Southwest
Oncology Group
A National Clinical Research Group

May 15, 2001

TO: ALL SOUTHWEST ONCOLOGY GROUP, CCOP, AFFILIATE AND UCOP MEDICAL ONCOLOGISTS, RADIATION ONCOLOGISTS AND PATHOLOGISTS

FROM: Southwest Oncology Group Operations Office

RE: Adverse Events Possibly Associated Rituximab

MEMORANDUM

Attached please find two memoranda from the National Cancer Institute regarding possible adverse events associated with rituximab in studies sponsored under the Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI) Investigational New Drug (IND) application for this agent.

ACTIVE PROTOCOLS

S0014 **S0019** **S0016** **E4494**

CLOSED PROTOCOLS

S9800

Protocol amendments are not necessary at this point, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. **Please forward these memoranda and reports to your Institutional Review Board (IRB) immediately for review**. Should any further information regarding these adverse events be made available, it will be forwarded to you.

A copy of this correspondence should be attached to the front of each of the above-noted protocols and kept in your files for future reference.

cc: Southwest Oncology Group Statistical Center
Nickey McCasland, R.N.
Richard I. Fisher, M.D.
Thomas P. Miller, M.D.
Oliver Press, M.D., Ph.D.
David Maloney, M.D., Ph.D.

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

National Institutes of Health
National Cancer Institute
Bethesda, Maryland 20892

DATE: December 18, 2000

FROM: Thomas Davis, M.D., Senior Clinical Investigator, Investigational Drug Branch, CTEP, DCTD, NCI

SUBJECT: Notification of MoAb: IDEC-C2B8 Safety Reports, AE # 1579247

TO: Investigators Using MoAb: IDEC-C2B8, IND 7028

The purpose of this memorandum is to provide investigators with a copy of reports of adverse events that occurred in association with MoAb: IDEC-C2B8 in studies sponsored under the Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI) Investigational New Drug (IND) application for this agent. There is no revision to the Agent Specific Expected Adverse Event List at this time and, therefore, no revision to the protocol and the informed consent form is required by the NCI. **However, please submit this information to your Institutional Review Board as required by FDA regulations.** Please continue to report events that are not on the Agent Specific Expected Adverse Event List according to the adverse event reporting guidelines in your protocol.

The Adverse Event Assessment that describes the following adverse event is attached:

A 65-year-old male with non-Hodgkin's lymphoma (NHL) metastatic to the bones, spleen, liver, and gastrointestinal tract experienced Grade 5 pneumonitis/pulmonary infiltrates. He was hospitalized and found to be hypoxic. The patient underwent a bronchoscopy with a lung biopsy, which revealed hypersensitivity pneumonitis. Bronchial washings were positive for *Candida albicans*. He was treated with multiple intravenous antibiotics and oral prednisone. The patient improved and was given a course of CHOP. Short thereafter, he experienced a recurrence of symptoms. The patient became leukopenic, thrombocytopenic, cachectic, and tachypneic, requiring intubation. Bone marrow cultures were positive for methicillen-resistent *Staphylococcus aureus*. Laboratory testing revealed many abnormal values. The patient became febrile and hypotensive. He was treated with broad spectrum antibiotics, dopamine drip, and Levaphed. The patient's condition worsened, and he developed bleeding from the gastrointestinal tract and multi-organ failure. He expired due to cardiac arrest under a Do Not Resuscitate order. A post-mortem examination was significant for extensive, bilateral intra-alveolar pulmonary hemorrhage, extensive anasarca in all body cavities, acute hepatic necrosis, splenomegaly, generalized purpuric and petechial lesions, and no grossly identifiable evidence of residual lymphoma.

