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ORIGINAL REPORT

Phase III Trial of Nanoparticle Albumin-Bound Paclitaxel Compared With Polyethylated Castor Oil–Based Paclitaxel in Women With Breast Cancer

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ABSTRACT

Purpose
ABI-007, the first biologically interactive albumin-bound paclitaxel in a nanameter particle, free of solvents, was compared with polyethylated castor oil–based standard paclitaxel in patients with metastatic breast cancer (MBC). This phase III study was performed to confirm preclinical studies demonstrating superior efficacy and reduced toxicity of ABI-007 compared with standard paclitaxel.

Patients and Methods
Patients were randomly assigned to 3-week cycles of either ABI-007 260 mg/m^2 intravenously without premedication (n = 229) or standard paclitaxel 175 mg/m^2 intravenously with premedication (n = 225).

Results
ABI-007 demonstrated significantly higher response rates compared with standard paclitaxel (33% *v* 19%, respectively; $P = .001$) and significantly longer time to tumor progression (23.0 *v* 16.9 weeks, respectively; hazard ratio = 0.75; $P = .006$). The incidence of grade 4 neutropenia was significantly lower for ABI-007 compared with standard paclitaxel (9% *v* 22%, respectively; $P < .001$) despite a 49% higher paclitaxel dose. Febrile neutropenia was uncommon (< 2%), and the incidence did not differ between the two study arms. Grade 3 sensory neuropathy was more common in the ABI-007 arm than in the standard paclitaxel arm (10% *v* 2%, respectively; $P < .001$) but was easily managed and improved rapidly (median, 22 days). No hypersensitivity reactions occurred with ABI-007 despite the absence of premedication and shorter administration time.

Conclusion
ABI-007 demonstrated greater efficacy and a favorable safety profile compared with standard paclitaxel in this patient population. The improved therapeutic index and elimination of corticosteroid premedication required for solvent-based taxanes make the novel albumin-bound paclitaxel ABI-007 an important advance in the treatment of MBC.

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INTRODUCTION

The currently available taxanes, paclitaxel (Taxol; Bristol-Myers Squibb Co, Princeton, NJ) and docetaxel (Taxotere; Aventis Pharmaceuticals Inc, Bridgewater, NJ), play a central role in the treatment of breast cancer. Because the taxanes are highly hydrophobic, commercially available formulations include synthetic solvents to enable parenteral administration; paclitaxel contains a combination of polyethylated castor oil (Cremophor EL; BASF, Ludwigshafen, Germany) and ethanol as the vehicle,[1] and polysorbate 80 and an ethanol diluent are the vehicles for docetaxel.[2]

Although paclitaxel and docetaxel proved to have significant activity against

breast cancer and other solid tumors, emerging data indicate that the solvents polyethylated castor oil and polysorbate 80 directly contribute to the severe toxicities observed in patients treated with paclitaxel or docetaxel. Among the well-characterized, solvent-related toxicities are hypersensitivity reactions, which can rarely be fatal even with corticosteroid premedication, and prolonged, sometimes irreversible, peripheral neuropathy associated with demyelination and axonal degeneration.[3-5] More recently, it has been recognized that these solvents may adversely affect efficacy because of entrapment of active drug in micelles formed in the plasma compartment,[6,7] leading to increased systemic drug exposure, decreased drug clearance, nonlinear pharmacokinetics, and lack of dose-dependent antitumor activity.[6-9] Drug entrapment affects not only the taxanes but also the coadministered drugs (eg, anthracyclines) and, thus, is an important consideration in the design of combination therapies.[6]

ABI-007 (Abraxane; American BioScience Inc, Santa Monica, CA) is a novel, biologically interactive, nanometer-sized albumin-bound paclitaxel particle initially developed to avoid the toxicities associated with polyethylated castor oil. It is the first of a new class of anticancer agents that incorporate albumin particle technology and exploit the unique properties of albumin, a natural carrier of lipophilic molecules in humans. Administered as a colloidal suspension of 130 nanometer particles, ABI-007 allows the safe infusion of significantly higher doses of paclitaxel than the doses used with standard paclitaxel therapy, with shorter infusion schedules (30 minutes *v* 3 hours, respectively) and no premedication. In addition, the albumin-bound nanoparticle was designed to preferentially deliver paclitaxel to tumors by biologically interacting with albumin receptors that mediate drug transport; in vitro studies have demonstrated a 4.5-fold increase in paclitaxel transport across endothelial cells for ABI-007 compared with standard paclitaxel.[10]

A phase I trial of ABI-007 in 19 patients with advanced solid tumors[11] determined the maximum-tolerated dose to be 300 mg/m^2, which is approximately 70% higher than the conventional paclitaxel (175 mg/m^2).[12] No severe hypersensitivity reactions occurred with ABI-007, despite the absence of premedication and administration over 30 minutes. Dose-limiting toxicities included sensory neuropathy, stomatitis, and superficial keratopathy, which occurred at a dose of 375 mg/m^2. Pharmacokinetic analysis revealed linear increases in paclitaxel maximum concentration and area under the concentration-time curve over the ABI-007 dose range of 135 to 300 mg/m^2.

