



NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

Date: April 10, 2009

To: NCCTG Primary Clinical Research Associates

From: Sara Braun
Protocol Development Coordinator

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 Bevacizumab at a non-NCCTG institution. You may have also received this communication directly from the drug manufacturer.

270965_10Apr2009

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

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Date: 13 November 2008

Evanthia Galanis, MD
Mayo Clinic College of Medicine
200 First Street SW
Rochester, MN 55905

RE: IND Safety Report/Expedited Case Safety Report

Investigational Product(s): **Bevacizumab**

GNE MCN: **270965 Initial** Other Reference Number(s):

Dear Dr. Galanis,

Attached is a case summary of a serious and unexpected adverse drug reaction that occurred in a subject exposed to bevacizumab. Good Clinical Practice regulations require that you promptly submit a copy of this IND safety report/expedited case safety report to your Institutional Review Board or Independent Ethics Committee. File a copy of this IND safety report/expedited case safety report in your protocol file so that it is available for review during a Sponsor monitoring visit and/or regulatory audit.

In the European Economic Area (EEA) Genentech, Inc. or its designee will directly inform the Institutional Review Boards/Ethics Committees, as appropriate.

This IND safety report/expedited case safety report must be filed with your Investigator Brochure (IB) for information only. This IND safety report/expedited case safety report is not considered an addendum to your safety reference document.

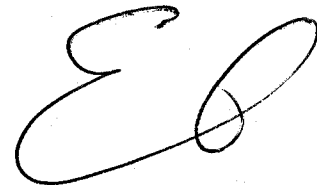
Although this adverse event has been documented and reported to the appropriate Regulatory agencies, the report does not necessarily reflect a conclusion by Genentech or the Regulatory agencies that bevacizumab contributed to the adverse event.

If questions arise, please contact the undersigned.

Sincerely,



Eric Hedrick
Medical Monitor
AVF4271s
AVF4430S



SUSPECT ADVERSE EVENT REPORT

I EVENT INFORMATION

PAGE 1 OF 7

1. PATIENT INITIALS (FIRST, LAST) (IN CONFIDENCE)	1A. COUNTRY I	2. DATE OF BIRTH			2A. AGE (YRS) 78 YR	3. SEX M	4-6. EVENT ONSET			8-12. CHECK ALL APPROPRIATE
		DA	MO	YR			DA	MO	YR	
7. DESCRIBE REACTIONS INCLUDING RELEVANT TESTS/LAB DATA 2006-005520-16. BO20603. A RANDOMIZED, DOUBLE-BLIND PLACEBO-CONTROLLED STUDY COMPARING THE EFFECT OF AVASTIN IN COMBINATION WITH MABTHERA PLUS CHOP, AND MABTHERA PLUS CHOP ALONE, ON PROGRESSION-FREE SURVIVAL IN PREVIOUSLY UNTREATED PATIENTS WITH CD20-POSITIVE DIFFUSE LARGE B-CELL LYMPHOMA. A 78 YEAR OLD MALE PATIENT EXPERIENCED FATAL SEPTIC SHOCK WHILST PARTICIPATING IN THE ABOVE STUDY. HIS MEDICAL HISTORY WAS SIGNIFICANT FOR CHRONIC OBSTRUCTIVE PULMONARY DISEASE. HIS CONCOMITANT MEDICATIONS INCLUDED OMEPRAZOLE, ACICLOVIR, ITRACONAZOLE, FUROSEMIDE AND TRAMADOL. ON 04 JUNE 2008, INTRAVENOUS (IV) BLINDED BEVACIZUMAB EVERY 21 DAYS WAS STARTED. ON NEXT DAY, I.V RITUXIMAB (550 MG), I.V DOXORUBICIN (73 MG), I.V CYCLOPHOSPHAMIDE (1100 MG), I.V VINCRIStINE (2 MG) WITH							<input checked="" type="checkbox"/> PATIENT DIED <input type="checkbox"/> INVOLVED OR PROLONGED INPATIENT HOSPITALIZATION <input type="checkbox"/> INVOLVED SIGNIFICANT DISABILITY OR INCAPACITY? <input type="checkbox"/> LIFE THREATENING			
CONTINUED										

II SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUGS (INCLUDE GENERIC NAME) BEVACIZUMAB (BEVACIZUMAB)		20. DID EVENT ABATE AFTER STOPPING DRUGS? <input type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> NA
CONTINUED		
15. DAILY DOSE(S) / STRENGTH 1 X per 21 DAY /	16. ROUTE(S) OF ADMINISTRATION INTRAVENOUS	21. DID EVENT REAPPEAR AFTER REINTRODUCTION? <input type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> NA
17. INDICATION(S) FOR USE CD20-POSITIVE DIFFUSE LARGE B-CELL LYMPHOMA/DIFFUSE LARGE B-CELL LYMPHOMA/MEDDRA 11.1		
18. THERAPY DATES (FROM/TO) FROM 4-JUN-2008 TO 28-OCT-2008	19. THERAPY DURATION 147 DAYS	

III CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION (EXCLUDE THOSE USED TO TREAT EVENT) OMEPRAZOL (OMEPRAZOLE) 27-OCT-2008 / 28-OCT-2008	CONTINUED
23. OTHER RELEVANT HISTORY (E.G. DIAGNOSES, ALLERGIES, PREGNANCY, WITH LMP, ETC.) MEDICAL HISTORY TERM(S): CD20-POSITIVE DIFFUSE LARGE B-CELL LYMPHOMA/DIFFUSE LARGE B-CELL LYMPHOMA/MEDDRA 11.1	CONTINUED

IV MANUFACTURER INFORMATION

24. NAME AND ADDRESS OF MANUFACTURER	
24b. MFR. CONTROL NO. 594311	
24c. DATE RECEIVED BY MANUFACTURER 29-OCT-2008	24d. REPORT SOURCE <input checked="" type="checkbox"/> STUDY <input type="checkbox"/> LITERATURE <input checked="" type="checkbox"/> HEALTH PROFESSIONAL
25a. REPORT TYPE <input type="checkbox"/> INITIAL <input type="checkbox"/> FOLLOWUP	

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

7. DESCRIBE REACTIONS INCLUDING RELEVANT TESTS/LAB DATA - continued

THE FREQUENCY OF EVERY 21 DAYS AND ORAL PREDNISONE (100 MG) WERE STARTED. ON 27 OCTOBER 2008, THE PATIENT DEVELOPED SEPTIC SHOCK AND HE WAS HOSPITALISED TO EMERGENCY DEPARTMENT FOR FEVER AND ABDOMINAL PAIN. HE REFERRED DIARRHEA IN THE LAST TWO DAYS WITH SEVERE HYPOREXIA FOR WHICH HE HAD NOT TAKEN HIS ORAL THERAPY. BLOOD TESTS IN E.R SHOWED NEUTROPENIA GRADE III, ANAEMIA GRADE III, THROMBOCYTOPENIA GRADE IV. CHEST X-RAY PERFORMED SHOWED RIGHT PULMONARY DENSIFICATION WITH PLEURAL EFFUSION SUGGESTIVE FOR PNEUMONIA. HAEMOCULTURE WERE PERFORMED ON 27 OCTOBER 2008 WHICH SHOWED POSITIVE FOR GRAM NEGATIVE BACILLUS. WBC WAS 0.96 X1000/MMC (NORMAL RANGE: 4.5-11) AND HAEMOGLOBIN WAS 6.2 G/DL (NORMAL RANGE: 13-17). EMPYRICAL ANTIBIOTIC TREATMENT WAS COMMENCED WITH MEROPENEM (MERRAM) 3 GRAM, AMIKACIN (BBK8) 500 MG, METRONIDAZOLE (DEFLAMON) 1500 MG, GRANULOKINE (30 MU) AND ANTITHROMBIN (KYBERNIN) 1000 UI. G CSF STIMULATION WAS GUARANTEED. BLOOD AND PLATELETS PACKS WERE TRANSFUSED. ON 28 OCTOBER 2008, FEVER DISAPPEARED AND NEUTROPENIA WAS RESOLVED. HOWEVER THE PATIENT DEVELOPED PULMONARY OEDEMA WHICH WAS NOT RESPONSIVE TO DIURETIC TREATMENT. AT THE SAME TIME, COAGULATION PARAMETER WORSENERD WITH PT PROLONGATION 2.06 RATIO (NORMAL RANGE: 0.8-1.25) AND C-REACTIVE PROTEIN WAS 33.48 MG/DL (NORMAL RANGE: LESS THAN 0.8). ON THE SAME DAY, THE PATIENT DEVELOPED RAPID DECLINE OF RESPIRATORY FUNCTION NOT RESPONSIVE TO OXYGEN THERAPY AND THE PATIENT DIED DUE TO SEPTIC SHOCK.

