Phase II Study of Weekly Albumin-Bound Paclitaxel for Patients with Metastatic Breast Cancer Heavily Pretreated with Taxanes

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Abstract

Purpose: Nanoparticle albumin-bound paclitaxel, a solvent-free, albumin-bound paclitaxel, demonstrated antitumor activity in patients with taxane-naive metastatic breast cancer (MBC). We examined albumin-bound paclitaxel (100 mg/m^2 or 125 mg/m^2 administered weekly) to determine the antitumor activity in patients with MBC whose disease progressed despite conventional taxane therapy. **Patients and Methods:** Women with MBC that was previously treated with taxanes were eligible for participation. Taxane failure was defined as metastatic disease progression during taxane therapy or relapse within 12 months of adjuvant taxane therapy. Primary objectives were response rates (RRs) and the safety/tolerability of albumin-bound paclitaxel. **Results:** Women were treated with albumin-bound paclitaxel 100 mg/m^2 (n = 106) or 125 mg/m^2 (n = 75) on days 1, 8, and 15 of a 28-day cycle. Response rates were 14% and 16% for the 100-mg/m^2 and 125-mg/m^2 cohorts, respectively; an additional 12% and 21% of patients, respectively, had stable disease (SD) ≥ 16 weeks. Median progression-free survival times were 3 months at 100 mg/m^2 and 3.5 months at 125 mg/m^2; median survival times were 9.2 months and 9.1 months, respectively. Survival was similar for responding patients and those with SD. No severe hypersensitivity reactions were reported. Patients who developed treatment-limiting peripheral neuropathy typically could be restarted on a reduced dose of albumin-bound paclitaxel after a 1-2–week delay. Grade 4 neutropenia occurred in < 5% of patients. **Conclusion:** Albumin-bound paclitaxel 100 mg/m^2 given weekly demonstrated the same antitumor activity as albumin-bound paclitaxel 125 mg/m^2 weekly and a more favorable safety profile in patients with MBC that had progressed with previous taxane therapy. Survival of patients with SD ≥ 16 weeks was similar to that of responders.

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Introduction

Nanoparticle albumin-bound paclitaxel is a novel, solvent-free, 130-nanometer particle formulation of paclitaxel. Results of animal human xenograft studies of albumin-bound paclitaxel[1] indicate that the active ingredient, paclitaxel, is distributed into tumor tissue more rapidly and at higher concentrations with this new formulation than with conventional, solvent-based paclitaxel.[2] In a phase II clinical study, albumin-bound paclitaxel was tolerated at a higher dose (300 mg/m^2 every 3 weeks) than that approved for the solvent-based formulation (175 mg/m^2 every 3 weeks) and was well tolerated.[3] In addition, the infusion time is shorter for albumin-bound paclitaxel than for solvent-based paclitaxel (30 minutes vs. 3 hours), and the *nab* formulation can be given without steroid or antihistamine premedication, special infusion sets, or in-line filters.

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In a phase III study, albumin-bound paclitaxel was compared with solvent-based paclitaxel in patients with taxane-naive metastatic breast cancer (MBC).[4] Albumin-bound paclitaxel demonstrated a significantly higher response rate (RR; 33% vs. 19%; $P = .001$) and significantly longer time to tumor progression (23 weeks vs. 16.9 weeks; hazard ratio, 0.75; $P = .006$) than the solvent-based formulation.

Weekly schedules of solvent-based paclitaxel have been compared with every-3-week schedules in patients with breast cancer in 2 phase III studies.[5,6] Weekly paclitaxel demonstrated greater antitumor activity than the every-3-week regimen but was associated with increased rates of neurotoxicity.

The current study was designed to explore albumin-bound whether albumin-bound paclitaxel (100 mg/m^2 or 125 mg/m^2 administered weekly for 3 weeks followed by 1 week of rest) has antitumor activity in patients with MBC that had progressed with conventional taxane therapy.

Patients and Methods

The protocol was approved by the US Oncology Institutional Review Board, and the study was conducted in compliance with Good Clinical Practice guidelines of the International Conference on Harmonization. Each patient provided written informed consent before the study drug was administered.

Patients

Women aged ≥ 18 years had histologically or cytologically confirmed breast cancer with evidence of recurrence or metastasis that was measurable according to Response Evaluation Criteria in Solid Tumors (RECIST).[7] Patients must have developed progressive disease (PD) while receiving a taxane for their metastatic disease or relapsed within 12 months of taxane-containing adjuvant therapy. Patients with HER2-positive MBC must have been treated previously with trastuzumab. Patients had to have adequate hematologic, hepatic, and renal function and expected survival of > 12 weeks.

