Cancer Research

Phase I Study of Monoclonal Antibody-Ricin A Chain Immunotoxin XomaZyme-791 in Patients with Metastatic Colon Cancer

V. S. Byers, R. Rodvien, K. Grant, et al.

Cancer Res 1989;49:6153-6160.

[CANCER RESEARCH 49, 6153–6160, November 1, 1989]

Phase I Study of Monoclonal Antibody-Ricin A Chain Immunotoxin XomaZyme-791 in Patients with Metastatic Colon Cancer

V. S. Byers, R. Rodvien, K. Grant, L. G. Durrant, K. H. Hudson, R. W. Baldwin, and P. J. Scannon

XOMA Corporation, Berkeley, California [V. S. B., K. H. H., P. J. S.]; Cancer Research Campaign Laboratories, University of Nottingham, Nottingham, England [V. S. B., L. G. D., R. W. B.]; and Pacific Medical Center, San Francisco, California [R. R., K. G., K. H. H.]

ABSTRACT

Monoclonal antibody 791T/36, recognizing a M_r 72,000 antigen on the surface of colon carcinoma cells, has been used to construct an immunotoxin by conjugating to it the ribosomal inhibitor protein, ricin toxin A chain. The antibody 791T/36 has been shown to bind to membranes of freshly disaggregated tumor cells from human colon tumors, and to localize in tumors *in vivo*. Subacute toxicology testing in rats receiving immunotoxin i.v. showed, at highest doses, weight loss, decreased serum albumin, and hepatocyte vacuolization without elevation in liver function tests.

A Phase I dose escalation study was carried out in which 17 patients with metastatic colorectal cancer were treated with doses of immunotoxin ranging from 0.02 to 0.2 mg/kg/day in 1-h i.v. infusions for a 5-day course. Side-effects included a composite of signs and symptoms thought to be generic to ricin A chain immunotoxins, including decreased serum albumin, mild fever, and flu-like symptoms, all being reversible. Two additional findings, reversible proteinuria and mental status changes, were also noted which may be characteristic of this immunotoxin.

By 10–20 days after therapy, most patients developed IgM and IgG antibodies against both the ricin toxin A chain and the immunoglobulin portion of the immunotoxin, which were asymptomatic. A strong anticombining site antibody response was seen. Biological activity manifest as mixed tumor regression was seen in five patients.

INTRODUCTION

MoAbs[1] directed against human tumor-associated antigens have allowed drug targeting to be explored as a therapeutic modality in cancer (1–3). Cytotoxic moieties, when coupled to MoAbs, can be directed specifically to the relevant target cell. One such moiety, RTA, has been used to construct several immunotoxins (1, 4, 5). RTA is a ribosomal inhibiting protein which functions as an RNA *N*-glycosidase specific for the 28-S ribosomal subunit (6). Since RTA alone is poorly internalized, it is functionally inactive as a free agent. When coupled to monoclonal antibodies, however, it can be targeted to tumor cells, internalized, and is cytotoxic to the cells.

MoAb 791T/36 recognizes a M_r 72,000 antigen present on tumor cells derived from ovarian, colorectal, and osteogenic sarcoma tissues (7–9). Flow cytometric analysis of tumor cells from colorectal and ovarian tumors, derived by enzymatic disaggregation of the tumors, demonstrated that 791T/36 MoAb binds to the majority of cells from over 80% of both types of tumors (8, 9), indicating the antigen is expressed on the cell surface. *In vivo,* this MoAb localizes in tumors, as demonstrated by studies in which the antibody, labeled with ^{131}I or ^{111}In, images primary and metastatic ovarian and colorectal cancers (9–11).