A phase II trial (Ibrahim et al, submitted for publication) evaluating ABI-007 at 300 mg/m^2 in patients with metastatic breast cancer (MBC) demonstrated an overall response rate (ORR) of 48%, with a response rate of 64% for patients who received ABI-007 as first-line therapy. Time to tumor progression (TTP) was 26.6 weeks for all patients and 48.1 weeks for patients with confirmed tumor responses; median overall survival was 63.6 weeks. The observed adverse events (AEs) of myelosuppression and peripheral neuropathy were less frequent and less severe than what would be expected with comparable doses of standard paclitaxel.[12] No severe ocular events occurred, and no hypersensitivity reactions were reported despite the absence of premedication. These findings suggested that ABI-007 may offer important advantages over standard paclitaxel and supported the conduct of this phase III trial.

The present study was designed to directly compare the efficacy and safety of ABI-007 with standard paclitaxel in patients with MBC in a randomized trial. The dose of ABI-007 was reduced from the maximum-tolerated dose used in the phase II study to 260 mg/m^2 with the expectation that the ABI-007 regimen would not be more toxic than the standard dose of standard paclitaxel (175 mg/m^2).

PATIENTS AND METHODS

This international, randomized, open-label, phase III study was conducted at 70 sites (28 Russia/Ukraine sites, 350 patients; 22 United States/Canada sites, 37 patients; and 20 United Kingdom sites, 67 patients). The protocol and related materials were approved by the appropriate institutional review boards and independent ethics committees. The study was conducted in compliance with Good Clinical Practice, Guidelines of the International Conference on Harmonization, and the Declaration of Helsinki. Written informed consent was required from all patients.

Patient Population

Nonpregnant, nonlactating females at least 18 years of age with histologically or cytologically confirmed, measurable MBC and an expected survival of more than 12 weeks were eligible for participation. Patients were included if they were candidates for single-agent paclitaxel therapy; had not received paclitaxel or docetaxel for metastatic carcinoma; had not relapsed with metastatic disease within 1 year of adjuvant paclitaxel or docetaxel treatment; had no other malignancy within the previous 5 years except nonmelanoma skin cancer, cervical intraepithelial neoplasia, or in situ cervical cancer; and had acceptable clinical laboratory test results at baseline.

Patients were excluded from participation if they had clinical evidence of active brain metastasis or a clinically serious concurrent illness; an Eastern Cooperative Oncology Group (ECOG) performance status of more than 2; received hormone therapy for 2 weeks or chemotherapy, immunotherapy, or another investigational drug for 4 weeks before administration of the first study dose; pre-existing peripheral neuropathy of grade 1 according to National Cancer Institute Common Toxicity Criteria; or a history of allergic or hypersensitivity reactions to the study drug or any of its excipients.

Treatment

Eligible patients were randomly assigned (1:1) to receive treatment every 3 weeks with either ABI-007 (260 mg/m^2 intravenously over 30 minutes without corticosteroid or antihistamine premedication or special infusion sets) or standard paclitaxel (175 mg/m^2 intravenously over 3 hours with premedication and special infusion sets as

indicated in the prescribing information).[1] Within-country balance for anthracycline exposure was ensured by within-country stratification into anthracycline-exposed and -naive groups. Up to two dose reductions (40 mg/m^2 each) were allowed from the initial 260 mg/m^2 dose of ABI-007. Reductions in standard paclitaxel doses were allowed according to the package insert for each country.

Assessments

Imaging studies were performed at baseline, at weeks 5, 9, and 15, and at the end of treatment. Responses were assessed according to Response Evaluation Criteria in Solid Tumor guidelines.[13] Complete and partial responses required subsequent confirmation of response $\geq$ 4 weeks later.

The primary efficacy measure was ORR; secondary efficacy measures were TTP and overall survival. Quality-of-life (QOL) assessment data (ECOG performance status, scores from the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30, and body weight) were collected.