Patients were excluded from participation if they had clinical evidence of active brain metastases, serious concurrent illness, a Southwest Oncology Group performance score of > 2, or peripheral neuropathy of grade > 1 based on National Cancer Institute Common Toxicity Criteria (NCI CTC) Version 2.0. No restriction was placed on enrollment based on the number of previous chemotherapy regimens.

Study Design

This open-label, phase II study was designed to evaluate the antitumor activity (overall RR [ORR]), safety, and tolerability of weekly albumin-bound paclitaxel in patients with MBC that had previously been treated with taxanes. Secondary objectives were to evaluate progression-free survival (PFS) and overall survival (OS).

Initially, patients were planned to receive albumin-bound paclitaxel 100 mg/m^2 intravenously (I.V.) over 30 minutes on days 1, 8, and 15, followed by 1 week of rest. Because minimal toxicity was observed with this dose and schedule, the protocol was amended to include an additional cohort of patients to receive 125 mg/m^2 weekly on days 1, 8, and 15, followed by 1 week of rest. Separate analyses were conducted for each cohort to determine whether the higher dose was associated with greater antitumor activity.

Treatment

Patients received albumin-bound paclitaxel 100 mg/m^2 or 125 mg/m^2 I.V. over 30 minutes without steroid or antihistamine premedication, recombinant human granulocyte colony-stimulating factor support, specialized infusion sets, or in line filters. Doses were administered on days 1, 8, and 15 and followed by 1 week of rest every 28 days (4-week cycle). Patients continued on treatment until disease progression or unacceptable toxicity occurred. If an adverse event required dose interruption, albumin-bound paclitaxel dosing was reinitiated at the start of a treatment cycle only if the patient's absolute neutrophil count (ANC) was ≥ 1500 cells/μL, platelet count was ≥ 100,000 cells/μL, or any other toxicity had resolved to grade 1. For each subsequent albumin-bound paclitaxel dose within a treatment cycle (days 8 and 15), patients had to have an ANC ≥ 1000 cells/μL and a platelet count ≥ 75,000 cells/μL.

Up to 2 dose reductions were permitted for patients who had febrile neutropenia, sepsis, grade 3/4 thrombocytopenia, neurotoxicity, or any other grade 3/4 nonhematologic toxicity. Dose reductions were from 100 mg/m^2 to 80 mg/m^2 to 60 mg/m^2 or from 125 mg/m^2 to 100 mg/m^2 to 75 mg/m^2.

Assessments

Tumor lesions were measured using RECIST at baseline and at the end of every other treatment cycle.[7] Response analyses were based on investigator evaluation of radiologically and clinically detected target lesions and were categorized according to RECIST. Responses to treatment were confirmed by restaging ≥ 4 weeks after the initial documentation of response. An early-stopping rule was incorporated into the study design, which mandated that the study be stopped if no objective responses were observed in the first 30 patients, thereby ruling out (at the $P = .05$ level) that the RR to albumin-bound paclitaxel in this patient population was ≥ 10%. Stable disease (SD) was evaluated after a minimum of 4 cycles, ie, at ≥ 16 weeks.

Adverse events were coded using the Medical Dictionary for Regulatory Activities and then mapped to appropriate NCI CTC terms.

Statistical Methods

The primary efficacy endpoint was the percentage of patients who achieved a confirmed objective, complete, or partial response (PR; ie, ORR). Secondary efficacy endpoints were the percentage of patients who achieved SD after ≥ 16 weeks, PFS, and OS. Disease control rate was defined as the percentage of patients who achieved a complete or PR plus those who had SD for ≥ 16 weeks. Safety and tolerability endpoints were the incidences of adverse events, hematologic nadir, and the percentages of patients who discontinued study treatment or had their doses reduced or treatment delayed.

Table 1A Patient Demographics and Other Baseline Characteristics (N = 181)