Attachments: Adverse Events Assessment

cc: L. Grochow, M.D.
J. Zwiebel, M.D.
T. Davis, M.D.
D. Shoemaker, Ph.D.
M. Montello, M.S., R.Ph.
M. Christian, M.D.
A. Fallavollita, M.S.
A. Grillo-Lopez, M.D., IDEC
C. White, M.D., IDEC
A. Wei, IDEC
R. Cheiken, R.N., B.S.N., TRI
C. Campbell, M.S., TRI

ADVERSE EVENTS ASSESSMENT

IND 7028	ADVERSE EXPERIENCE REPORT NO. 11
NSC 687451	IND Safety Report:
MoAb: IDEC-C2B8 (Rituximab)	Events: **Gr. 5: Pneumonitis/pulmonary infiltrates**
	Protocol: **E4494**
AE 15792447	Date Protocol Filed: **December 12, 1997**

This patient is a 65-year-old male with non-Hodgkin's lymphoma (NHL) metastatic to the bones, spleen, liver, and gastrointestinal tract who died while on a phase 3 study involving the investigational agent rituximab in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP). He started treatment on July 13, 2000 and began his fifth course on October 11, 2000, with intravenous doses of rituximab 375 mg/m^2 (total dose 2306.25 mg) 48 to 72 hours prior to cyclophosphamide 750 mg/m^2 (total dose 6905 mg), doxorubicin 50 mg/m^2 (total dose 461.5 mg), and vincristine 1.4 mg/m^2 (12 mg) on day 1, and oral prednisone 100 mg (total dose 4550 mg), days 1-5, every 21 days. Rituximab was not given during the fourth course.

The patient was admitted to the hospital after receiving his fifth course of treatment with complaints of generalized weakness, low grade fevers (approximately 100° F), and a dry cough. He had also been experiencing weight loss over time. Upon admission, the patient was found to be hypoxic with an arterial oxygen pressure (PO_2) of 54 mmHg. On October 30, 2000, the patient underwent a bronchoscopy with lung biopsy and bronchoalveolar lavage (BAL). Bronchial washings were negative for *Pneumocystis carinii* pneumonia and positive for *Candida albicans*. The lung biopsy revealed hypersensitivity pneumonitis. The patient was treated with multiple intravenous antibiotics and oral prednisone 60 mg every day for 3-4 days with clinical improvement. He began to ambulate and reported improvement with breathing.

The patient was given an additional course of CHOP from November 3-7, 2000. However, he soon experienced a recurrence of generalized weakness, anorexia, shortness of breath, and a dry cough. Laboratory values showed a white blood cell count (WBC) of 0.4 × 10^9/L and a platelet count of 50,000/mm^3 on November 12, 2000. He became progressively cachectic and tachypneic, requiring intubation. Bone marrow cultures, obtained on November 16, 2000, showed methicillen-resistant *Staphylococcus aureus* (MRSA), and he was restarted on intravenous broad spectrum antibiotics. On November 24, 2000, laboratory values revealed WBC 16.3 4 × 10^9/L, platelet count 51,700/mm^3, hemoglobin 6.2 g/dL, hematocrit 19.2%, prothrombin time (PT) 16.5 seconds, partial thromboplastin time (PTT) 46.2 seconds, creatinine 1.4 mg/dL, blood urea nitrogen (BUN) 54 mg/dL, and total bilirubin 5.5 mg/dL. The PT and PTT peaked at 18.0 seconds and 61.7 seconds, respectively by November 25, 2000. He became febrile and hypotensive. A dopamine drip and Levaphed were initiated. On November 27, 2000, laboratory values showed WBC 17.2 × 10^9/L, platelet count 78,200/mm^3, hemoglobin 9.2 g/dL, hematocrit 27.0%, PT 16.5 seconds, PTT 45.9 seconds, creatinine 2.7 mg/dL, BUN 103 mg/dL, and total bilirubin 9.0 mg/dL. Of note: the patient's past medical history is significant for Hepatitis C.

The patient developed bleeding from the gastrointestinal tract and multi-organ failure. A Do Not Resuscitate (DNR) status was obtained. He experienced cardiac arrest and died on November 28, 2000. The post-mortem examination was significant for extensive, bilateral intra-alveolar

pulmonary hemorrhage; extensive anasarca in all body cavities; acute hepatic necrosis; splenomegaly; generalized purpuric and petechial lesions; and no grossly identifiable evidence of residual viable lymphoma.

There have been 3 reported cases of pneumonitis associated with rituximab administration under this IND. This is a previously known, but an unusually severe reaction with a possible causal relationship attributed to the investigational agent, CHOP therapy, and the presence of an infection. This event is considered unlikely related to the patient's disease.

