



NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

Date: May 9, 2008

To: NCCTG Primary Clinical Research Associates

From: Sara Braun

Re: N0682, A Phase II Clinical Trial of Denileukin Diftitox in Combination with Rituximab in Previously Untreated Follicular B-cell Non-Hodgkin's Lymphoma

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

AE_556768

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/df
enclosure

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

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

MFR report # 556768

DF/importer report #

FDA Use only

Page 1 of 4

A. PATIENT INFORMATION

1. Patient Identifier _____ 2. Age at time of event: 55 YEARS 3. Sex: female male 4. Weight: 141.1 lbs or 64 kgs

In confidence

B. ADVERSE EVENT OR PRODUCT PROBLEM

1. Adverse event and/or Product problem (e.g., defects/malfunctions)

2. Outcomes attributed to adverse event (check all that apply):
 death 03/31/2008 (mm/dd/yyyy)
 life threatening
 hospitalization-initial or prolonged
 disability or permanent damage
 congenital anomaly/birth defect
 required intervention to prevent permanent impairment/damage (devices)
 other serious (important medical events)

3. Date of event (mm/dd/yyyy) 03/31/2008 4. Date of this report (mm/dd/yyyy) 04/11/2008

5. Describe event or problem

BOZ0603
 MULTI-CENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE III TRIAL COMPARING THE EFFICACY OF BEVACIZUMAB IN COMBINATION WITH RITUXIMAB AND CHOP (RA-CHOP) VERSUS RITUXIMAB AND CHOP (R-CHOP) IN PREVIOUSLY UNTREATED PATIENTS WITH CD20-POSITIVE DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL)

A 55-YEAR-OLD FEMALE PATIENT DIED OF AN UNKNOWN CAUSE DURING PARTICIPATION IN THE ABOVE STUDY.

ON 12 MARCH THE PATIENT REPORTED AN IMPROVEMENT IN HER DISEASE AND REPORTED LESS PAIN AND HER COUGHING ALMOST DISAPPEARING. ON 14 MARCH 2008 INTRAVENOUS BLINDED BEVACIZUMAB WAS STARTED. THE FOLLOWING DAY, INTRAVENOUS (IV) RITUXIMAB (375 MG/M2, ONCE EVERY THREE WEEKS), IV CYCLOPHOSPHAMIDE (750 MG/M2, ONCE EVERY THREE WEEKS), IV VINCRISTINE (1 MG/M2, ONCE EVERY THREE WEEKS), IV DOXORUBICIN (50 MG/M2, ONCE EVERY THREE WEEKS) AND ORAL PREDNISONE (100 MG GIVEN DAYS 1-5 OF THREE WEEK CYCLE) WERE

CONTINUED

6. Relevant tests/laboratory data, including dates

UNK

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

Medical History Terms
 DIFFUSE LARGE B-CELL LYMPHOMA/DIFFUSE LARGE B-CELL LYMPHOMA/MEDDRA 10.1
 NON-HODGKIN'S LYMPHOMA/NON-HODGKIN'S LYMPHOMA/MEDDRA 10.1 31-MAR-2008

C. SUSPECT PRODUCT(S)

1. Name (give labeled strength & mfr/labeler)
 #1 RITUXIMAB (RITUXIMAB)
 #2 BEVACIZUMAB (BEVACIZUMAB)

2. Dose, frequency & route
 #1 375 MG/M2 1 per 3 WEEK INTRAVENOUS
 #2 15 MG/KG 1 per 3 WEEK INTRAVENOUS

3. Therapy dates (if unk. give duration) from/to (or best estimate)
 #1 15-MAR-2008 / 15-MAR-2008
 #2 14-MAR-2008 / 14-MAR-2008

4. Diagnosis for use (indication)
 #1 DIFFUSE LARGE B-CELL LYMPHOMA/DIFFUSE LARGE B-CELL LYMPHOMA/MEDDRA 10.1
 #2 DIFFUSE LARGE B-CELL LYMPHOMA/DIFFUSE LARGE B-CELL LYMPHOMA/MEDDRA 10.1

