Randomized Phase II Study of BR96-Doxorubicin Conjugate in Patients With Metastatic Breast Cancer

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Purpose: **BMS-182248-1 (BR96-doxorubicin immunoconjugate) is a chimeric human/mouse monoclonal antibody linked to approximately eight doxorubicin molecules. The antibody is directed against the Lewis-Y antigen, which is expressed on 75% of all breast cancers but is limited in expression on normal tissues. Preclinical xenograft models demonstrated significant antitumor activity, including cures. A randomized phase II design was chosen to estimate the activity of the BR96-doxorubicin conjugate in metastatic breast cancer in a study population with confirmed sensitivity to single-agent doxorubicin.**

Patients and Methods: **Patients with measurable metastatic breast cancer and immunohistochemical evidence of Lewis-Y expression on their tumor received either BR96-doxorubicin conjugate 700 mg/m² IV over 24 hours or doxorubicin 60 mg/m² every 3 weeks. Patients were stratified on the basis of prior doxorubicin exposure, visceral disease, and institution. Cross-over to the opposite treatment arm was allowed with progressive or persistently stable disease.**

Results: **Twenty-three patients who had received a median of one prior chemotherapy regimen were assessable. There was one partial response (7%) in 14 patients receiving the BR96-doxorubicin conjugate and one complete response and three partial responses (44%) in nine assessable patients receiving doxorubicin. No patient experienced a clinically significant hypersensitivity reaction. The toxicities were significantly different between the two treatment groups, with the BR96-doxorubicin conjugate group having limited hematologic toxicity, whereas gastrointestinal toxicities, including marked serum amylase and lipase elevations, nausea, and vomiting with gastritis, were prominent.**

Conclusion: **The BR96-doxorubicin immunoconjugate has limited clinical antitumor activity in metastatic breast cancer. The gastrointestinal toxicities likely represent binding of the agent to normal tissues expressing the target antigen and may have compromised the delivery of the immunoconjugate to the tumor sites.**

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BMS 182248-01 (BR96-doxorubicin immunoconjugate) is an immunoconjugate developed to deliver doxorubicin specifically to tumor cells that express the tumor-associated surface antigen Lewis-Y while sparing normal tissues. The BR96-doxorubicin conjugate is a part human, part mouse chimeric immunoglobulin (Ig) conjugated to approximately eight doxorubicin molecules (Fig 1). In preclinical studies, after BR96-doxorubicin conjugate binds to the Lewis-Y surface antigen, it is rapidly internalized, the doxorubicin molecules are released from the immunoglobulin by hydrolysis of the acid-labile linkage, and cytotoxicity results.[1,2] Lewis-Y is abundantly expressed on the surface of many human carcinomas, including breast, lung, colon, and ovary carcinomas.[3] Most normal tissues do not express the Lewis-Y antigen, except for epithelial cells of the esophagus, stomach, and proximal small intestine and some acinar cells of the pancreas.[3]

The BR96-doxorubicin conjugate demonstrated a broad spectrum of antitumor activity in xenograft tumor models, including cures in established L2987 lung, RCA colon, and MCF-7 breast tumors.[1,4] This activity was in marked contrast to single-agent doxorubicin, which did not produce cures at its optimal dose and schedule in the same xenograft models.[1] Furthermore, equivalent antitumor activity was achieved with the BR96-doxorubicin conjugate at 13% of the comparable free doxorubicin dose. This finding suggests preferential delivery of the doxorubicin to the Lewis-Y–expressing tumor by the immunoconjugate.[1] In rodent toxicology studies, the BR96-doxorubicin conjugate was significantly less toxic, including cardiotoxicity, than equivalent doses of doxorubicin.[5] An acute enteropathy was observed in dogs that was not observed in rodents and that differed from the toxicity normally associated with doxorubicin.[6] The acute enteropathy was believed to be related to the binding of the antibody to Lewis-Y–related antigens expressed by gastrointestinal epithelial cells.