The MoAb has been used to construct an immunotoxin, XomaZyme-791, by conjugation with RTA chain (12, 13). *In vitro* studies indicate that the immunotoxin retains over 70% of its binding to cells carrying the M_r 72,000 antigen, and when tested on 791T target cells using a [^{75}Se]methionine incorporation assay, there was more than a 1000-fold difference between the molarity of immunotoxin and free RTA necessary to attain 50% inhibition of tumor cell growth *in vitro* (12). It specifically and effectively inhibits growth of human tumor xenografts (13). On the basis of these findings, animal toxicology studies were carried out, and XomaZyme-791 was then tested in a Phase I clinical trial for the treatment of metastatic colorectal cancer.

MATERIALS AND METHODS

Monoclonal Antibody. The generation of the hybridoma producing 791T/36 MoAb (IgG_{2b}) has been previously described (12, 14). The MoAb used for these clinical trials was produced by XOMA Corporation from murine ascites and purified by affinity adsorption on Sepharose-protein A (13). The homogeneity of the IgG_{2b} preparations, evaluated by SDS-PAGE, HPLC, and double immunodiffusion indicated preparations had purities of greater than 95%. Reactivity of the MoAb on normal tissues was assessed by immunoperoxidase staining on frozen sections of a range of normal adult and fetal tissue from five cadaveric donors using a modification of the ABC technique (15).

To measure reactivity with hematopoietic progenitor cells, mature T-lymphocytes were removed from human bone marrow aspirates by first treating the cells with soybean lectin and removing the resultant agglutinates, then forming E rosettes and removing them. This technique produces a 4 $\log_{10}$ depletion of T-lymphocytes (16). Binding to the remaining cells was assessed by indirect immunofluorescence, measured by flow cytometry.

The purified MoAb is free of xenotropic and ecotropic viruses as well as the twelve murine viruses measured by the mouse antibody production test (a test in which contamination with 12 murine viruses is evaluated by injection of the test article into mice and determination of antibody production to the viruses of interest[2]).

Ricin Toxin A Chain. RTA was purified from castor beans by a series of column based separations, including immunoaffinity chromatography (17). The RTA was greater than 95% pure as judged by SDS-PAGE, and contained no detectable ricin, or ricin toxin B chain by any assay including immunoprecipitation. The IC_{50} level of the purified RTA as measured by a reticulocyte lysate assay (17) was less than 10 pM. This assay measures inhibition of protein synthesis in a cell free system. In a mouse toxicity assay, RTA injected into BALB/c mice at 10 mg/kg produced no deaths.

Immunotoxin. Immunotoxin XomaZyme-791 was prepared for clinical trials by conjugating purified ricin A chain to the murine monoclonal antibody 791T/36 by means of *N*-succinionidyl-3-(2-pyridyldithio)propionate reagent, forming a disulfide bond (4, 12). It was purified by gel filtration. Each lot was subjected to a series of tests prior to release. The free IgG level and amount of immunotoxin present in the immunotoxin preparation was determined by size exclusion HPLC. Binding of the conjugate to 791T target cells was compared to that of

Received 9/9/88; revised 2/16/89, 5/17/89; accepted 8/4/89.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

[1] The abbreviations used are: MoAb, monoclonal antibody; RTA, ricin A chain; LDH, lactate dehydrogenase; SGOT, serum glutamic oxaloacetic acid transaminase; CT, computerized tomography; CEA, carcinoembryonic antigen; PBS, phosphate buffered saline; XomaZyme-791, immunotoxin made from 791T/36 MoAb (clinical material); CPK, creatinine phosphokinase; BUN, blood urea nitrogen; SDS-PAGE, sodium dodecyl sulfate-polyacrylamide gel electrophoresis; HPLC, high pressure liquid chromatography; EEG, electroencephalogram; ELISA, enzyme-linked immunosorbent assay; FITC, fluorescein isothiocyanate.