AT THE TIME OF DEATH, THERAPY OF BLINDED BEVACIZUMAB, RITUXIMAB, DOXORUBICIN, CYCLOPHOSPHAMIDE, VINCRISTINE AND PREDNISONE WAS MAINTAINED.

THE INVESTIGATOR CONSIDERED THE FATAL EVENT OF SEPTIC SHOCK TO BE RELATED TO BLINDED BEVACIZUMAB, RITUXIMAB, DOXORUBICIN, CYCLOPHOSPHAMIDE, VINCRISTINE AND PREDNISONE AND TO OTHER PNEUMONIA, COLITIS AND NEUTROPENIA. NO FURTHER INFORMATION WAS AVAILABLE.

THE DRUG CODE WAS BROKEN DUE TO REGULATORY REQUIREMENTS ON 07 NOVEMBER 2008. THE PATIENT RECEIVED BEVACIZUMAB 15MG/KG EVERY 3 WEEKS.

ANALYSIS OF SIMILAR EVENTS

THE INDEX CASE (MCN 594311) IS A 78 YEAR OLD MALE PATIENT WHO EXPERIENCED FATAL SEPTIC SHOCK WHILST PARTICIPATING IN A RANDOMIZED, DOUBLE-BLIND PLACEBO-CONTROLLED STUDY COMPARING THE EFFECT OF AVASTIN IN COMBINATION WITH MABTHERA PLUS CHOP, AND MABTHERA PLUS CHOP ALONE, ON PROGRESSION-FREE SURVIVAL IN PREVIOUSLY UNTREATED PATIENTS WITH CD20-POSITIVE DIFFUSE LARGE B-CELL LYMPHOMA. HIS MEDICAL HISTORY WAS SIGNIFICANT FOR CHRONIC OBSTRUCTIVE PULMONARY DISEASE. HIS CONCOMITANT MEDICATIONS INCLUDED OMEPRAZOLE, ACICLOVIR, ITRACONAZOLE, FUROSEMIDE AND TRAMADOL.