Statistical Analysis

The statistical power of this study was based on a noninferiority design, proving that ABI-007 was at least 75% as active as standard paclitaxel, assuming an ORR 20% greater than the ORR of standard paclitaxel. The design had 80% power, with a one-sided type I error of 0.025 (two-sided α = .050). All statistical analyses were performed with SAS Version 8.2 (SAS Institute Inc, Cary, NC). The primary efficacy analysis consisted of three nested tests, which were conducted sequentially and contingent on the prior test(s) being successful; these tests were noninferiority, with all patients; superiority, with all patients; and superiority, with patients receiving study drug as first-line therapy. Treatment differences in TTP and survival were analyzed using the Kaplan-Meier method.[14] QOL, which was measured using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30, was analyzed as change from baseline at each cycle. ECOG performance status was analyzed by cycle and as the worst score at any time during the study. The influence of prognostic factors on ORR was assessed using a logistic regression model with effects for country, treatment group, prognostic factor, and treatment group-by-prognostic factor interaction. AEs and laboratory toxicities were classified and graded according to National Cancer Institute Common Toxicity Criteria and analyzed by maximum grade using the Cochran-Mantel-Haenszel test.[15]

RESULTS

Patient Population

From November 2001 to November 2002, 460 patients were enrolled onto the study and randomly assigned to treatment groups. All patients were female, 97% were white, and 83% were postmenopausal. The study population typically had more than three metastatic lesions (76%), visceral (lung, abdominal, or liver) disease (79%), prior chemotherapy (86%), and progression after first-line therapy for metastatic disease (59%). No important between-group differences were noted in demographic or other baseline characteristics (Table 1).

Six patients (1%) did not receive study drug; the remaining 454 patients (ABI-007, n = 229; standard paclitaxel, n = 225) were considered the intent-to-treat (ITT) population. Almost all (> 99%) of the ABI-007 infusions were administered in 50 minutes or less, and 81.5% were infused over 30 minutes; 22.9% of the standard paclitaxel infusions were longer than the planned infusion time of 180 minutes. Actual delivered paclitaxel dose-intensity was 49% higher in the ABI-007 group than in the standard paclitaxel group (mean $\pm$ standard deviation, 85.13 $\pm$ 3.118 mg/m^2 *v* 57.02 $\pm$ 3.008 mg/m^2 per week, respectively). At least six treatment cycles were administered to 129 patients (56%) in the ABI-007 group and 112 patients (50%) in the standard paclitaxel group. The last patient came off study in April 2004.

Efficacy

Efficacy analyses were based on the ITT population. The ORR was significantly greater for ABI-007 than for standard paclitaxel for all patients (33% *v* 19%, respectively; P = .001), patients who received first-line therapy (42% *v* 27%, respectively; P = .029), patients who received second-line or greater therapy (27% *v* 13%, respectively; P = .006), and patients who had received prior anthracycline therapy in either the adjuvant/metastatic setting (34% *v* 18%, respectively; P = .002) or the metastatic setting only (27% *v* 14%, respectively; P = .010; Table 2). Tumor response rate was also significantly higher for ABI-007 than for standard paclitaxel in patients with visceral dominant lesions (34% *v* 19%, respectively; P = .002) and in patients aged younger than 65 years (34% *v* 19%, respectively; P < .001; Table 2). ORR also was greater for ABI-007 compared with standard paclitaxel in patients with nonvisceral dominant lesions (34% *v* 19%, respectively) and in patients $\geq$ 65 years old (27% *v* 19%, respectively), but the results did not reach statistical significance because of the small number of patients in these subsets.

Maximum responses occurred by cycle 3 in 91% of responders in the ABI-007 group and in 81% of responders in the standard paclitaxel group. For ORR, no significant interaction with treatment effect was observed for the prognostic factors assessed, indicating that the treatment effect of ABI-007 versus standard paclitaxel was consistent between the strata of these factors.

Median TTP was significantly longer with ABI-007 than with standard paclitaxel for all patients (23.0 *v* 16.9 weeks, respectively; hazard ratio [HR] = 0.75; P = .006, log-rank test; Fig 1). TTP was longer for patients who received first-line therapy compared with other patients (24.0 *v* 19.7 weeks, respectively), although the difference was not statistically significant. TTP also was significantly longer with ABI-007 than with standard paclitaxel for patients who received study drug as second-line or greater therapy (20.9 *v* 16.1 weeks, respectively; HR = 0.73; P = .020).