[2] Xoma Corporation, unpublished observations.

the native antibody by flow cytometry analysis as previously described (18). The cytotoxicity of the immunotoxin against relevant and irrelevant target cells was determined using an *in vitro* assay in which target cell survival is determined by [^{3}H]thymidine incorporation. Target cells (791T) or the erythroleukemia cell line, Molt-4 (ATCC Bethesda, MD) which does not carry the M_r 72,000 antigen recognized by this MoAb, were plated at 4×10^4 cells/well in 100 ml of RPMI 1640 (GIBCO, Grand Island, NY) with 10% fetal calf serum (Hyclone Labs, Logan, UT). After incubation at 37°C for 3 h, various concentrations of immunotoxin ranging from 20 to 2000 ng/ml were added in 100-μl aliquots to triplicate wells. After 48 h, 1 μCi of [^{3}H]thymidine was added to each well and 72 h later the wells were harvested and incorporated radioactivity determined. Results are expressed as amount of immunotoxin/ml producing 50% inhibition (IC_{50}). These tests were repeated at monthly intervals after immunotoxin production with minimal change in reactivity. XomaZyme-791 was prepared for clinical use at a concentration of 1 mg/ml in phosphate buffered saline, pH 7.3. It was clear to visual inspection and was filtered through a low protein binding 0.22-μm filter into about 100 ml of normal saline just prior to infusion.

Animal Toxicology Studies. The LD_{50} level was assessed on BALB/c mice; subacute toxicology studies were performed in Sprague-Dawley rats, both from Charles River laboratories. Mice were injected i.v. through the tail vein and observed for 5 days. After at least 7 days quarantine, three groups of rats, 12 per group, were dosed i.v. with either saline, or 1 mg/kg or 5 mg/kg of 791T/36-RTA (RTA:MoAb ratio of 4.3:1; 3.7% free RTA) through the tail vein daily for 10 days (study days 1–10). Each group of animals was weighed daily, and three in each group were bled, sacrificed, and necropsied on days 6, 11, or 17. Other Sprague-Dawley rats (three rats per group, Simonsen Labs) were given i.v. injections of 0.2, 1.0, or 5 mg/kg of RTA alone or of saline (2 ml/kg) for 5 sequential days. Animals were bled and necropsied on day 5. Serum chemistries included SGOT, serum glutamic pyruvate transaminase, bilirubin, BUN, creatinine, total protein, albumin, CPK, uric acid, LDH, glucose, and electrolytes. Hematology included indices and platelets were estimated.

Patient Population and Treatment Plan. Seventeen patients were entered in the trial. All had at least one measurable lesion. No patient had received a murine monoclonal antibody prior to this therapy. No patient studied had significant organ dysfunction; *i.e.*, neurological, cardiological, and pulmonary functions were within normal ranges. Signed informed consent was obtained from all patients prior to entry into the study which was conducted under a U. S. FDA investigational new drug exemption notice. All patients signed informed consent.

XomaZyme-791 was given as 1-h daily i.v. infusions for 5 days, with the ability to postpone doses for up to 3 days if suspected side effects intervened. Immunotoxin doses, from 0.02 to 0.2 mg/kg/day, were infused over 1 h. Most patients were skin tested prior to the first dose with 100 μg of unconjugated antibody; some received an i.v. challenge of the equivalent amount of diluted immunotoxin, with infusions proceeding 15 min later if no reaction was seen. No adverse reactions to the test dose were noted. Physical exams and laboratory evaluation, including hematological and serum chemistry panel and urinalyses, were done daily through study day 6, and then at study days 15, 28, and 60. Prothrombin time, partial thromboplastin time, complement levels and electrocardiograms were carried out on study days 0 and 6. Where indicated, EEG and CT examinations of the head were performed. Patients were evaluated by sequential chest X-rays or CT scans of the abdomen, CEA levels, blood chemistries, and urinalyses for up to 6 months after completion of therapy. In most patients proteinuria was quantitated by dipstick where 1^+ = 30 mg/dl and 4^+ = 2000 mg/dl. One patient with 4^+ proteinuria had quantitation of the urinary protein over a 24-h period and identification of the protein by urine electrophoresis.