ON 04 JUNE 2008, INTRAVENOUS (IV) BLINDED BEVACIZUMAB EVERY 21 DAYS WAS STARTED. ON NEXT DAY, I.V RITUXIMAB (550 MG), I.V DOXORUBICIN (73 MG), I.V CYCLOPHOSPHAMIDE (1100 MG), I.V VINCRISTINE (2 MG) WITH THE FREQUENCY OF EVERY 21 DAYS AND ORAL PREDNISONE (100 MG) WERE STARTED. ON 27 OCTOBER 2008, THE PATIENT DEVELOPED SEPTIC SHOCK AND HE WAS HOSPITALISED TO THE EMERGENCY DEPARTMENT FOR FEVER AND ABDOMINAL PAIN. HE WAS REFERRED WITH DIARRHEA IN THE LAST TWO DAYS WITH SEVERE HYPOREXIA FOR WHICH HE HAD NOT TAKEN HIS ORAL THERAPY. BLOOD TESTS IN ER SHOWED NEUTROPENIA GRADE III, ANAEMIA GRADE III, THROMBOCYTOPENIA GRADE IV. CHEST X-RAY PERFORMED SHOWED RIGHT PULMONARY DENSIFICATION WITH PLEURAL EFFUSION SUGGESTIVE OF PNEUMONIA. HAEMOCULTURE WERE PERFORMED ON 27 OCTOBER 2008 WHICH SHOWED POSITIVE FOR GRAM NEGATIVE BACILLUS. WBC WAS 0.96 X1000/MMC (NORMAL RANGE: 4.5-11) AND HAEMOGLOBIN WAS 6.2 G/DL (NORMAL RANGE: 13-17). EMPYRICAL ANTIBIOTIC TREATMENT WAS COMMENCED WITH MEROPENEM (MERRAM) 3 GRAM, AMIKACIN (BBK8) 500 MG, METRONIDAZOLE (DEFLAMON) 1500 MG, GRANULOKINE (30 MU) AND ANTITHROMBIN (KYBERNIN) 1000 UI. G CSF STIMULATION WAS GUARANTEED. BLOOD AND PLATELETS PACKS WERE TRANSFUSED.

ON 28 OCTOBER 2008, FEVER DISAPPEARED AND NEUTROPENIA WAS RESOLVED. HOWEVER THE PATIENT DEVELOPED PULMONARY OEDEMA WHICH WAS NOT RESPONSIVE TO DIURETIC TREATMENT. AT THE SAME TIME, COAGULATION PARAMETER WORSENERD WITH PT PROLONGATION 2.06 RATIO (NORMAL RANGE: 0.8-1.25) AND C-REACTIVE PROTEIN WAS 33.48 MG/DL (NORMAL RANGE: LESS THAN 0.8). ON THE SAME DAY, THE PATIENT DEVELOPED RAPID DECLINE OF RESPIRATORY FUNCTION NOT RESPONSIVE TO OXYGEN THERAPY AND THE PATIENT DIED DUE TO SEPTIC SHOCK.

AT THE TIME OF DEATH, THERAPY OF BLINDED BEVACIZUMAB, RITUXIMAB, DOXORUBICIN, CYCLOPHOSPHAMIDE, VINCRISTINE AND PREDNISONE WAS MAINTAINED. THE INVESTIGATOR CONSIDERED THE FATAL EVENT OF SEPTIC SHOCK TO BE RELATED TO BLINDED BEVACIZUMAB, RITUXIMAB, DOXORUBICIN, CYCLOPHOSPHAMIDE, VINCRISTINE AND PREDNISONE AND TO OTHER PNEUMONIA, COLITIS AND NEUTROPENIA. NO FURTHER INFORMATION WAS AVAILABLE. THE DRUG CODE WAS BROKEN DUE TO REGULATORY REQUIREMENTS ON 07 NOVEMBER 2008. THE PATIENT RECEIVED BEVACIZUMAB 15MG/KG EVERY 3 WEEKS.

ON 10 NOVEMBER 2008 THE ROCHE SAFETY DATABASE WAS SEARCHED FOR BEVACIZUMAB CASES WITH A

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MEDDRA PREFERRED TERM OF SEPTIC SHOCK OUTCOME DEATH. THE FOLLOWING 54 CASES INCLUDING THE INDEX CASE WERE IDENTIFIED:

MCNS: 354766, 367017, 367982, 374505, 385596, 386133, 390131, 394791, 396914, 399087, 404996, 405119, 409650, 411247, 419128, 423632, 425062, 426202, 426213, 441081, 441735, 460445, 470218, 484351, 485588, 491057, 495735, 499676, 501055, 506345, 510196, 510383, 512074, 514924, 516570, 520978, 524570, 525827, 527575, 527828, 539702, 542615, 548600, 553550, 556864, 559590, 575643, 577226, 577586, 578212, 583370, 585080, 585504, 587592, 594311.