Table 1. Demographic and Other Baseline Characteristics

Characteristic	ABI-007 (n = 229)		Standard Paclitaxel (n = 225)	
	No. of Patients	%	No. of Patients	%
Sex, female	229	100	225	100
Age, years				
Mean		53.1		53.3
SD		10.18		10.05
Range		26-79		30-83
< 65	199	87	193	86
≥ 65	30	13	32	14
Ethnicity*				
White	221	97	218	97
Black	1	< 1	5	2
Hispanic	3	1	2	< 1
South Asian	2	< 1	0	0
Asian	1	< 1	0	0
Other	1	< 1	0	0
Body weight, kg				
No. of patients	225		223	
Mean		70.6		69.4
SD		14.09		12.38
Range		42-125		40-105
ECOG status*				
1	134	59	138	61
0	81	35	82	36
2-3	14	6	5	2
Menopausal status				
Postmenopausal	189	83	187	83
Premenopausal	40	17	38	17
No. of lesions*				
> 3	180	79	163	72
2-3	42	18	53	24
1	7	3	9	4
Dominant metastatic organ site*				
Liver	92	40	97	43
Lung	74	32	79	35
Only lymph nodes, soft tissue, and/or breast	37	16	30	13
Bone	13	6	13	6
Abdominal	10	4	6	3
Unknown	3	1	0	0
Prior metastatic chemotherapy regimens*				
0, study drug administered as first-line therapy	97	42	89	40
1	94	41	96	43
2	23	10	35	16
≥ 3	15	7	5	2
Prior therapy*				
Chemotherapy				
No	28	12	34	15
Yes	201	88	191	85
Anthracycline therapy				
No	53	23	50	22
Yes	176	77	175	78
Metastatic only	115	50	130	58

Abbreviations: ECOG, Eastern Cooperative Oncology Group; SD, standard deviation.
*Percentages may not total 100 because of rounding.

At the time of these analyses (October 2004), the median censoring time for overall patient survival was 103 weeks for the ABI-007 group and 101 weeks for the standard paclitaxel group. There was a trend for greater median survival for all patients treated with ABI-007 than with standard paclitaxel (65.0 *v* 55.7 weeks, respectively;

Table 2. Response Rates

Response	ABI-007 (260 mg/m^2) No. of Patients/Total No. of Patients	%	95% CI (%)	Standard Paclitaxel (175 mg/m^2) No. of Patients/Total No. of Patients	%	95% CI (%)	*P*
Complete and partial response							
All patients	76/229	33	27.09 to 39.29	42/225	19	13.58 to 23.76	.001
First-line therapy	41/97	42	32.44 to 52.10	24/89	27	17.75 to 36.19	.029
Second-line or greater therapy	35/132	27	18.98 to 34.05	18/136	13	7.54 to 18.93	.006
Prior anthracycline therapy							
Adjuvant and/or metastatic	60/176	34	27.09 to 41.09	32/175	18	12.56 to 24.01	.002
Metastatic only	31/115	27	18.85 to 35.07	18/130	14	7.91 to 19.78	.010
Dominant metastatic organ site							
Visceral	59/176	34	26.55 to 40.50	34/182	19	13.02 to 24.34	.002
Nonvisceral	17/50	34	20.87 to 47.13	8/43	19	6.97 to 30.24	NS
Age, years							
< 65	68/199	34	27.58 to 40.76	36/193	19	13.16 to 24.15	$< .001$
≥ 65	8/30	27	10.84 to 42.49	6/32	19	5.23 to 32.27	NS

Abbreviation: NS, not significant statistically.

$P = .374$; Fig 2A). Although no difference in survival was observed in first-line patients, the difference was statistically significant in patients who received ABI-007, compared with standard paclitaxel, as second-line or greater therapy (56.4 *v* 46.7 weeks, respectively; HR = 0.73; $P = .024$; Fig 2B).

Safety

All 454 patients in the ITT population were included in the safety analysis. Although the patients in the ABI-007 group received an average paclitaxel dose-intensity 49% greater than that received by patients in the standard paclitaxel group, treatment compliance was high, with 96% of patients in the ABI-007 group receiving 90% of the protocol-specified dose. Similarly, of the patients who received standard paclitaxel at 175 mg/m^2, 94% received 90% of the protocol-specified dose. Furthermore, AE-related discontinuations, dose reductions, and dose delays were infrequent (3% to 7%) in both treatment arms, with no statistically significant differences noted between the groups. Consistent with the safety data, no differences in QOL were noted between the two treatment groups despite the higher dose administered to the ABI-007 group (Fig 3).

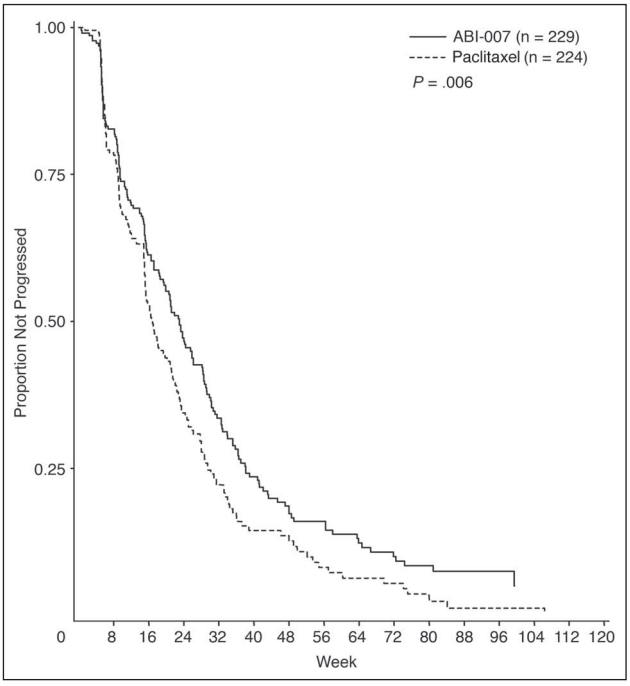

Fig 1. Median time to disease progression.