Assessment of Human Immune Response to Immunotoxin. The IgG and IgM antibody response to the immunoglobulin moiety or the RTA moiety of the immunotoxin were tested on days 0, 13–16, 21–23, 35–40, and 60 using an ELISA assay. ELISA microplates were coated with purified 791T/36 (250 ng/well in PBS) or RTA (2.5 μg/well in PBS) or purified myeloma IgG_{2a} or IgG_{2b} (Sigma, Poole, UK, 250 ng/ml) in PBS. The plates were incubated for 1 h at room temperature with serial dilutions (1/10 to 1/10,000) of patient's serum diluted in 50 mM sodium citrate buffer, pH 4.5, containing 5% bovine serum albumin. Following extensive washing, the plates were incubated for 1 h at room temperature with a 1:1,000 dilution of alkaline phosphatase conjugated goat anti-human IgG or anti-human IgM (Sigma, Poole, UK) antiserum. After washing, the assay was developed with *p*-nitrophenolphosphate (Sigma, Poole, UK) as the alkaline phosphatase substrate. The optical densities of each well were read at 405 nM and serum titers determined as the serum dilution producing 50% of the maximum ELISA value (19). Anti-combining site antibodies were detected using a flow cytometry assay in which the capacity of patient's serum to block binding of FITC conjugated 791T/36 (791T/36-FITC) to target cells was determined (20). This was expressed as titer of serum which produced 50% inhibition of the maximum 791T/36-FITC binding to target cells.

RESULTS

Reactivity of MoAb and Immunotoxin

Apart from tumor cells, reactivity of the MoAb assessed by immunoperoxidase staining is primarily with stromal (noncellular) tissue, although there is cytoplasmic staining in the region of the juxtaglomerular apparatus and occasional reactivity with pulmonary epithelium and isolated kidney glomeruli in some sections. There is no detectable binding to progenitor cells by flow cytometry.[2] Other studies have found weak antigen binding mitogen stimulated (but not resting) lymphocytes (21). Two preparations of immunotoxin were used for clinical trials (Table 1). Analysis by SDS-PAGE indicated several species of immunoconjugate were present with antibody:RTA ratio of 1:1 to 1:5. Less than 10% aggregates were present by weight. The intrinsic variation of the binding assay is 15% and that of the cytotoxicity assay is 50%; monthly analysis during the time the lots were in clinical use indicated all variations were within this range. No increase in free antibody or change MoAb:RTA ratio was noted.

While both lots fell within the accepted ranges, the first had a higher MoAb:RTA ratio than the other and correspondingly less free antibody. The binding to target cells was decreased as compared to the lot with lower conjugation ratios but the *in vitro* cytotoxicity was similar.

Patient Characteristics. The characteristics and sites of disease of the 17 cancer patients (10 females and 7 males) evaluated in the immunotoxin study are summarized in Table 2. The age range was 30–70 years. Sixteen patients had colorectal cancer; one patient (Patient 14) had the diagnosis of colorectal cancer later revised to ovarian cancer after laparotomy. Sixteen had liver metastases documented by CT scan; one patient (Patient 4) did not. Ten patients also had pulmonary metastases. All measurable lesions were less than 12 cm in size. Most patients had had the primary tumor removed. Some had received other therapy such as 5-fluorouracil chemotherapy of IL2-LAK cell immunotherapy no less than one month prior to immunotoxin

Table 1 *Characteristics of clinical lots of XomaZyme-791*

Lot	Free antibody (%)	MoAb:RTA molar substitution ratio[a]	Antibody reactivity %[b]	Cytotoxicity against cell line[c] (IC_{50})	
				791T	Molt 4
1	1	1:3.3	62	13 ng	62 μg
2	9	1:2	93	12 ng	ND

[a] Determined by SDS-PAGE.
[b] Relative to antibody 791T/36: determined by competitive inhibition of binding of MoAb 791T/36-FITC to 791T cells.
[c] Determined by *in vitro* cytotoxicity of immunotoxin for cultured target cells. Cell survival determined by [^{3}H]thymidine incorporation. Values expressed in terms of amount of immunotoxin/ml necessary to produce 50% inhibition.