Characteristic	Albumin-Bound Paclitaxel	
	100 mg/m² (n = 106)	125 mg/m² (n = 75)
No. of Patients	106	75
Median Age, Years (Range)	53 (34-76)	53 (33-74)
< 65	86 (81)	56 (75)
≥ 65	20 (19)	19 (25)
Ethnicity (%)		
White	90 (85)	58 (77)
Black	7 (7)	6 (8)
Hispanic/Latino	4 (4)	11 (15)
Asian	3 (3)	0
Unknown	2 (2)	0
SWOG Performance Score (%)		
Number of patients	105*	75
0	48 (46)	34 (45)
1	51 (49)	32 (43)
2	5 (5)	9 (12)
3	1 (< 1)	0
Menopause Status (%)		
Postmenopausal	99 (93)	71 (95)
Premenopausal	7 (7)	4 (5)
Total Number of Metastatic Organ Sites (%)		
0	1 (< 1)	0
1	2 (2)	4 (5)
2-3	34 (32)	19 (25)
> 3	69 (65)	52 (69)
Dominant Lesion Site (%)		
Number of patients	105*	75
Visceral	99 (94)	67 (89)
Nonvisceral	6 (6)	8 (11)
Previous Trastuzumab Therapy (%)	23 (22)	26 (35)
Previous Taxane Therapy, by Schedule (%)		
Weekly	61 (58)	41 (55)
Every 3 weeks	73 (69)	43 (57)
Some other schedule	5 (5)	8 (11)
Multiple schedules	31 (29)	19 (25)

*Baseline evaluation was not available for 1 patient who was considered a nonresponder.
Abbreviation: SWOG = Southwest Oncology Group

The following were presented for each dose cohort for the primary efficacy analysis: sample size, number, and percentage of patients with a confirmed complete or PR, and 95% binomial confidence interval for the RR. All patients who received ≥ 1 dose of albumin-bound paclitaxel were included in the response and toxicity analyses.

Table 1B Patient Demographics and Other Baseline Characteristics (N = 181)

Characteristic	Albumin-Bound Paclitaxel	
	100 mg/m² (n = 106)	125 mg/m² (n = 75)
Previous Taxane Therapy on a Weekly Schedule for Metastatic Disease (%)		
Number of patients	58	41
Paclitaxel	23 (40)	18 (44)
Docetaxel	20 (34)	15 (37)
Paclitaxel/docetaxel	15 (26)	8 (20)
Previous Adjuvant Chemotherapy (%)		
Any	85 (80)	59 (79)
Anthracycline-containing	80 (75)	42 (56)
Taxane-containing	31 (29)	20 (27)
Patients with Metastatic Breast Cancer that Progressed with Previous Taxane Therapy (%)		
Tumor progression while on taxane therapy for metastatic disease	93 (88)	67 (89)
Paclitaxel	30 (28)	20 (27)
Docetaxel	34 (32)	28 (37)
Paclitaxel/docetaxel (sequential)	29 (27)	19 (25)
Relapse within 12 months of adjuvant taxane therapy	13 (12)	8 (11)
Median Number of Previous Chemotherapy Regimens for Metastatic Disease (Range)	3 (0-7)	3 (1-14)
Preexisting Peripheral Neuropathy by Grade (%)		
0	59 (56)	49 (65)
1	43 (41)	26 (35)
2	1 (< 1)	0
Unknown	3 (3)	0

Patients can appear in > 1 dosing regimen category.

Results

Between May 31, 2002 and December 29, 2003, 181 patients were enrolled at 43 sites in the United States (Table 1): 106 patients received albumin-bound paclitaxel 100 mg/m² under the original protocol; 75 additional patients were enrolled under the protocol amendment and received albumin-bound paclitaxel 125 mg/m².

Efficacy

The early-stopping rule was not activated because responses to albumin-bound paclitaxel occurred in some of the 30 initial patients. Thus, the stopping rule had no effect on the conduct of the study.

Complete or PRs were reported for 15 patients (14%) in the 100 mg/m² cohort and 12 patients (16%) in the 125-mg/m²

Table 2 Overall Response and Disease Control Rates (N = 181)

	Albumin-Bound Paclitaxel			
	Overall Response Rate		Disease Control Rate*	
	100 mg/m² (n = 106)	125 mg/m² (n = 75)	100 mg/m² (n = 106)	125 mg/m² (n = 75)
Number of Patients (%)	15 of 106 (14)	12 of 75 (16)	28 of 106 (26)	28 of 75 (37)
95% CI	7.52-20.79	7.7-24.3	18.02-34.81	26.39-48.28
P Value	.7309		.1175	
Response				
Complete response	0	1 of 75 (1)	0	1 of 75 (1)
Partial response	15 of 106 (14)	11 of 75 (15)	15 of 106 (14)	11 of 75 (15)
Stable disease ≥ 16 weeks	–	–	13 of 106 (12)	16 of 75 (21)
Number of Patients, by Previous Taxane Therapy for Metastatic Disease (%)				
By drug				
Paclitaxel	4 of 30 (13)	4 of 20 (20)	9 of 30 (30)	9 of 20 (45)
Docetaxel	7 of 34 (21)	6 of 28 (21)	11 of 34 (32)	13 of 28 (46)
Paclitaxel/docetaxel	2 of 29 (7)	0	6 of 29 (21)	4 of 19 (21)
By schedule (any taxane)†				
Weekly	7 of 58 (12)	7 of 41 (17)	14 of 58 (24)	16 of 41 (39)
Every 3 weeks	6 of 48 (13)	4 of 29 (14)	13 of 48 (27)	9 of 29 (31)
Number of Patients, by Previous Weekly Taxane Therapy for Metastatic Disease (%)				
Paclitaxel	0	3 of 18 (17)	3 of 23 (13)	6 of 18 (33)
Docetaxel	6 of 20 (30)	4 of 15 (27)	8 of 20 (40)	7 of 15 (47)
Paclitaxel/docetaxel	1 of 15 (7)	0	3 of 15 (20)	3 of 8 (38)