	IND Drug (Rituximab)	Non-IND Drug(s) (CHOP)	Disease (NHL)	Other (Infection)
Unrelated				
Unlikely			X	
Possible	X	X		X
Probable				
Definite				

Date: 12/20/00 Signature:

Thomas Davis, M.D.
(IDB Monitor for Rituximab)

If this assessment is changed, we will notify your office.

cc: Antonio J. Grillo-Lopez, M.D.
Christine A. White, M.D.
Alice M. Wei
IDEC Pharmaceuticals Corporation

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

National Institutes of Health
National Cancer Institute
Bethesda, Maryland 20892

DATE: January 25, 2001

FROM: Helen Chen, M.D., Senior Clinical Investigator, Investigational Drug Branch, CTEP, DCTD, NCI

SUBJECT: Notification of MoAb: IDEC-C2B8 (Rituximab) Safety Reports, AE # 1403372

TO: Investigators Using Rituximab, IND 7028

The purpose of this memorandum is to provide investigators with a copy of reports of adverse events that occurred in association with rituximab in studies sponsored under the Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI) Investigational New Drug (IND) application for this agent. There is no revision to the Agent Specific Expected Adverse Event List at this time and, therefore, no revision to the protocol and the informed consent form is required by the NCI. **However, please submit this information to your Institutional Review Board as required by FDA regulations.** Please continue to report events that are not on the Agent Specific Expected Adverse Event List according to the adverse event reporting guidelines in your protocol.

The Adverse Events Assessment that describes the following adverse event is attached:

A 70-year-old male with chronic lymphocytic leukemia (CLL) experienced Grade 4 infection with neutropenia, lymphopenia, thrombocytopenia, bone marrow hypocellularity, and hypogammaglobulinemia 2.5 months following completion of the investigational protocol (6 months after the fludarabine + rituximab induction, and 2.5 months after consolidation with rituximab alone). The patient presented with pancytopenia with nadirs of ANC 180, platelet count 73,000/mm3, as well as lymphopenia and hypogammaglobulinemia. Flow cytometric analysis of the peripheral blood showed absence of B-cells and no evidence of CLL. A bone marrow study revealed significant hypocellularity (10% cellularity), markedly decreased and left-shifted granulopoiesis but normal number of megakaryocytes and maturation of erythroid cells, and no evidence of monoclonal B-cells. The patient was admitted to the hospital the next day with hypotension and *Pseudomonas aeruginosa* sepsis; during the hosptial stay he was also diagnosed with *Echovirus* in CSF indicating possible viral meningitis. The patient is still hospitalized at the time of this report. The hematological parameters partially recovered 16 days after the hospital admission. The marrow hypocellularity and neutropenia represent a significant decline from the levels at the beginning of consolidative Rituximab; however, no CBC was repeated during rituximab therapy until the current event.

Attachments: Adverse Events Assessment

cc: L. Grochow, M.D.
J. Zwiebel, M.D.
H. Chen, M.D.
D. Shoemaker, Ph.D.
M. Montello, M.S., R.Ph.
M. Christian, M.D.
A. Fallavollita, M.S.
C. A. White, M.D., IDEC Pharmaceutical Corp.
B. Dallaire, Pharm. D., IDEC Pharmaceutical Corp.
A. M. Wei, IDEC Pharmaceutical Corp.
R. Cheiken, R.N., B.S.N., TRI
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ADVERSE EVENTS ASSESSMENT

IND 7028

NSC 687451
Rituximab (C2B8 antibody)

AE 1403372

ADVERSE EXPERIENCE REPORT NO. 12
IND Safety Report:
Events:
1. **Gr. 4: Infection (documented clinically or microbiologically) with grade 3 or 4 neutropenia (ANC < 1.0 x 10^9/L)**
2. **Gr. 4: Bone marrow cellularity**
3. **Gr. 3 : Lymphopenia**
4. **Grade 2: Thrombocytopenia**

Protocol: **CALGB-9712**
Date Protocol Filed: **February 18, 1998**

The patient is a 70-year-old male with chronic lymphocytic leukemia (CLL) who developed arthralgia, myalgia, supraventricular arrhythmia, confusion, infection with grade ≥3 neutropenia, lymphopenia, and bone marrow hypocellularity on a phase 2 study involving the investigational agent rituximab (C2B8 antibody) in combination with fludarabine. He started his first course of treatment on January 3, 2000, with rituximab 375 mg/m^2 on day 1 and fludarabine 25 mg/m^2 on days 1-5 of weeks 1, 5, 9, 13, 17, and 21 (induction phase), ending June 16, 2000. Starting September, the patient received rituximab at 375 mg/m^2 weekly for 4 weeks (consolidation phase), ending October 9, 2000. Protocol treatment was complete at this time, and based on bone marrow analysis, the patient was free from CLL.