THE DRUG WAS USED FOR THE FOLLOWING INDICATIONS: 28 COLORECTAL CANCER METASTATIC, 3 PANCREATIC CARCINOMA METASTATIC, 5 NON-SMALL CELL LUNG CANCER, 1 ACUTE MYELOID LEUKAEMIA, 1 RENAL CELL CARCINOMA, 4 DIFFUSE LARGE B-CELL LYMPHOMA, 8 BREAST CANCER METASTATIC, 1 RECTAL CANCER METASTATIC, 1 RECTAL CANCER RECURRENT, 1 GASTRIC CANCER, 1 DRUG USE FOR UNKNOWN INDICATION. THE PATIENTS AGES RANGED BETWEEN 40 AND 81 YEARS. 5 PATIENTS WERE BETWEEN THE AGE OF 40 AND 49, 14 BETWEEN 50 AND 59 YEARS, 10 BETWEEN THE AGE OF 60 AND 69 YEARS, 16 BETWEEN 70 AND 75 YEARS, 8 BETWEEN 76 AND 79 YEARS AND ONE PATIENT WAS 81 YEARS OLD. THE MAJORITY OF THE PATIENTS HAD MULTIPLE CONCOMITANT MEDICATIONS AND CHEMOTHERAPY AS CONFOUNDERS.

AFTER REVIEW OF THE CLINICAL DETAILS OF THE INDEX CASE AND SIMILAR PREVIOUS CASES, THE SPONSOR DOES NOT BELIEVE THAT CHANGES TO THE CONDUCT OF THE CLINICAL TRIAL ARE WARRANTED IN RESPONSE TO THIS CASE REPORT.

ADVERSE EVENT TERM(S):

SEPTIC SHOCK/SEPTIC SHOCK/MEDDRA 11.1

RELEVANT TEST(S)/LAB DATA:

Lab Test Name: C-REACTIVE PROTEIN
Date (Day-Month-Year): 28-OCT-2008
Lab Result (Low-High Unit): 33-48 mg/dL
Normal (Low-High): -
Lab Result Text: NORMAL RANGE: <0.8

Lab Test Name: CHEST X-RAY
Date (Day-Month-Year): --
Lab Result (Low-High Unit): -
Normal (Low-High): -
Lab Result Text:

Lab Test Name: CULTURE NOS
Date (Day-Month-Year): 27-OCT-2008
Lab Result (Low-High Unit): -
Normal (Low-High): -
Lab Result Text: LAB TEST: HAEMOCULTURE
RESULT: + FOR G -VE

Lab Test Name: HAEMOGLOBIN
Date (Day-Month-Year): 27-OCT-2008
Lab Result (Low-High Unit): 6.2- g/dL
Normal (Low-High): 13-17
Lab Result Text:

Lab Test Name: PROTHROMBIN TIME
Date (Day-Month-Year): 28-OCT-2008
Lab Result (Low-High Unit): 2.06-
Normal (Low-High): 0.8-1.25
Lab Result Text: UNIT: RATIO

Lab Test Name: WBC
Date (Day-Month-Year): 27-OCT-2008
Lab Result (Low-High Unit): 0.96-
Normal (Low-High): 4.5-11
Lab Result Text: UNIT: X1000/MMC

CHEST X-RAY

RESULT: RIGHT PULMONARY DENAPICATION WITH PLEURAL EFFUSION SUGGESTIVE FOR PNEUMONIA. BLOOD TESTS IN E.R SHOWED NEUTROPENIA GRADE III, ANAEMIA GRADE III, THROMBOCYTOPENIA GRADE IV.