Clinical trials were initiated shortly after the broad spectrum of antitumor activity was demonstrated preclini-

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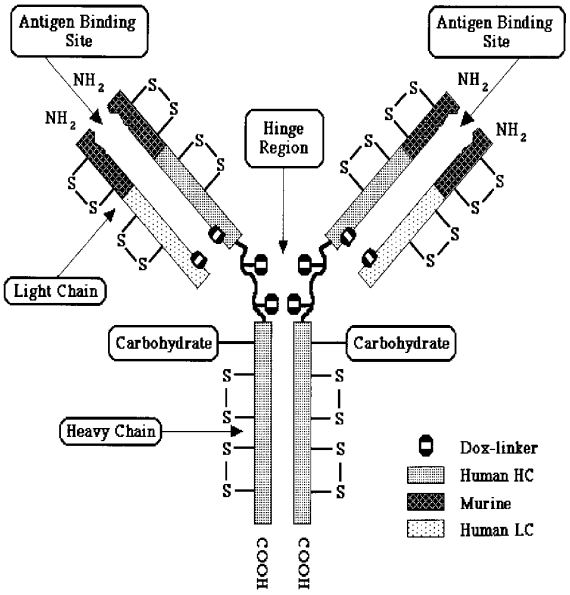

Fig 1. Schematic of BR96-doxorubicin immunoconjugate (BMS-182248-01). Abbreviations: HC, immunoglobulin heavy chain; LC, immunoglobulin light chain; Dox-linker, acid labile doxorubicin linkage.

cally. In the phase I studies, vomiting with hematemesis was dose-limiting, and an exudative gastritis was found at endoscopy.[6,7] Premedication with corticosteroids, 5-hydroxytryptamine-3 antagonists, and a 24-hour infusion schedule led to the recommended phase II dosage of 700 mg/m^2 BR96-doxorubicin every 3 weeks (21 mg/m^2 conjugated doxorubicin).[8] In addition to the reversible gastritis, toxicities included asymptomatic alterations in pancreatic enzymes, most prominently serum lipases, mild hypersensitivity reactions characterized by fever or rash without anaphylactic reactions, modest hematologic toxicity of anemia, and rare cases of neutropenia. No alopecia, mucositis, or cardiomyopathy was reported. During the phase I study of this schedule, two partial responses were observed in patients with breast and gastric carcinoma.[8]

On the basis of provocative preclinical data and the encouraging phase I study, we initiated a randomized phase II study to determine the antitumor activity of BR96-doxorubicin conjugate in metastatic breast cancer. The randomized phase II design using a single-agent doxorubicin reference arm was chosen to estimate the activity of the BR96-doxorubicin conjugate in metastatic breast cancer and confirm the sensitivity of the enrolled population to single-agent doxorubicin. Moreover, this design would permit a rapid determination of the future development of this drug in breast cancer.

PATIENTS AND METHODS

Eligibility

Patients aged 18 years or older with histologically confirmed, measurable metastatic breast cancer were eligible for this study. Patients were permitted to have had one prior chemotherapy regimen in either the adjuvant or metastatic setting. Prior chemotherapy for metastatic disease could not contain anthracyclines. However, prior adjuvant chemotherapy could include an anthracycline if the patient had relapsed more than 12 months after the completion of the chemotherapy and the cumulative dose was equal to or less than 300 mg/m^2 doxorubicin. Patients who received nonanthracycline-containing adjuvant chemotherapy must have relapsed more than 3 months after treatment completion. Patients were permitted prior hormone therapy for adjuvant and metastatic disease; however, patients who had previously responded to hormone therapy had to have discontinued it at least 4 weeks before randomization and tumor evaluation was repeated after a 4-week washout interval. Prior radiotherapy was acceptable if it was completed 4 weeks before study entry.

Before randomization, all patients were required to have a breast cancer specimen positive for Lewis-Y antigen by immunohistochemistry, a normal left ventricular ejection fraction, an Eastern Cooperative Oncology Group performance status of 0 or 1, or a Karnofsky performance status of more than 80%. Laboratory requirements included the following: a hemoglobin count of more than 10 g/dL; a granulocyte count of 1,500 cells/μL or higher; blood urea nitrogen and serum creatinine levels within 1.25 times the upper limit of normal; a bilirubin level of less than 1.5 mg/dL; AST and ALT levels within 2.5 times the institutional upper limit of normal; and serum lipase or amylase levels that were less than twice the institutional upper limit. Alkaline phosphatase elevations of more than 2.5 times the upper limit of normal were permitted if bone metastases were documented. Women of child-bearing potential were required to have a negative serum or urine pregnancy test result within 72 hours before the start of study medication and to practice contraception.