In mid-November 2000, the patient started experiencing myalgia. He also had an episode of recurrent atrial fibrillation and was put on Coumadin. On December 29, 2000, he was admitted to the hospital with diffuse pain over large muscle groups of limbs, chest wall, and hips, decreased hearing, and depression. Laboratory analysis revealed neutropenia (ANC 315) and mild anemia (see below). Flow cytometric analysis of the peripheral blood cells showed predominance of T cells and absence of B-lymphocytes and no evidence of CLL. A bone marrow aspirate and biopsy taken on December 29, 2000 showed significant hypocellularity (10% cellularity), markedly decreased and left-shifted granulopoiesis but normal number of megakaryocytes and maturation of erythroid cells. The patient was also found to have hypogammablobulinemia. The marrow hypocellularity and neutropenia represent a significant decline from the levels at the beginning of consolidative Rituximab; however, according to the site, no CBC was repeated during rituximab therapy until the current event. A summary of BM and peripheral blood parameters is as follows:

	12/99 baseline	4/00 after Fludarabine /Rituximab	9/00 Before consolidative rituximab	12/29/00 (last rituximab 10/9/01)	Nadir 12/30/00-1/4/01
CBC (/mm3)					
WBC	191,000 (CLL)	1,800	2,300	2,100	500
ANC		1,350	1,840	315	180
Lymphocyte				1,533	360
Hb		11.7	10.4	10.3	7.9
Platelet		53,000	140,000	151,000	73
BM					
Cellularity	95% CLL	30-40%	20-30%	10%	
CLL	+	-	-	-	

ADVERSE EVENTS ASSESSMENT

On December 30, 2000, the patient became feverish, hypotensive and had tachycardia. He was transferred to the Intensive Care Unit and treated for suspected sepsis. A blood culture taken that day was positive for *Pseudomonas aeruginosa*. His condition stabilized until January 4, 2001, when his mental status suddenly changed with agitation and confusion. A lumbar puncture was performed and CSF culture was positive for *Echovirus* indicating the possibility of viral meningitis. During 12/20/00 to 1/4/01, the patient's hemotologic indices reached the nadir of WBC 500, ANC 180, Hb 7.9 and platelet count 73,000.

The patient's clinical condition has not recovered as of January 16, 200 and he is still hospitalized. The hematological parameters partially recovered; on 1/16/2001, blood analysis showed WBC 1,500, ANC 780, lymphocytes 420, platelet count 112,000/mm^3, and a Hgb level of 9.8 g/dL.

In summary, this patient has suffered from Grade 4 bacterial and viral infection, in association with bone marrow hypocellularity, neutropenia, B-cell depletion and hypogammaglobulinemia. These severe adverse events occurred 2.5 months after the last dose of rituximab and 6 months after the combination fludarabine + rituximab, and are assessed to be causally related to the investigational agent. The cytopenia may have been exacerbated by concurrent sepsis and viral infection. In addition, Fludarabine administered 6 months ago can also be a contributing factor to compromised immune system and increased risk of infection.

There have been 19 previously reported cases of infection with grade ≥3 neutropenia associated with rituximab administration under this IND with possible (n=2), probable (n=1), unlikely (n=9), and unrelated (n=7) attributions to the investigational agent. Delayed neutropenia has been reported in other clinical trials using rituximab.

ADVERSE EVENTS ASSESSMENT

	IND Drug (Rituximab)	Non-IND Drug (Fludarabine)	Disease (Chronic lymphocytic leukemia)	Other (Bacterial sepsis/viral meningitis)
Unrelated				
Unlikely		4	1, 2,3,4	3
Possible	4	1, 2		2
Probable	1, 2	3		4
Definite	3			1

Date: 1/16/01 Signature:

Helen Chen, M.D.
(IDB Monitor for Rituximab)

If this assessment is changed, we will notify your office.

cc: Chirlstine A. White, M.D.
Brian Dallaire, Pharm.D.
Alice M. Wei
IDEC Pharmaceuticals Corporation