Table 2 *Patient population treated with immunotoxin XomaZyme-791*

Patient	Sex	Age	Time since other treatment (months)[a]	Site of disease[b]	Liver function tests at entry (mg/dl)		
					Bili	LDH	SGOT
					0.1–1.3[c]	50–210[c]	12–45[c]
1	F	49	4	Liver, lymph nodes, peritoneum, lung	0.3	205	40
2	F	60	1	Liver, lymph nodes, spine, lung	0.1	618	24
3	F	30	None	Liver, lymph nodes, lung, periaortic mass	0.7	172	32
4	F	60	4	Right peritoneal mass, peritoneal mets	0.3	248	21
5	F	32	5	Liver, pelvic mass, lymph nodes	0.4	202	66
6	M	58	1	Liver, lungs	0.7	233	35
7	M	69	None	Liver, lymph nodes	1.7	437	61
8	M	67	None	Liver, lymph nodes, lungs	0.9	208	26
9	F	68	15	Liver, lung, lymph nodes	1.8	158	58
10	M	53	2	Liver, lung	0.5	386	58
11	M	45	None	Liver, lymph nodes, lung	0.5	280	40
12	F	58	17	Liver, lymph nodes, lungs, presacral mass	0.8	519	120
13	M	62	4	Liver, lungs, retroperitoneal mass, bone	0.7	595	59
14	F	36	None	Liver, periaortic nodes, pelvic mass	0.3	482	23
15	F	40	Unknown	Liver, peritoneum, lymph nodes, bone	0.5	118	30
16	F	50	12	Liver, recurrent rectal tumor	0.4	199	30
17	M	70	None	Liver	0.5	381	48

[a] Patients received no other therapy (none) or radiation, chemotherapy (principally 5-fluorouracil) or IL-2/LAC cells (Patient 5).
[b] All except Patient 14 had diagnosis of colorectal cancer made histologically, Patient 14 was subsequently rediagnosed as having ovarian cancer.
[c] Normal range.

treatment. Karnofsky scores were greater than 70; all had normal levels of blood urea nitrogen and serum creatinine; and no more than 1^+ proteinuria by dipstick. Complement and coagulation parameters were within normal limits as were hemoglobin and white blood cell counts. Of the 17 patients, five had normal liver function tests, 10 patients had mildly elevated LDH levels, and seven had elevation of SGOT. Most patients had values less than twice normal for each test; one had values less than three times normal, and two had mild bilirubin elevations less than 30% above normal. Serum albumin was normal in all. None had other serious diseases or tumors apart from colon (or in one case ovarian) carcinoma. Fifteen patients received a full course of five doses of immunotoxin; doses were temporarily postponed in two patients (Patients 9 and 13) because of neurological events (increased unilateral tremor and transient mental status change) thought possibly due to drug (Table 3). One patient (Patient 6) received only one infusion because of an anaphylactoid reaction consisting of periorbital edema. His skin test was negative prior to immunotoxin treatment. Another patient (Patient 17) received only four doses because of mental status change which required more than 3 days to resolve.

Clinical Observations. Clinical observations associated with immunotoxin therapy are summarized in Table 3. Patients generally tolerated the immunotoxin well. Decrease in serum albumin levels was noted in all patients, beginning during the 5 days of infusion. This occurred with all doses of immunotoxin, and serum albumin levels fell to 12–48% of the starting level. There was no obvious correlation between dose of immunotoxin and degree of albumin drop. In all cases the albumin levels either stabilized or began to increase by day 15 (Fig. 1*a*). Weight gain of 5% or greater was noted in seven of 17 patients and was manifest as peripheral edema. Pulmonary edema was not seen.