Patients were excluded if they had been exposed to therapeutic or diagnostic murine, murine/human chimeric, or humanized monoclonal antibodies within 6 months before randomization. A history of neoplasm other than breast cancer within 5 years of study entry was a reason for exclusion, with the exception of nonmelanoma skin cancer or curatively treated carcinoma-in-situ of the cervix. Patients were not permitted to have CNS metastases that required active treatment or receive concomitant cytotoxic, hormone, radiation, or investigational therapy while participating in this study.

The study was approved by each participating institution's institutional review board, and written informed consent according to the guidelines of the participating institutions was obtained from patients before study entry.

Study Design

Patients who met the eligibility criteria were randomized after stratification to receive either BR96-doxorubicin conjugate 700 mg/m^2 intravenously (IV) or single-agent doxorubicin 60 mg/m^2 IV every 3 weeks.

BR96-doxorubicin conjugate (BMS-182248-01; Bristol-Myers Squibb, Wallingford, CT) was administered by continuous IV infusion over 24 hours once every 21 days. The full calculated dose was divided into four equal doses and prepared in 250 ml of normal saline or 5% dextrose water; each of the four doses was administered over 6 hours. Premedication consisted of oral dexamethasone 20 mg daily starting 2 days before the start of infusion and continued for 2 days after therapy.

Antiemetics, including 5-hydroxytryptamine-3 antagonists, were administered according to institutional policy. Lorazepam 1 to 2 mg orally (PO) or IV was administered at least 30 minutes before the start of infusion. Vital signs were monitored in all patients receiving the BR96-doxorubicin conjugate immediately before, 15 minutes and 1 hour after the start, and at the completion of the infusion.

Doxorubicin was reconstituted with sodium chloride injection USP (0.9% normal saline) or sterile water for injection. Doxorubicin was given as a bolus injection IV once every 3 weeks. Vitals signs were monitored before treatment and at completion of the infusion.

Toxicity Evaluation and Dose Modifications

Toxicity was evaluated and graded according to the National Cancer Institute common toxicity criteria, with the exception that serum lipase was graded using the same scale as serum amylase.

The drug dose was reduced 25% when febrile neutropenia occurred or a platelet transfusion was required. Failure to recover the absolute neutrophil count to 1,000/μL or higher or the platelet count to 100,000 cells/μL or higher required a delay of treatment until recovery and a 25% dose reduction. Grade 3 or 4 nausea and vomiting for more than 48 hours' duration required a 25% dose reduction. If symptoms persisted at the planned time of re-treatment, patient participation was delayed until recovery. Gastrointestinal hemorrhage up to grade 1 was permitted as long as patients had recovered by the day of re-treatment. Grade 2 or greater gastrointestinal hemorrhage required discontinuation of therapy. Pancreatic toxicity was defined as elevations of serum amylase or lipase with or without symptoms consistent with pancreatic inflammation. Any grade 4 pancreatic toxicity, or the presence of symptoms regardless of grade, required a 25% dose reduction and a resolution of the biochemical toxicity to grade 0 to 3 with resolution of symptoms before re-treatment.

All other grade 3 or 4 nonhematologic toxicities, with the exception of alopecia, warranted a 25% dose modification with resolution of toxicity to grade 0 or 1 by the date of re-treatment. Grade 1 cardiovascular toxicities were permitted provided that patients recovered by the time of re-treatment. Any grade 2 or greater cardiovascular toxicity required discontinuation from further treatment.

Treatment Duration and Cross-Over Criteria

Patients were treated with either BR96-doxorubicin conjugate 700 mg/m^2 IV over 24 hours or doxorubicin 60 mg/m^2 every 21 days for a maximum of six cycles. Tumor response was assessed every two cycles. Any patient receiving a lifetime cumulative dose of unconjugated doxorubicin of 550 mg/m^2 was discontinued from treatment. Patients were permitted to receive additional cycles of therapy in the absence of disease progression if it was considered in their best interest by the treating physician.

Patients were permitted to cross-over to the alternate treatment arm if they demonstrated either disease progression or stable disease after four cycles and if it was considered in the patient's best interest by the treating physician. Cross-over was permitted only if the patient met the original eligibility criteria.

All patients who received one dose of the study drug were assessable for toxicity. All patients who received at least two cycles of treatment were considered assessable for response.