The incidence of hypersensitivity reactions (any grade) was low for both arms ($<$ 1% for ABI-007 and 2% for standard paclitaxel). No severe (grade 3 or 4) treatment-related hypersensitivity reactions occurred in any of the patients in the ABI-007 group despite the absence of premedication. In contrast, grade 3 hypersensitivity reactions occurred in the standard paclitaxel group despite standard premedication (chest pain, two patients; allergic reaction, three patients). Per protocol, corticosteroids and antihistamines were not administered routinely to patients in the ABI-007 group; however, premedication was administered for emesis, myalgia/arthralgia, or anorexia in 18 patients (8%) in the ABI-007 group in 2% of the treatment cycles, whereas 224 patients ($>$ 99%) in the standard paclitaxel group received premedication in 95% of the cycles.

The most frequently reported AEs (all grades) are presented in Figure 4A, and treatment-related grade 3 and 4 AEs are presented in Figure 4B. Despite the higher dose of paclitaxel administered to patients in the ABI-007 group, the incidence of treatment-related grade 4 neutropenia

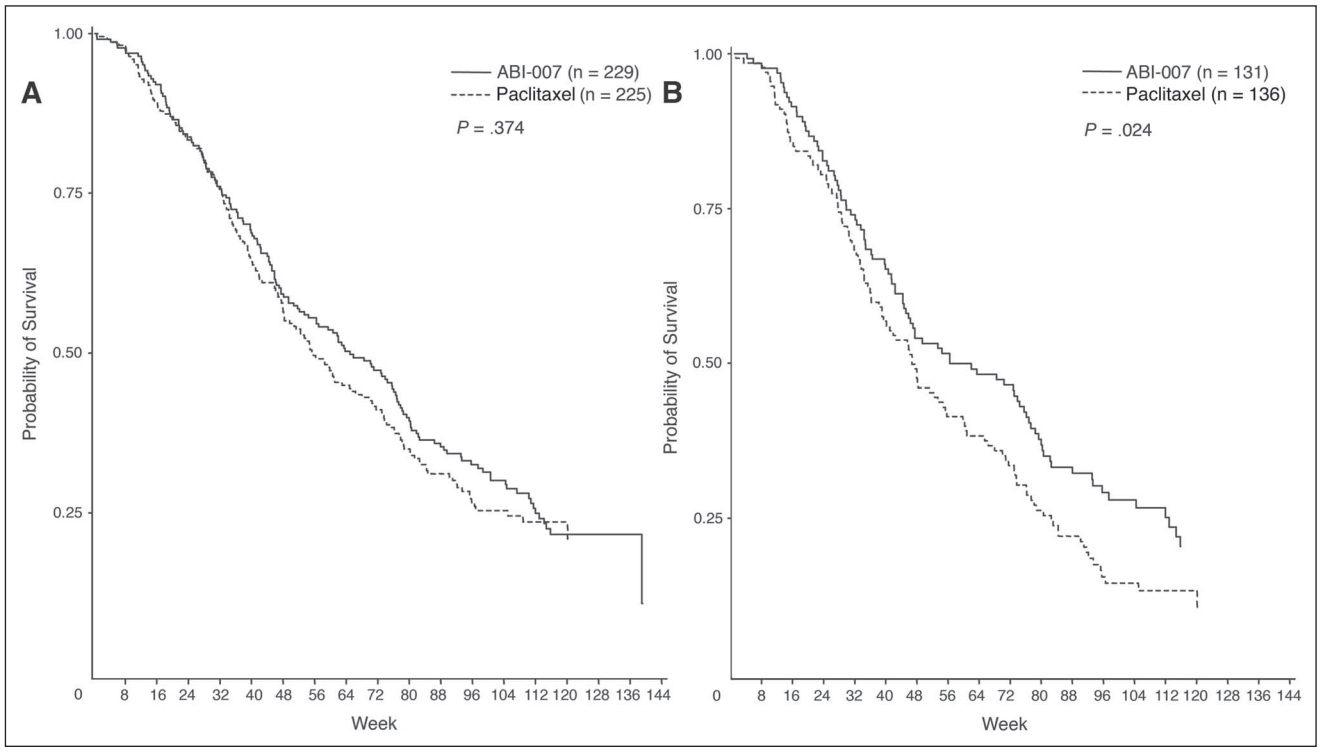

Fig 2. (A) Patient survival over time. (B) Patient survival over time in patients who received second-line or greater therapy. *P* values from log-rank test. Survival indicates time from first dose of study drug to date of death.