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CONTINUATION SHEET FOR CIOMS FORM

MFR. CONTROL NO. 594311

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14-19. SUSPECT DRUGS - continued

Suspect Drug: RITUXIMAB
 Generic Name: RITUXIMAB
 Daily Dose(s)/Strength: 550 MG 1 X per 21 DAY /
 Route: INTRAVENOUS
 Indication: CD20-POSITIVE DIFFUSE LARGE B-CELL LYMPHOMA/DIFFUSE LARGE
 B-CELL LYMPHOMA/MEDDRA 11.1
 Therapy From Date: 5-JUN-2008
 Therapy To Date: 28-OCT-2008
 Therapy Duration: 146 DAYS

Suspect Drug: DOXORUBICIN
 Generic Name: DOXORUBICIN
 Daily Dose(s)/Strength: 73 MG 1 X per 21 DAY /
 Route: INTRAVENOUS
 Indication: CD20-POSITIVE DIFFUSE LARGE B-CELL LYMPHOMA/DIFFUSE LARGE
 B-CELL LYMPHOMA/MEDDRA 11.1
 Therapy From Date: 5-JUN-2008
 Therapy To Date: 28-OCT-2008
 Therapy Duration: 146 DAYS

Suspect Drug: CYCLOPHOSPHAMIDE
 Generic Name: CYCLOPHOSPHAMIDE
 Daily Dose(s)/Strength: 1100 MG 1 X per 21 DAY /
 Route: INTRAVENOUS
 Indication: CD20-POSITIVE DIFFUSE LARGE B-CELL LYMPHOMA/DIFFUSE LARGE
 B-CELL LYMPHOMA/MEDDRA 11.1
 Therapy From Date: 5-JUN-2008
 Therapy To Date: 28-OCT-2008
 Therapy Duration: 146 DAYS

Suspect Drug: VINCRISTINE
 Generic Name: VINCRISTINE
 Daily Dose(s)/Strength: 2 MG 1 X per 21 DAY /
 Route: INTRAVENOUS
 Indication: CD20-POSITIVE DIFFUSE LARGE B-CELL LYMPHOMA/DIFFUSE LARGE
 B-CELL LYMPHOMA/MEDDRA 11.1
 Therapy From Date: 5-JUN-2008
 Therapy To Date: 28-OCT-2008
 Therapy Duration: 146 DAYS

Suspect Drug: PREDNISONE
 Generic Name: PREDNISONE
 Daily Dose(s)/Strength: 100 MG /
 Route: ORAL
 Indication: CD20-POSITIVE DIFFUSE LARGE B-CELL LYMPHOMA/DIFFUSE LARGE
 B-CELL LYMPHOMA/MEDDRA 11.1
 Therapy From Date: 5-JUN-2008
 Therapy To Date: 28-OCT-2008
 Therapy Duration: 146 DAYS

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION - continued

ACICLOVIR
 (ACYCLOVIR)
 27-OCT-2008 / 28-OCT-2008

ITRACONAZOLE
 (ITRACONAZOLE)
 27-OCT-2008 / 28-OCT-2008

FUROSEMIDE
 (FUROSEMIDE)
 27-OCT-2008 / 28-OCT-2008

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TRAMADOL
(TRAMADOL HYDROCHLORIDE)
27-OCT-2008 / 28-OCT-2008

23. OTHER RELEVANT HISTORY - continued

CHRONIC OBSTRUCTIVE PULMONARY DISEASE/CHRONIC OBSTRUCTIVE PULMONARY
DISEASE/MEDDRA 11.1

CIOMS TEXT

A POSSIBLE ALTERNATIVE EXPLANATION FOR THE FATAL EVENT OF SEPTIC SHOCK IN THIS PATIENT
RECEIVING BEVACIZUMAB AND RITUXIMAB WAS PNEUMONIA AND COLITIS.
BASED UPON THIS SINGLE REPORT, THERE IS NO CHANGE IN THE OVERALL SAFETY PROFILE OF THE
PRODUCT.