One patient developed fever of 39°C during or within 6 h of immunotoxin infusion. Asymptomatic proteinuria not associated with other renal abnormalities was first noted on days 5–10 of study and increased through day 15 (Fig. 1*b*). Decreased serum albumin and weight gain occurred before onset of this delayed proteinuria. In all cases but one, the proteinuria resolved to 1^+ or less after 30–45 days. The one patient (Patient 3) in whom proteinuria persisted had an accompanying urinary tract infection. This delayed proteinuria was noted in 11/11 patients treated with doses at or greater than 0.1 mg/kg/day, and in three of five patients treated with 0.05 mg/kg/day or less. Protein was quantitated in one of two patients with 4+ proteinuria (receiving a dose of 0.1 mg/kg/day) and totalled 2 g protein in a 24-h period. Urine protein electrophoresis demonstrated that the protein was primarily albumin. Urine sediment in all patients was unremarkable. In no case was there any decrease in serum complement levels (C3, C4, or CH50). No patient's serum albumin level decreased after the onset of proteinuria (Fig. 1). No increase in serum creatinine or BUN was seen in any patient. In most patients there was a slight decrease in platelet counts within the first 6 days of an average of 79,000 which was not related to dose. The lowest count reached was 146,000 in one patient. Counts returned to baseline or above within 15–20 days in all patients. There was no decrease in white blood cells or red cells and no change in prothrombin time, partial thromboplastin time, or fibrinogen levels.

On study day 6, only one patient (Patient 12) had a significant increase in any liver function test; this was a twofold increase in the total bilirubin value which had returned to base line by day 15 occurring in a patient with liver metastases. Over the initial 28-day study period, one patient had SGOT and bilirubin values increasing by at least twofold.

In one patient, there was worsening of a preexistant tremor of the left hand and four of 17 patients had reversible mental status changes; all had been treated at a dose of 0.1 mg/kg or higher (Table 3). In three patients, mild fatigue, slurred speech,

Table 3 *Clinical observations in patients treated with XomaZyme-791*

Patient number	Dose (mg/kg)	Total dose (mg)	Maximum drop in serum albumin (%)	Weight gain % (peak day)	Neurological[a] events	Fevers[b]
1	0.02[c]	5.0	12	2 (15)	–	37.2
2	0.02[c]	5.0	13	2 (4)	–	37.1
3	0.05	13.0	28	1 (6)	–	37.9
4	0.05[c]	11.0	24	3 (6)	–	38.6
5	0.05	14.5	45	5 (5)	–	39.4
6	0.1[d]	6.8	18	0 (2)	–	37.9
7	0.1	42.5	26	4 (16)	–	38.1
8	0.1	37.5	40	1 (5)	–	37.8
9	0.1[e]	25.0	45	12 (16)	+	37.9
10	0.1	38.0	26	2 (15)	–	38.4
11	0.1[c]	40.0	29	10 (16)	+	38.3
12	0.1[c]	26.5	26	12 (15)	–	38.3
13	0.1[c]	27.7	22	8 (8)	+	38.1
14	0.1	27.4	28	7 (15)	–	37.6
15	0.15	45.0	36	4 (17)	–	37.8
16	0.15	61.4	27	4 (5)	+	37.8
17	0.2	52.8	48	14 (10)	+	38.5

[a] Headache, dementia, or tremor.
[b] During therapy.
[c] RTA:MoAb ratio of 2.0:1; other patients treated with lots with RTA: MoAb ratio of 3.5:1.
[d] Received only one dose.
[e] Postponed 4th and 5th dose study day 2–4.