(based on the central laboratory test values) was significantly lower in the ABI-007 group than in the standard paclitaxel group (20 of 226 patients, 9% *v* 48 of 222 patients, 22%, respectively; $P < .001$), with a higher mean neutrophil nadir (1.67 *v* 1.31 $\times$ 10^9/L, respectively; $P = .046$), suggesting that polyethylated castor oil may have contributed to this toxicity in patients who received standard paclitaxel.

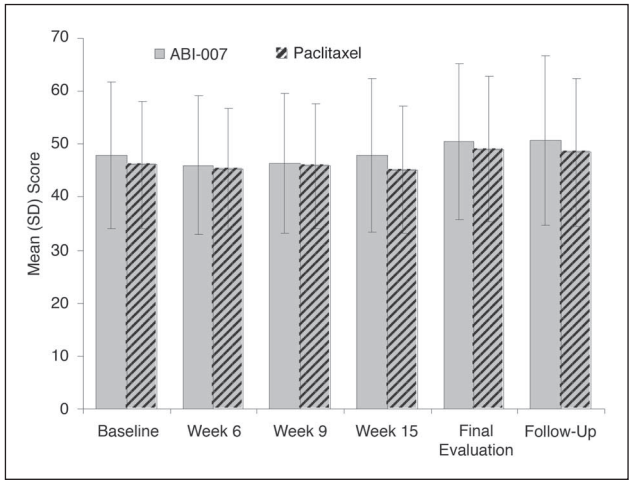

Fig 3. Quality-of-life measurements (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30) for patients receiving ABI-007 or standard paclitaxel. SD, standard deviation.

Febrile neutropenia was uncommon (< 2%) in both study arms, and no septic deaths occurred. Eight patients (3%) in the ABI-007 group and 14 patients (6%) in the standard paclitaxel group received growth factor treatment for neutropenia or leukopenia during the study.

As expected with a higher dose of paclitaxel, treatment-related grade 3 sensory neuropathy occurred more frequently in the ABI-007 arm than in the standard paclitaxel arm (24 patients, 10% *v* five patients, 2%, respectively; $P < .001$; Fig 4B); however, these episodes improved with interruption of treatment to grade 2 or 1 in a median 22 days and were easily managed with treatment interruption and dose reduction (Fig 5). By day 28 after its first occurrence, the number of patients with persistent grade 3 sensory neuropathy was the same (n = 4) in both study arms. No episodes of motor neuropathy or grade 4 sensory neuropathy were reported in either group, and no differences in physician or patient grading of peripheral neuropathy were observed between the two groups when these parameters were analyzed on the basis of total paclitaxel dose administered. The only clinical chemistry value that was notably different between the two treatment arms was higher serum glucose levels in the standard paclitaxel–treated patients, who also had a higher incidence of hyperglycemia reported as an AE compared with ABI-007–treated patients (15 patients, 7% *v* three patients, 1%, respectively; $P = .003$).

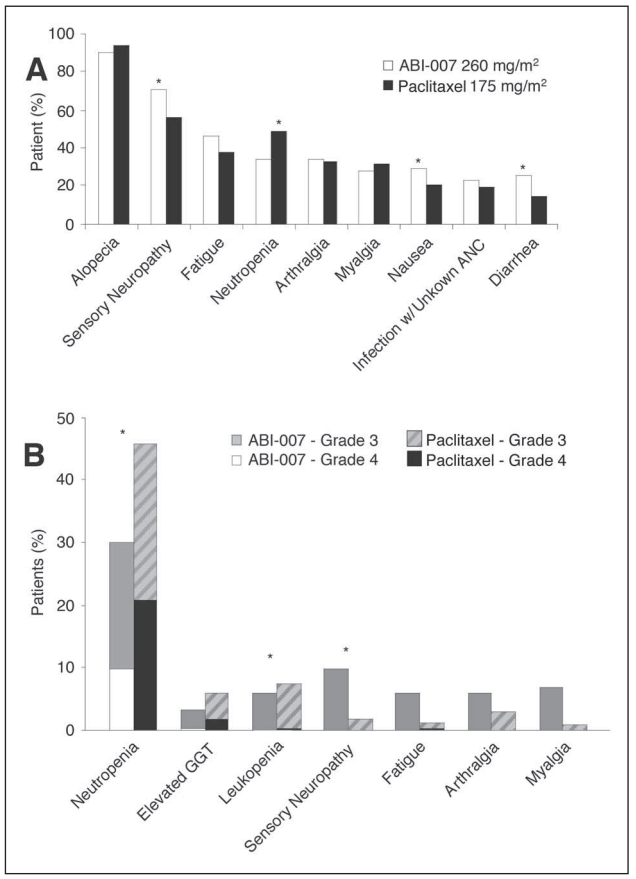

Fig 4. (A) Adverse events (all grades) reported in more than 20% of patients in either treatment group. ANC, absolute neutrophil count. (B) Treatment-related grade 3 and 4 adverse events reported in ≥ 5% of patients in either group. Data are based on adverse event reporting. (*) $P < .05$, Cochran-Mantel-Haenszel test. GGT, gamma glutamyl transferase.

