Chronic tonsillitis[10009152] (??/??/1984 -)

Concurrent Disease:
Gastritis erosive[10017865] (07/15/2008 -) (Continuing: Yes)
Sigmoid polyp[10049138] (07/17/2008 -)

Cont...

Submission of a report does not constitute an admission that medical personnel, user facility, importer, distributor, manufacturer or product caused or contributed to the event.

| C. SUSPECT PRODUCT(S) | |
|--|---|
| 1. Name (Give labeled strength & mfr/labeler) | |
| #1 ABI-007 (Abraxane [®] for Injectable Suspension (paclitaxel) | |
| #2 CARBOPLATIN (CARBOPLATIN) | Cont... |
| 2. Dose, Frequency & Route Used | |
| #1 (100 mg/m ²), Intraveno- | 3. Therapy Dates (If unknown, give duration) from/to (or best estimate) |
| #2 (6 AUC), Intravenous | #1 07/24/2008 - ongoing |
| | #2 07/24/2008 - ONGOING |
| 4. Diagnosis for Use (Indication) | |
| #1 Non-small cell lung cancer[10061873] | 5. Event Abated After Use Stopped or Dose Reduced? |
| #2 Non-small cell lung cancer[10061873] | #1 <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply |
| | #2 <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply |
| 6. Lot # | |
| #1 C236-018 | 7. Exp. Date |
| #2 202800 | #1 -Jan-2009 |
| | #2 -OCT-2009 |
| 9. NDC # or Unique ID | |
| | 8. Event Reappeared After Reintroduction? |
| | #1 <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply |
| | #2 <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply |

10. Concomitant Medical Products and Therapy Dates (Exclude treatment of event)
Concomitant Medications Not Available

| G. ALL MANUFACTURERS | |
|--|---|
| 1. Contact Office - Name/Address (and Manufacturing Site for Devices) | 2. Phone Number |
| Abraxis BioScience 11755 Wilshire Blvd., Ste 2000 Los Angeles, CA 90025 USA (Initial Unit) | Cont... |
| 4. Date Received by Manufacturer (mm/dd/yyyy) 11/05/2008 | 3. Report Source (Check all that apply) |
| | <input checked="" type="checkbox"/> Foreign |
| | <input checked="" type="checkbox"/> Study |
| | <input type="checkbox"/> Literature |
| | <input type="checkbox"/> Consumer |
| | <input checked="" type="checkbox"/> Health Professional |
| | <input type="checkbox"/> User Facility |
| | <input type="checkbox"/> Company Representative |
| | <input type="checkbox"/> Distributor |
| | <input type="checkbox"/> Other: |
| 5. (A)NDA # IND # 55,974 | |
| 6. If IND, Give Protocol # | |
| 7. Type of Report (Check all that apply) | |
| <input type="checkbox"/> 5-day <input type="checkbox"/> 30-day | |
| <input type="checkbox"/> 7-day <input type="checkbox"/> Periodic | |
| <input type="checkbox"/> 10-day <input checked="" type="checkbox"/> Initial | |
| <input checked="" type="checkbox"/> 15-day <input type="checkbox"/> Follow-up # _____ | |

| | |
|--|---|
| 9. Manufacturer Report Number CA031-08-0473 (0) | 8. Adverse Event Term(s) 1) ACUTE ATRIAL |
| | Cont... |

| E. INITIAL REPORTER | |
|---|-------------------------|
| 1. Name and Address Edward Vozniy Moscow City Clinical Hospital #57 32/61, 11th Parkovaya str. Moscow, 105077 RUSSIA | Phone # (495) 465 83 85 |

| | | |
|--|----------------------------|--|
| 2. Health Professional? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No | 3. Occupation Physician | 4. Initial Reporter Also Sent Report to FDA <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Unk. |
|--|----------------------------|--|

B. ADVERSE EVENT OR PRODUCT PROBLEM

B.5 Describe Event or Problem (Cont...)

weakness, dyspnea, cough, body temperature increase and right ventricular hypertrophy.
Concomitant medications were not provided.

The investigator reported the events as possibly related to ABI-007 and carboplatin.

B.7 Other Relevant History, Including Preexisting Medical Conditions (Cont...)

(Continuing: Yes)
Weakness[10047862] (03/??/2008 -) (Continuing: Yes)
Dyspnea[10013963] (03/??/2008 -) (Continuing: Yes)
Cough[10011224] (03/??/2008 -) (Continuing: Yes)
Body temperature increased[10005911] (03/??/2008 -) (Continuing: Yes)
Ventricular hypertrophy[10047295] (07/21/2008 -) (Continuing: Yes)

C. SUSPECT PRODUCT(S) (Cont...)

| | |
|----------------------------------|--|
| Seq No. | : 1 |
| C.1 Suspect Product | : ABI-007(Abraxane® for Injectable Suspension (paclitaxel protein-bound particles) (albumin-bound)) (PACLITAXEL) |
| C.2 Dose, Frequency & Route Used | : 1) (100 mg/m2), Intravenous |

G. ALL MANUFACTURERS

G.2 Phone Number

(310) 883-1300

G.8 Adverse Event Term(s)

1) ACUTE ATRIAL FIBRILLATION (Atrial fibrillation, Atrial fibrillation)

Company Comments:

Given the paucity of information provided, an accurate assessment of causality is not possible. Further information has been requested.

Analysis of Similar Events:

A search of the database revealed seven cases of atrial fibrillation. Six of the cases were deemed unrelated to ABI-0007. One case was deemed possibly related by the investigator. The sponsor believes the event is related to comorbidity.

CA023-07-0844 A 45 yo female experienced atrial fibrillation while enrolled in a clinical trial for metastatic breast cancer. The subject's medical history was relevant for morbid obesity and cardiomegaly; the event was deemed possibly related by the principal investigator.

AX 200-08-0176 A 75 yo male enrolled in an investigator initiated trial for non small cell lung cancer experienced atrial fibrillation. The subject had additional medical history relevant for paroxysmal atrial fibrillation, hypertension, and dual lead transvenous pacemaker.

ABX14-06-0107 A 79 yo male enrolled in an investigator initiated trial for non small cell lung cancer experienced atrial fibrillation while hospitalized for pneumonia with chronic obstructive pulmonary disease. The subject had additional medical history relevant for hypertension and atrial fibrillation.

ABX55-08-0472 A 69 yo male enrolled in an investigator initiated trial for malignant melanoma experienced atrial fibrillation, deemed possibly related to the concomitant drug bevacizumab by the principal investigator. The relationship to ABI-007 by the investigator was unknown.

CA40-08-0416 A 71 year old male experienced paroxysmal atrial fibrillation while enrolled in a clinical trial for metastatic pancreatic cancer. The subject had additional medical history relevant for sick sinus syndrome, atrial fibrillation, atrial flutter, atrial flutter ablation and hypertension.

CA014-04-0312 An 81 yo female experienced atrial fibrillation while enrolled in a clinical trial for metastatic melanoma. Additional history was relevant for hypertension and atrial fibrillation.

CA028-06-0057 An 60 yo female experienced paroxysmal atrial fibrillation while enrolled in

Abraxis BioScience
11755 Wilshire Blvd., Ste 2000
Los Angeles, CA 90025
USA

Continuation Sheet for FDA-3500A Form

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Date of This Report : 11/19/2008

a clinical trial for non small cell lung cancer. Additional relevant medical history included essential hypertension, hypertrophic cardiomyopathy, ischemic heart disease, left ventricle aneurysm, cardiac repolarization abnormality and paroxysmal ciliary arrhythmia.