A complete response (CR) was defined as disappearance of all clinically evident tumor, including normalization of any tumor markers determined by two observations not less than 4 weeks apart. A partial response (PR) was defined as a 50% or greater decrease in the sum of the products of the bidimensional measurements of the measured lesions determined by two observations not less than 4 weeks apart. No simultaneous increase in the size of any lesion or appearance of new lesions could occur. Nonmeasurable lesions were required to remain stable or regress to meet the PR criterion. Stable disease was defined as a decrease of less than 50% in total tumor size up to an increase of less than 25% in the total tumor size. To meet the stable disease criterion, no new lesions could develop. Progressive disease was the unequivocal increase of at least 25% from the best response or baseline in one or more measurable lesions. The appearance of new lesions constituted progressive disease.

Anti-Immunoconjugate Antibody Assessment (Human Anti-Mouse Antibody)

Serum samples were collected from patients for human anti-mouse antibody (HAMA) analysis before they received BR96-doxorubicin, after the first cycle of therapy (day 22), and 3 to 6 weeks after completion of treatment. Serum samples were assessed for immunogenicity using an enzyme-linked immunoadsorbent assay specific for F(ab′)$_2$ fragments of BMS-182248, BR96 F(ab′)$_2$ Dox. Briefly, Immulon II enzyme-linked immunoadsorbent assay plates (Dynex, Chantilly, VA) were coated overnight with BR96 F(ab′)$_2$ Dox 100 μL at 2 μg/mL in phosphate-buffered saline [PBS]). Plates were blocked with 100 μL of PBS containing 5% goat sera. The plates were washed (PBS/0.5% goat sera Tween 20, pH 7.4), and two-fold serial dilutions of the test sera in PBS/5% goat sera were added to the appropriate wells and incubated for 2 to 4 hours at 37°C. After washing, bound human antibodies were detected using alkaline phosphatase–conjugated, Fc-specific goat anti-human IgG and IgM antibodies (Sigma, St. Louis, MO) and IgA antibody (Biosource, Camarillo, CA) (100 μL at 1:10,000, 1:7,500, and 1:5,000, respectively) incubated for 1 to 2 hours at 37°C. Subsequently, the plates were washed and substrate (1 mg/mL *p*-nitrophenyl phosphate in diethanolamine buffer) was added to each well. After incubation for 30 minutes at 25°C, 50 μL of 3N NaOH stop reagent was added and the absorbance was read (dual wavelength, 405 and 550 nm). Results are reported as units per milliliter based on the hyperimmunized monkey anti-murine BR96 reference standard. The plate background absorbance was subtracted, and unit-per-milliliter values were calculated for each dilution of each patient's sample by comparing it to the standard curve. The unit-per-milliliter value for each patient's sample was then determined by calculating the mean of three consecutive dilutions with the lowest coefficient of variability. Plate background was determined as the absorbance measurement recorded in the absence of serum. A patient was considered to have seroconverted when the individual's response was greater than the mean plus three standard deviations of all the patients' predose values (predose values were estimated from the means in the three ongoing clinical studies, n = 32) and also greater than two times the pretreatment value for that individual patient.

Statistical Analysis

The study was designed as a randomized phase II study assessing antitumor activity and the safety of BR96-doxorubicin conjugate every 21 days and doxorubicin every 21 days. Eligible patients were stratified according to prior doxorubicin exposure, the dominant site of disease (visceral *v* other), and institution. Randomization occurred at a central office (Wallingford, CT). A Gehan two-stage design was used to optimize the number of patients entered onto this phase II study.[9] The purpose of the first stage was to determine whether the given dose and schedule of the BR96-doxorubicin conjugate were worth further study in metastatic breast cancer. Before study initiation, an acceptable level

of antitumor activity was defined as more than or equal to 30% for continued accrual beyond 15 patients to occur. After the entry of nine patients to each arm, the investigators met to decide whether accrual should continue based on the response rate observed in the experimental arm compared with the reference arm. Analysis at that time suggested that if the drug had a 30% response rate, one or more successes should have been observed in the first nine patients entered into the experimental arm (rejection error, ≤ 5%, beta).[9] Therefore, it was decided that the protocol should be amended, further randomization to the doxorubicin arm should cease, and further accrual should continue only to the BR96-doxorubicin arm to determine whether the experimental agent met the conventional phase II level of 20% antitumor activity.

The toxicities (hematologic and biochemical) experienced by the two treatment groups were compared on the first cycle, and worst toxicity (both hematologic and nonhematologic) was compared over all cycles, using a two-sided Monte Carlo simulation, a permutation of a Wilcoxon rank sum statistic. The Bonferroni method was used because a large number of variables were compared, and the significance level of each variable was set at .002 to ensure a 0.05 experiment-wise error rate.