5. Event abated after use stopped or dose reduced
 #1 yes no doesn't apply
 #2 yes no doesn't apply

6. Lot #
 #1 UNK #2 UNK

7. Exp. date
 #1 UNK #2 UNK

8. Event reappeared after reintroduction
 #1 yes no doesn't apply
 #2 yes no doesn't apply

9. NDC # or Unique ID
 #1 NA #2 NA

10. Concomitant medical products and therapy dates (exclude treatment of event)
 UNK

G. ALL MANUFACTURERS

1. Contact Office-name/address (& mailing site for devices) _____ 2. Phone Number _____

3. Report source (check all that apply):
 foreign
 study
 literature
 consumer
 health professional
 user-facility
 company representative
 distributor
 other: _____

4. Date received by manufacturer (mm/dd/yyyy) 04/03/2008 5. (A)NDA# _____ IND # _____

6. # IND. protocol # NA STN # 103705

7. Type of report (check all that apply):
 5-day 15-day
 7-day periodic
 10-day 30-day
 initial follow-up # _____

8. Adverse event term(s)
 DEATH CAUSE UNKNOWN/DEATH/MEDDRA 10.1 +++

9. MFR. report number 556768
 +++ adverse event that generated submission

E. INITIAL REPORTER

1. Name, address _____ Phone # _____

2. Health professional? yes no 3. Occupation _____ 4. Initial reporter also sent report to FDA yes no unk

Where MedDRA is used the following format applies:
 Reported term/MedDRA PT/version number



3500A Facsimile

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

B.5. Describe event or problem - continued

STARTED. APPROXIMATELY ELEVEN DAYS LATER, ON 26 MARCH 2008, SHE COMPLAINED OF A DRY COUGH AGAIN AND WAS ADVISED TO VISIT THE OUTPATIENT CLINIC, HOWEVER SHE DID NOT ARRIVE. TWO DAYS LATER, SHE COMPLAINED OF CHEST PAIN AND WAS AGAIN ADVISED TO GO TO THE CLINICAL; AGAIN SHE DID NOT ARRIVE. ON 31 MARCH 2008, THE PATIENT DIED. THE INVESTIGATOR DISCOVERED HER DEATH IN A NEWSPAPER AND, AT THE TIME OF THE REPORT, THE CAUSE OF DEATH WAS NOT KNOWN. NO ACTION WAS TAKEN WITH STUDY THERAPY, WHICH WAS ONGOING AT THE TIME OF DEATH.

FOLLOWING MEDICAL ASSESSMENT, FOR THE EVENT OF DEATH CAUSE UNKNOWN, THE COMPANY UPGRADED THE CAUSALITY ASSESSMENT TO UNKNOWN FOR RITUXIMAB AND BLINDED BEVACIZUMAB, TO ENABLE APPROPRIATE SUBMISSIONS. THE INVESTIGATOR ASSESSED THE EVENT OF DEATH CAUSE UNKNOWN AS UNRELATED TO RITUXIMAB AND BLINDED BEVACIZUMAB AND POSSIBLY RELATED TO LYMPHOMA NON-HODGKIN. NO OTHER INFORMATION WAS AVAILABLE.

THE DRUG CODE WAS BROKEN DUE TO REGULATORY REQUIREMENTS ON 08 APRIL 2008. THE PATIENT RECEIVED BEVACIZUMAB (15 MG/KG, ONCE EVERY THREE WEEKS).

ASIME -MCN 556768 - DEATH-CAUSE UNKNOWN

THE INDEX CASE (MCN 556768) IS A 55 YEAR OLD FEMALE WHO DIED OF AN UNKNOWN CAUSE DURING PARTICIPATION IN A MULTI-CENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE III TRIAL (BO20603) OF BEVACIZUMAB IN COMBINATION WITH RITUXIMAB AND CHOP (RA-CHOP) VERSUS RITUXIMAB AND CHOP (R-CHOP) IN PREVIOUSLY UNTREATED PATIENTS WITH CD20-POSITIVE DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL)

THE PATIENT'S MEDICAL HISTORY AND DRUG HISTORY WERE NOT REPORTED.