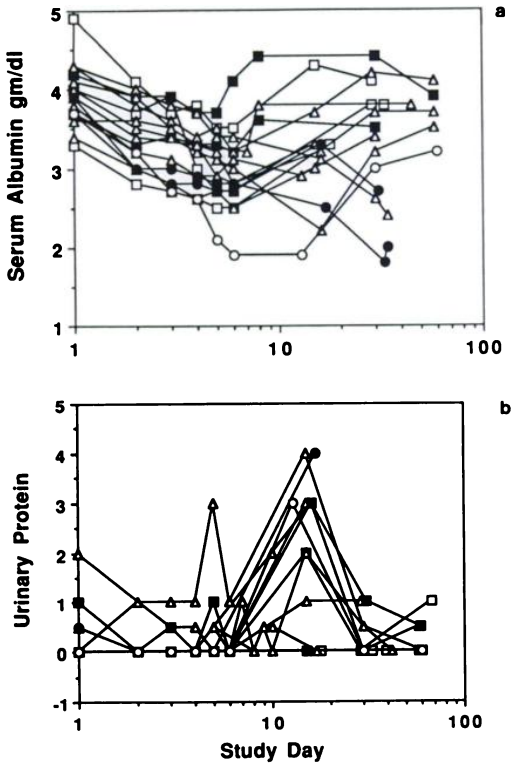

Fig. 1. *a*, serum albumin levels in colorectal cancer patients treated with immunotoxin XomaZyme-791 (dose range, 0.02–0.2 mg/kg/day). Study days are plotted on a log scale to allow comparison between serum albumin and proteinuria, and patients are identified by dose in mg/kg; 0.02 (■), 0.05 (□), 0.15 (●), 0.1 (△), and 0.2 (○). *b*, proteinuria assayed by dipstick, scale 1–4 in colorectal patients treated with XomaZyme-791.

irritability, or expressive aphasia were noted. These events usually began about study day 4 and were largely resolved within 2 days although complete resolution could take seven days. One patient treated at the highest dose (0.2 mg/kg) became frankly demented; the patient received steroids and this conditon reversed after 3 days. EEGs done on the four patients with mental status changes after therapy revealed diffuse slowing and/or paroxysmal bursts, and both the clinical examination and EEG were most compatible with a mild toxic encephalopathy. The patient who developed dementia had a normal head CT scan and no other etiology for the dementia. Nausea with vomiting was noted in four other patients during therapy; headaches were seen in two.

Biological Activity. Although this was a Phase I dose escalation study, observations concerning antitumor activity were made. Of 16 patients with hepatic metastases (Table 4), two (Patients 10 and 16) had objective evidence by abdominal CT scans of decreasing size in large metastases and disappearance of smaller lesions. These changes were seen at 3 months without additional intervening treatment. In another case (Patient 7), new calcification of the hepatic metastases, with stabilization of growth, was noted at 2 months, but there was increased size at 6 months. Three patients (Patients 8, 11 and 14) had fixed supraclavicular nodes which decreased in size or disappeared by study day 30. Three also had liver metastases which increased in size or number over the 2-month follow-up period. One patient (Patient 6) had both liver and pulmonary metastases; the liver metastases increased in size but the lung metastases decreased in size 5 months after therapy. These patients received no additional chemotherapy after the immunotoxin therapy.

Although there were transient decreases in the CEA values of some patients (Table 4), these could not be correlated with decreased tumor size. Of the three patients (Patients 7, 10, and 14) who had calcification or decrease in size of the hepatic metastases, one had CEA values that decreased during the period of observation.

Immunological Studies. Thirteen patients were skin tested with the unmodified antibody prior to initiation of therapy and all tests were negative. Between days 10 and 15, onset of erythema and induration at the skin test site was noted in 12 of 13 patients. The exception was one patient (Patient 4), treated at 0.05 mg/kg/day. In all cases the reaction lasted 3–5 days and then resolved.

Humoral antibody responses to murine 791T/36 immunoglobulin and RTA components of the immunotoxin were observed in all but one patient, including Patient 6 who received a single injection of immunotoxin (Table 5). Most patients produced IgM and IgG responses to 791T/36 immunoglobulin; the one patient who did not (Patient 15) was only tested as late

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.