RESULTS

A total of 25 patients were entered onto this study: 10 patients were randomized to receive the BR96-doxorubicin conjugate, and 10 patients were randomized to single-agent doxorubicin. After the protocol was amended, five additional patients received the BR96-doxorubicin conjugate without randomization. Two randomized patients (one patient in each treatment arm) were never treated. One of these patients refused their assigned single-agent doxorubicin treatment, and one patient rapidly deteriorated from disease before BR96-doxorubicin conjugate treatment. The median age of patients entered was 52 years (range, 25 to 65 years), and they had a median of two sites of metastatic disease. Thirteen patients had received prior chemotherapy (eight patients in the BR96-doxorubicin conjugate arm and five in the doxorubicin arm). Two patients treated with BR96-doxorubicin conjugate and one patient randomized to the doxorubicin arm had received prior adjuvant doxorubicin. All patients treated were assessable for response and toxicity. Patient characteristics are listed in Table 1.

Table 1. Patient Characteristics

	BR96-doxorubicin	Doxorubicin
No. of patients entered	15	10
No. of patients treated	14	9
Age, years		
Median	52	51
Range	32-65	25-63
No. of patients with prior radiotherapy	9	5
No. of patients with prior chemotherapy	8	5
Adjuvant chemotherapy alone	7	5
Metastatic chemotherapy alone	1	0
Both	1	0
No. of patients with prior doxorubicin adjuvant	2	1
No. of patients with prior hormone therapy	13	4
Median no. of hormone therapies	1	0
Range	0-3	0-3
Sites of disease		
Soft tissue	3	2
Lymph node	5	5
Lung	4	3
Hepatic	9	4
Breast	3	1

Forty-five cycles were administered to the 14 patients treated initially with BR96-doxorubicin. In addition, 25 cycles were administered to four patients who crossed over to receive BR96-doxorubicin conjugate after progression or persistently stable disease during single-agent doxorubicin treatment. Forty-one cycles of single-agent doxorubicin were administered to the nine randomized patients, whereas two cycles of doxorubicin were given to one patient who crossed over after disease progressed during BR96-doxorubicin treatment. Patients treated with the BR96-doxorubicin conjugate as initial therapy received a median of three cycles of therapy (range, two to five cycles), whereas patients treated with single-agent doxorubicin initially received a median of four cycles (range, two to six cycles). In the four patients who crossed over to receive BR96-doxorubicin conjugate after disease progression during doxorubicin treatment, the median number of courses was five (range, one to 14 courses).

Toxicity Data

There were significant differences between the toxicities experienced by patients on the two randomized treatment arms. Hematologic toxicity, particularly neutropenia and leukopenia, was significantly more frequent with single-agent doxorubicin compared with BR96-doxorubicin conjugate treatment ($P \leq .0004$). Abnormalities of serum amylase and lipase occurred frequently among patients treated with BR96-doxorubicin conjugate, whereas this toxicity was not observed in patients who received doxorubicin ($P = .002$ and $P = .002$, respectively). Nonhematologic toxicities associated with BR96-doxorubicin included marked nausea, vomiting, symptoms of gastritis, and hematemesis in two patients. Vomiting occurred in 93% of patients treated with BR96-doxorubicin, and 43% of patients experienced grade 3 or 4 vomiting. The doxorubicin arm had significantly less severe nausea and less frequent vomiting ($P = .0028$). No episodes of hematemesis were noted in the doxorubicin arm. In addition, a nonspecific, poorly localized abdominal pain without sequelae was observed in five patients who received BR96-doxorubicin. There was no evidence of cardiac toxicity nor clinically significant (> grade 1) hepatic or renal toxicity in either of the two treatment arms.

No clinically significant hypersensitivity reactions occurred in patients randomized initially to the BR96-

doxorubicin conjugate. Fever was noted in three patients and wheezing was observed in two patients treated with the BR96-doxorubicin conjugate. One patient who crossed over and received the BR96-doxorubicin conjugate experienced four hypersensitivity reactions on successive cycles, with symptoms characterized by cough and wheezing. This patient could be re-treated safely after temporary interruption of the infusion. The toxicities are summarized in Tables 2 and 3.