Subgroup analyses revealed that the safety profiles of ABI-007 and standard paclitaxel in patients who received the drugs as first-line therapy were similar to those in the overall study population. In subgroup analyses by age, the reported AEs were similar in patients less than 65 years old and patients ≥ 65 years old in both groups. Of the patients ≥ 65 years old, the incidences of the following AEs were notably lower in the ABI-007 group than in the standard paclitaxel group: neutropenia (23% *v* 59%, respectively), leukopenia (10% *v* 31%, respectively), nausea (20% *v* 38%, respectively), hyperglycemia (0% *v* 19%, respectively), and flushing (0% *v* 16%, respectively). These data indicate no additional safety concerns for ABI-007 in patients ≥ 65 years old compared with younger patients.

Six patients (3%) in the ABI-007 group and eight patients (4%) in the standard paclitaxel group died during the study, all as a result of disease progression. No treatment-related deaths occurred in the ABI-007 group; one patient (< 1%) in the standard paclitaxel group died of multiorgan failure, which was considered by the investigator to be possibly related to treatment but may also have been a result of sepsis and/or progressive disease.

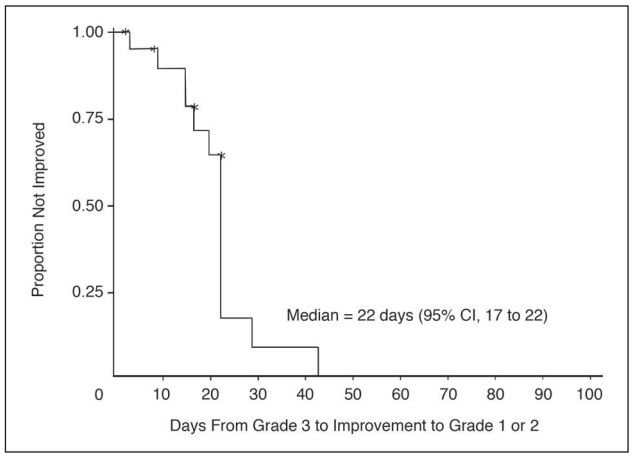

Fig 5. Time to improvement in ABI-007–treated patients who developed grade 3 peripheral neuropathy. (*) Censored.

DISCUSSION

In this large, international phase III study, ABI-007, a novel 130 nanometer albumin-bound paclitaxel particle, was superior to standard paclitaxel for both ORR and TTP in all patients with MBC. The ABI-007 dose used in this study (≈50% higher than the dose delivered with solvent-based paclitaxel) could be administered safely over 30 minutes without premedication. Paclitaxel particles were well tolerated, requiring minimal dose modification for AEs, and no severe hypersensitivity reactions to ABI-007 occurred despite the absence of corticosteroid premedication.

The robustness of the efficacy data is underscored by the consistent finding of greater tumor response to ABI-007 than to standard paclitaxel in subgroup analyses. The ORR of ABI-007 was superior for all patients, patients who received study drug as first-line therapy, patients who received study drug as second-line or greater therapy, patients with prior anthracycline exposure, elderly patients, and patients with poor prognostic factors, including visceral tumor involvement. Median TTP for all patients was significantly longer in the ABI-007 group than in the standard paclitaxel group ($P = .006$). Patients receiving ABI-007 as second-line or greater therapy, whose clinical course would be less affected by subsequent therapies, had significantly prolonged survival, with the risk for death being reduced by 28%.

Preclinical models demonstrated increased antitumor activity and higher intratumor paclitaxel concentrations for ABI-007 compared with equal doses of standard paclitaxel.[16] In addition, ABI-007 was less toxic than standard paclitaxel, permitting the administration of 50% higher doses. These two factors of higher intratumor paclitaxel

concentrations and higher dose administered may explain the increased antitumor activity demonstrated for ABI-007 compared with standard paclitaxel in this randomized study.