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CONTINUATION SHEET FOR CIOMS FORM

MFR. CONTROL NO. 594311

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REPORTER INFORMATION

Reporter:
 Name:
 Organisation:
 Address 1:
 Address 2:
 Address 3:
 Address 4:
 City:
 Country:
 Address Phone:
 Address Fax:
 Representative Phone:
 Representative Fax:
 Reporter Type:
 Occupation:

CLINICAL TRIAL INFORMATION

Clin. Study Id: BO20603
 Clin. CRTN
 Design and Phase: DOUBLE BLIND III
 Clin. Patient Id:
 Clin. Investigator Id:

DRUG-EVENT INFORMATION

Event: SEPTIC SHOCK/SEPTIC SHOCK/MEDDRA 11.0
 SOC: INFECTIONS AND INFESTATIONS
 Outcome: OUTCOME DEATH
 Severity:
 Seriousness: DEATH
 Onset Date: 27 OCT 2008
 Resolved Date:
 Duration Reported:

Relation To: BLINDED BEVACIZUMAB
 Unblinded: BEVACIZUMAB
 Drug Continued: MAINTAINED
 AE Abated: NOT APPLICABLE
 AE Reappeared: NOT APPLICABLE
 Labeled US: NOT APPLICABLE
 Labeled Local: NOT APPLICABLE - I
 Labeled IB: NO
 Labeled SPC: NO
 Labeled Core: NO
 Drug Related(Comp): YES
 Drug Related(Rept): YES
 Latency Reported (First Dose):
 Latency Reported (Last Dose):

Relation To: RITUXIMAB
 Drug Continued: MAINTAINED
 AE Abated: NOT APPLICABLE
 AE Reappeared: NOT APPLICABLE
 Labeled US: NOT APPLICABLE
 Labeled Local: NOT APPLICABLE - I
 Labeled IB: YES
 Labeled SPC: NO
 Labeled Core: NO
 Drug Related(Comp): YES
 Drug Related(Rept): YES
 Latency Reported: (First Dose)
 Latency Reported (Last Dose):

Relation To: DOXORUBICIN
 Drug Continued: MAINTAINED
 AE Abated: NOT APPLICABLE
 AE Reappeared: NOT APPLICABLE

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CONTINUATION SHEET FOR CIOMS FORM

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Labeled US: NOT APPLICABLE
 Labeled Local: NOT APPLICABLE - I
 Labeled IB: NOT APPLICABLE
 Labeled SPC: NOT APPLICABLE
 Labeled Core: NOT APPLICABLE
 Drug Related(Comp): YES
 Drug Related(Rept): YES
 Latency Reported: (First Dose)
 Latency Reported (Last Dose):

Relation To: CYCLOPHOSPHAMIDE
 Drug Continued: MAINTAINED
 AE Abated: NOT APPLICABLE
 AE Reappeared: NOT APPLICABLE
 Labeled US: NOT APPLICABLE
 Labeled Local: NOT APPLICABLE - I
 Labeled IB: NOT APPLICABLE
 Labeled SPC: NOT APPLICABLE
 Labeled Core: NOT APPLICABLE
 Drug Related(Comp): YES
 Drug Related(Rept): YES
 Latency Reported: (First Dose)
 Latency Reported (Last Dose):

Relation To: VINCRISTINE
 Drug Continued: MAINTAINED
 AE Abated: NOT APPLICABLE
 AE Reappeared: NOT APPLICABLE
 Labeled US: NOT APPLICABLE
 Labeled Local: NOT APPLICABLE - I
 Labeled IB: NOT APPLICABLE
 Labeled SPC: NOT APPLICABLE
 Labeled Core: NOT APPLICABLE
 Drug Related(Comp): YES
 Drug Related(Rept): YES
 Latency Reported: (First Dose)
 Latency Reported (Last Dose):

Relation To: PREDNISONE
 Drug Continued: MAINTAINED
 AE Abated: NOT APPLICABLE
 AE Reappeared: NOT APPLICABLE
 Labeled US: NOT APPLICABLE
 Labeled Local: NOT APPLICABLE - I
 Labeled IB: NOT APPLICABLE
 Labeled SPC: NOT APPLICABLE
 Labeled Core: NOT APPLICABLE
 Drug Related(Comp): YES
 Drug Related(Rept): YES
 Latency Reported: (First Dose)
 Latency Reported (Last Dose):

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