Treatment Modification and Delay

A dose reduction was required in eight of 45 cycles of BR96-doxorubicin conjugate and one of 41 cycles of single-agent doxorubicin. The reasons for dose reduction in the BR96-doxorubicin conjugate arm were all nonhematologic toxicities: grade 3 or 4 nausea and vomiting (two cycles), nausea, vomiting, gastritis, and abdominal pain (one cycle), gastritis/pancreatitis symptoms (one cycle), and marked elevation in serum lipase more than or equal to five times the upper limit of normal (four cycles). None of the patients who received the BR96-doxorubicin conjugate after cross-over required a dose reduction. The one dose reduction and delay in the doxorubicin arm was due to febrile neutropenia with documented bacteremia. There were eight treatment delays in three patients receiving the BR96-doxorubicin conjugate; however, none of them were due to toxicity.

HAMA Analysis

Five of nine patients assessable for analysis met the criteria for a positive HAMA response. The ratio of postdose to predose values at day 22 and after treatment completion ranged from 0.60 to 12.64 and from 0.51 to 12.88, respectively. Only two patients had at either time point a more than or equal to 10-fold rise in titer; therefore, the response in these patients would be considered mild to moderate. The results are summarized in Table 4.

Table 2. Hematologic Toxicities by Grade for Randomized Patients Cycle 1 and All Cycles by Initial Treatment Arm

	BR96-doxorubicin (n = 9)				Doxorubicin (n = 9)				
Toxicity	1	2	3	4	1	2	3	4	*P*
Cycle 1									
ANC	0	0	0	0	0	1	2	5	< .0004
WBC	0	0	0	0	1	3	3	1	< .0004
Platelets	0	0	0	0	1	0	0	0	.999
Hemoglobin	3	2	0	0	2	1	0	0	.5
All cycles									
ANC	0	0	0	0	0	2	1	6	≤ .0004
WBC	1	0	0	0	1	4	2	2	≤ .0004
Platelets	1	0	0	0	1	0	0	0	1.0
Hemoglobin	4	4	0	0	3	1	1	0	.24

Abbreviations: ANC, absolute neutrophil count; WBC, WBC count.

Table 3. Worst Nonhematologic Toxicities by Grade in Randomized Patients for All Cycles by Initial Treatment Arm

	BR96-doxorubicin (n = 9)				Doxorubicin (n = 9)				
Toxicity	1	2	3	4	1	2	3	4	*P**
Amylase	3	1	3	0	0	0	0	0	.002
Lipase	2	1	1	3	0	0	0	0	.002
Fever	1	0	0	0	0	0	0	0	
Wheezing	1	0	0	0	0	0	0	0	
Abdominal pain	1	1	1	0	1	0	0	0	
Back pain	1	1	1	0	1	0	0	0	
Nausea	3	2	4	0	4	2	1	0	
Vomiting	1	3	3	2	5	2	0	0	.003
Gastritis	0	0	1	0	1	0	0	0	
Hematemesis	2	0	0	0	0	0	0	0	
Pancreatitis	0	0	0	1	0	0	0	0	
Alopecia	0	0	0		0	8	1		.00004
Bone pain	2	1	0	0	1	0	0	0	
Arthralgia	2	1	0	0	1	0	0	0	
Sepsis	0	0	0	0	0	0	1	0	
Cardiac	0	0	0	0	0	0	0	0	

**P* values are provided for those toxicities that met or approached the criteria for significance as defined in the Patients and Methods section.

Response Data

One partial response (7%; hepatic metastases) was observed in 14 patients (95% confidence interval, 0 to 34%) initially treated with BR96-doxorubicin conjugate. In contrast, four patients responded (one CR and three PR [44%]; 95% confidence interval, 14% to 79%) among the nine patients who received single-agent doxorubicin. Two patients who crossed over to the BR96-doxorubicin arm after persistently stable disease through four cycles of doxorubicin had a PR in hepatic metastases.

The response duration was 3 months for the patient treated initially with BR96-doxorubicin conjugate and 6 and 6+ months for the patients who responded to BR96-doxorubicin after cross-over. The response durations for the four patients randomized to doxorubicin and who responded were 2, 4, 10, and 15 months.

DISCUSSION

The immunoconjugate BR96-doxorubicin was developed to selectively deliver doxorubicin to tumors that express the tumor-associated surface antigen Lewis-Y while avoiding doxorubicin's systemic toxicity. We determined that the BR96-doxorubicin conjugate on this schedule and dose has modest antitumor activity in metastatic breast cancer. This is in contrast to the doxorubicin arm, which as part of this randomized study, demonstrated a 44% response rate, includ-

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