AN IMPROVEMENT WAS NOTED IN THE PATIENT'S DISEASE STATUS ON 12 MARCH WHEN SHE REPORTED LESS PAIN AND APPARENTLY HER COUGHING HAD ALMOST DISAPPEARED. ON 14 MARCH 2008 INTRAVENOUS BLINDED BEVACIZUMAB WAS STARTED. THE FOLLOWING DAY, INTRAVENOUS (IV) RITUXIMAB (375 MG/M2, ONCE EVERY THREE WEEKS), IV CYCLOPHOSPHAMIDE (750 MG/M2, ONCE EVERY THREE WEEKS), IV VINCRIStINE (1 MG/M2, ONCE EVERY THREE WEEKS), IV DOXORUBICIN (50 MG/M2, ONCE EVERY THREE WEEKS) AND ORAL PREDNISONE (100 MG GIVEN DAYS 1-5 OF THREE WEEK CYCLE) WERE STARTED. APPROXIMATELY ELEVEN DAYS LATER, SHE ONCE AGAIN COMPLAINED OF A DRY COUGH AND WAS ADVISED TO VISIT THE OUTPATIENT CLINIC WHICH SHE DID NOT ATTEND. THE PATIENT UNFORTUNATELY DIED ON 31 MARCH 2008. THE INVESTIGATOR DISCOVERED HER DEATH IN A NEWSPAPER AND, AT THE TIME OF THE REPORT, THE CAUSE OF DEATH WAS NOT KNOWN. NO ACTION WAS TAKEN WITH STUDY THERAPY, WHICH WAS ONGOING AT THE TIME OF DEATH. THE DRUG CODE WAS BROKEN DUE TO REGULATORY REQUIREMENTS ON 08 APRIL 2008 AND IT WAS NOTED THAT THE PATIENT WAS RECEIVING IV BEVACIZUMAB 15 MG/KG, ONCE EVERY THREE WEEKS.

THE INVESTIGATOR ASSESSED THE EVENT OF DEATH CAUSE UNKNOWN AS UNRELATED TO RITUXIMAB AND BLINDED BEVACIZUMAB AND RELATED TO LYMPHOMA NON-HODGKIN. FOLLOWING MEDICAL ASSESSMENT, FOR THE EVENT OF DEATH CAUSE UNKNOWN, THE COMPANY UPGRADED THE CAUSALITY ASSESSMENT TO UNKNOWN FOR RITUXIMAB AND BLINDED BEVACIZUMAB, TO ENABLE APPROPRIATE SUBMISSIONS. NO FURTHER INFORMATION WAS AVAILABLE.

IN THE ABSENCE OF A REPORTED CAUSE OF DEATH NO MEANINGFUL ASSESSMENT OF THIS REPORT IS POSSIBLE.

ON THE 08 APRIL 2008, THE ROCHE SAFETY DATABASE WAS SEARCHED FOR BEVACIZUMAB CASES WITH A MEDDRA PREFERRED TERM OF "DEATH" AND "SUDDEN DEATH" AND 196 CASES WERE IDENTIFIED INCLUDING THE INDEX CASE.

THE MCNS:

364122,366624,366800,367683,367693,373639,383914,383973,383975,384689,385446,387864,388676,
390289,390529,391177,391493,391666,391746,391776,392169,393274,394160,397727,399086,403919,
404717,408498,411135,411870,412320,412653,416432,416441,421063,421120,421121,422109,423197,
424703,425062,425719,428122,428951,430481,431600,435812,437292,437335,441316,441699,441703,
444408,445293,445718,446677,447494,447503,448504,448730,448787,448907,450060,450142,450284,
451289,455095,457923,459635,460541,460896,462257,462502,465102,465505,465516,465649,467706,
469552,469572,472821,474217,476085,476086,476094,477232,477456,478629,480257,480968,480980,
481281,481797,482119,483370,483477,483618,483626,484077,485526,485532,485793,486122,486274,
486588,487790,488218,490266,491507,492444,492619,493884,494677,494817,495874,499706,500307.