*Disease control rate is the complete/PRs plus SD ≥ 16 weeks.
†Five additional patients in the 125-mg/m² cohort received taxanes as adjuvant therapy.

cohort (Table 2). Stable disease for ≥ 16 weeks was observed in an additional 13 patients (12%) in the 100-mg/m² cohort and 16 patients (21%) in the 125-mg/m² cohort. Median PFS was 3 months for 100 mg/m² and 3.5 months for 125 mg/m². Median OS was 9.2 months and 9.1 months, respectively. Overall survival was similar for patients with confirmed responses and for nonresponders with SD ≥ 16 weeks (P = .7106, log-rank; Figure 1). Based on Kaplan-Meier curves for patient survival, the probability of surviving 1 year was 39% and 32% for the 100-mg/m² and 125-mg/m² cohorts, respectively. No statistically significant differences in ORR, disease control rate, or PFS were observed between the 100-mg/m² and 125-mg/m² cohorts or between patients who achieved an objective response and nonresponders who had SD ≥ 16 weeks (Table 2; Figure 1). Four patients (4%) in the 100-mg/m² cohort and 7 patients (9%) in the 125 mg/m² cohort had SD for ≥ 24 weeks.

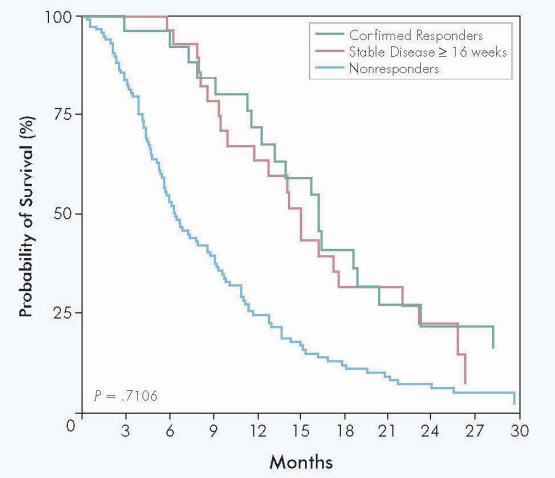
Of the patients who received previous taxane therapy on a weekly schedule, the percentage of objective responders was greater at both dose levels for those who had received docetaxel alone (30% with albumin-bound paclitaxel 100 mg/m², 27% with 125 mg/m²) than for those who had received paclitaxel alone (0 for 100 mg/m², 17% for 125 mg/m²; Table 2). No significant differences in objective response or disease control rates according to hormone receptor status or site of metastatic disease were seen with albumin-bound paclitaxel treatment (Table 3).

Safety

Treatment was well tolerated; 87% of patients in the 100-mg/m² cohort and 68% of patients in the 125-mg/m² cohort received albumin-bound paclitaxel at the protocol-specified dose throughout the study. Patients received a mean of 5.3 and 4.7 cycles of albumin-bound paclitaxel treatment in the 100-mg/m² and 125-mg/m² dose groups, respectively. Patients received a mean of 15.2 doses in the 100-mg/m² cohort and 13.1 doses in the 125-mg/m² cohort; median cumulative doses were 900.5 mg/m² and 1125 mg/m², respectively. The median delivered dose intensity was 98 mg/m² (range, 36-103 mg/m²) per week in the 100-mg/m² cohort and 114 mg/m² (range, 77-131 mg/m²) per week in the 125-mg/m² cohort.