500309,500969,501958,504304,506811,507530,508107,509293,510608,510679,511421,512160,512161,513206,513397,513428,513501,514234,515678,516701,517211,518256,519596,519785,520281,521411,521672,522415,523614,524649,525128,527649,527830,529038,529068,529668,530727,531593,533075,533077,533101,533339,533493,533873,534620,535163,536434,540153,540203,540489,540849,542372,542982,543238,543876,544723,545551,546584,546898,547448,547698,549440,549947,550390,551481,552439,553070,553090,553253,553491,554043,554253,554587,555244,555592,556394,556768,556779,557044,557048

AFTER REVIEW OF THE CLINICAL DETAILS OF THE INDEX CASE, THE SPONSOR DOES NOT BELIEVE THAT CHANGES TO THE CONDUCT OF THE CLINICAL TRIAL ARE WARRANTED IN RESPONSE TO THIS CASE REPORT.
THESE EVENTS WILL NOT BE AN ADDENDUM TO THE BEVACIZUMAB INVESTIGATOR BROCHURE.

C.1. thru C.9. Suspect medication(s) - continued

Suspect medication #2

C6. Lot # (if known)
14040, 14376, 11395

Suspect medication #3

C.1. Name and Strength (give mfr/labeler, if known)
CYCLOPHOSPHAMIDE (CYCLOPHOSPHAMIDE)

C.2. Dose, frequency and route
750 MG/M2 1 per 3 WEEK INTRAVENOUS

C.3. Therapy dates (if unk. give duration) from/to or best estimate
15-MAR-2008 / 15-MAR-2008

C.4. Diagnosis for use (indication)
DIFFUSE LARGE B-CELL LYMPHOMA/DIFFUSE LARGE B-CELL LYMPHOMA/MEDDRA 10.1

C.5. Event abated after use stopped or dose reduced
DOESN'T APPLY

C.6. Lot # (if known)
UNK

C.7. Exp. date
UNK

C.8. Event reappeared after reintroduction
DOESN'T APPLY

C.9. NDC # - for product problems only
NA

Suspect medication #4

C.1. Name and Strength (give mfr/labeler, if known)
VINCRIStINE (VINCRIStINE)

C.2. Dose, frequency and route
1 MG/M2 1 per 3 WEEK INTRAVENOUS

C.3. Therapy dates (if unk. give duration) from/to or best estimate
15-MAR-2008 / 15-MAR-2008

C.4. Diagnosis for use (indication)
DIFFUSE LARGE B-CELL LYMPHOMA/DIFFUSE LARGE B-CELL LYMPHOMA/MEDDRA 10.1

C.5. Event abated after use stopped or dose reduced
DOESN'T APPLY

C.6. Lot # (if known)
UNK

C.7. Exp. date
UNK

C.8. Event reappeared after reintroduction
DOESN'T APPLY

C.9. NDC # - for product problems only
NA

Suspect medication #5

C.1. Name and Strength (give mfr/labeler, if known)
DOXORUBICIN (DOXORUBICIN)

C.2. Dose, frequency and route
50 MG/M2 1 per 3 WEEK INTRAVENOUS

C.3. Therapy dates (if unk. give duration) from/to or best estimate
15-MAR-2008 / 15-MAR-2008

C.4. Diagnosis for use (indication)
DIFFUSE LARGE B-CELL LYMPHOMA/DIFFUSE LARGE B-CELL LYMPHOMA/MEDDRA 10.1

C.5. Event abated after use stopped or dose reduced
DOESN'T APPLY

C.6. Lot # (if known)
UNK

C.7. Exp. date
UNK

C.8. Event reappeared after reintroduction
DOESN'T APPLY

C.9. NDC # - for product problems only
NA

Suspect medication #6

C.1. Name and Strength (give mfr/labeler, if known)
PREDNISONE (PREDNISONE) 50 MG

C.2. Dose, frequency and route
60 MG/M2 5 per 3 WEEK ORAL

C.3. Therapy dates (if unk. give duration) from/to or best estimate
15-MAR-2008 / 20-MAR-2008

C.4. Diagnosis for use (indication)
DIFFUSE LARGE B-CELL LYMPHOMA/DIFFUSE LARGE B-CELL LYMPHOMA/MEDDRA 10.1

C.5. Event abated after use stopped or dose reduced
DOESN'T APPLY

C.6. Lot # (if known)
UNK

C.7. Exp. date
UNK

C.8. Event reappeared after reintroduction
DOESN'T APPLY

C.9. NDC # - for product problems only
NA