Treatment-related adverse events (all grades) resulted in discontinuation of therapy for 6 patients (6%) in the 100-mg/m² cohort and 7 patients (9%) in the 125 mg/m² cohort (primarily for sensory neuropathy); dose reductions for 13

Figure 1 Survival Curves for the 100-mg/m^2 and 125-mg/m^2 Cohorts Combined (N = 181)



Confirmed responders (n = 27); patients with SD ≥ 16 weeks, excluding confirmed responders (n = 29); and nonresponders (n = 125). Survival was similar for patients with confirmed responses and nonresponders with SD ≥ 16 weeks (P = .7106, log-rank).

patients (12%) and 24 patients (32%) in the 100-mg/m^2 and 125-mg/m^2 cohorts, respectively (primarily for sensory neuropathy); and dose delays for 19 patients (18%) and 32 patients (43%) in the 100-mg/m^2 and 125-mg/m^2 cohorts, respectively (primarily for neutropenia).

Despite the high degree of pretreatment, grade 4 neutropenia and leukopenia occurred in < 5% of patients in both cohorts (Table 4). Grade 4 febrile neutropenia occurred in 1 patient (< 1%) in the 100-mg/m^2 cohort.

No treatment-related grade 4 nonhematologic adverse events were reported for > 1 patient in either group. No severe hypersensitivity reactions were observed in either group, despite the absence of steroid premedication.

In the 100-mg/m^2 cohort, 9 patients (8%) developed treatment-related grade 3 sensory neuropathy (ie, sensory loss or paresthesia interfering with activities of daily living), 3 of whom had preexisting grade 1 neuropathy; onset occurred after a median of 5 treatment cycles (range, 1-23 cycles). In the 125-mg/m^2 cohort, 14 patients (19%) developed grade 3 sensory neuropathy, 3 of whom had preexisting grade 1 peripheral neuropathy; onset occurred after a median of 3 cycles (range, 2-6 cycles). Of the 23 patients with grade 3 sensory neuropathy (both cohorts combined), 15 patients restarted albumin-bound paclitaxel treatment at a reduced dosage, 4 patients continued treatment on schedule with no treatment modification, 3 patients discontinued treatment, and 1 patient discontinued treatment because of PD at the time grade 3 sensory neuropathy occurred. Patients who continued treatment were able to resume dosing, typically in 1-2 weeks.

Treatment-related alopecia was reported in both groups. In the 100-mg/m^2 cohort, 16 patients (15%) had grade 1 (mild) alopecia and 37 patients (35%) had grade 2 (pronounced) alopecia; in the 125-mg/m^2 cohort, 3 patients (4%) and 36 patients (48%) reported grade 1/2 alopecia, respectively. However, many of the patients in this heavily pretreated study population (31% in the 100-mg/m^2 cohort, 41% in the 125-mg/m^2 cohort) had alopecia at time of enrollment. In general, the toxicity profile for patients aged ≥ 65 years was similar to that for patients aged < 65 years in both cohorts (Figure 2).

Table 3 Response Rates by Hormone Receptor Status and Site of Metastatic Disease (N = 181)

	Albumin-Bound Paclitaxel			
	Overall Response Rate		Disease Control Rate*	
	100 mg/m^2 (n = 106)	125 mg/m^2 (n = 75)	100 mg/m^2 (n = 106)	125 mg/m^2 (n = 75)
Number of Patients, by Hormone Receptor Status (%)				
ER$^+$, PgR$^+$	5 of 39 (13)	5 of 31 (16)	11 of 39 (28)	15 of 31 (48)
ER$^+$, PgR$^-$	1 of 13 (8)	2 of 11 (18)	1 of 13 (8)	3 of 11 (27)
HER2$^+$	4 of 35 (11)	6 of 37 (16)	10 of 35 (29)	14 of 37 (38)
ER$^-$, PgR$^-$, HER2$^-$	3 of 21 (14)	1 of 7 (14)	5 of 21 (24)	1 of 7 (14)
Number of Patients, by Site of Metastatic Disease (%)				
Bone	10 of 44 (23)	4 of 31 (13)	17 of 44 (39)	11 of 31 (35)
Lungs	8 of 75 (11)	4 of 46 (9)	16 of 75 (21)	14 of 46 (30)
Liver	7 of 66 (11)	5 of 48 (10)	13 of 66 (20)	16 of 48 (33)
Lymph nodes	4 of 22 (18)	3 of 13 (23)	5 of 22 (23)	6 of 13 (46)
Abdomen†	4 of 14 (24)	2 of 14 (14)	5 of 14 (36)	5 of 14 (36)
Skin	0	3 of 10 (30)	3 of 10 (30)	5 of 10 (50)

*Disease control rate is complete/PRs plus SD ≥ 16 weeks.
†Peritoneal carcinomatosis.
Abbreviations: ER = estrogen receptor; PgR = progesterone receptor

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