The findings of improved efficacy with high doses of albumin-bound paclitaxel (ABI-007) in patients with MBC are in contrast to the recently reported failure of high doses of polyethylated castor oil–based paclitaxel (standard paclitaxel) to improve outcome in similar patients. In a large study conducted by the Cancer and Leukemia Group B (CALGB),[8] the response rates for first- or second-line patients treated with standard paclitaxel 175, 210, or 250 mg/m^2 administered as a 3-hour infusion every 3 weeks were 23%, 26%, and 21%, respectively. By contrast, tumor response with ABI-007 260 mg/m^2 was significantly greater than that achieved with standard paclitaxel 175 mg/m^2 (33% *v* 19%, respectively; $P = .001$). Similarly, TTP, which was comparable for standard paclitaxel 175 mg/m^2 in both the CALGB trial and the present study (17.0 and 16.1 weeks, respectively), improved significantly with ABI-007 ($P = .03$) but not with standard paclitaxel 250 mg/m^2 ($P = .12$).

The failure of higher doses of solvent-based paclitaxel to improve outcome may not reflect on paclitaxel per se, but rather on the increasing concentrations of the polyethylated castor oil vehicle, which is known to entrap paclitaxel in micelles, thereby limiting bioavailability and antitumor activity.[3,6,17-20] Results of the present study indicate that such limitations may be overcome by the use of albumin-bound paclitaxel.

There may also be a fundamental difference between ABI-007 and standard paclitaxel with respect to albumin receptor–mediated drug transport and binding of the albumin-drug complex to proteins expressed in tumor tissue. Albumin-bound macromolecules can leave the circulation through leaky tumor microvasculature and accumulate in the interstitium because of the enhanced permeation and retention effects characteristic of neoplasia.[21] In addition, albumin is actively transported across microvessel endothelial cells via a unique receptor-mediated transport mechanism using the gp60 receptor.[22] Binding of albumin to its gp60 receptor on endothelial cells activates caveolin-1, which leads to the formation of vesicles (caveolae) that transport the albumin-drug complex and other fluid-phase components across the endothelial cells and into the tumor interstitium.[10,22-25] We have recently demonstrated in vitro that polyethylated castor oil inhibits this transport mechanism.[26] SPARC (secreted protein, acidic and rich in cysteine), another albumin-binding protein expressed by tumor cells and secreted into the tumor interstitium, is known to be overexpressed in breast cancer[27] and has been implicated in tumor progression and angiogenesis.[28] SPARC overexpression may account for preferential accumulation of the albumin-drug complex at sites of tumor.[29]

Despite a 50% increase in the dose of paclitaxel, patients treated with ABI-007 experienced significantly less neutropenia ($P < .001$). Polyethylated castor oil is believed to contribute to taxane-associated myelosuppression by inhibiting MDR1 P-glycoprotein in hematopoietic progenitor cells.[30] Because of its low volume of distribution, polyethylated castor oil remains within the vasculature compartment in continuous contact with bone marrow and may enhance myelosuppression, while having less effect on MDR1 in tumor tissues.[30]

In the CALGB trial,[8] the incidence and severity of myelosuppression were markedly increased with the higher doses of standard paclitaxel. In contrast, with ABI-007 260 mg/m^2, the incidence of grade 4 neutropenia was markedly lower than that expected with high-dose paclitaxel (9% for ABI-007 *v* 53% for standard paclitaxel 250 mg/m^2 in the CALGB trial). ABI-007–induced neutropenia also was substantially less frequent and less severe than that reported for solvent-based docetaxel.[2,31] In one study,[31] more than 90% of patients treated with docetaxel 100 mg/m^2 experienced severe neutropenia; clinical consequences included febrile neutropenia (12% of patients) and septic death (1.5% of patients).[2] Taken together, it seems that ABI-007 causes substantially less myelosuppression than the solvent-based taxanes.

Sensory and motor neuropathy are well-recognized AEs of solvent-based taxanes.[3,32-34] The incidence of grade 3 sensory neuropathy was higher with ABI-007 260 mg/m^2 than with standard paclitaxel 175 mg/m^2 (10% *v* 2%, respectively). However, this incidence was substantially lower than that reported with standard paclitaxel 250 mg/m^2 in the CALGB trial (32% grade 3 sensory neuropathy).[8]

Polyethylated castor oil has been shown to cause axonal degeneration and demyelination that can lead to prolonged, sometimes irreversible sensory neuropathy.[32,35-37] As a class effect, peripheral neuropathy would be expected to occur with solvent-free paclitaxel; however, without the damage induced by polyethylated castor oil, neuropathy might resolve more rapidly. Indeed, with ABI-007, sensory neuropathy improved rapidly (median, 22 days) from grade 3 to lower grades with treatment interruption.

Other well-recognized taxane-associated AEs (eg, myalgia and arthralgia) typically were self-limited, treated with acetaminophen, and resolved without dose modification or interruption. Similar to the experience with ABI-007 in phase II trials,[13,38] nail changes, excessive fluid retention, and lacrimal gland damage were not problematic in this phase III trial.

Because of the tolerability of high-dose ABI-007, it was possible to maintain most patients on the protocol-specified dose, with minimal disruption caused by AEs. In contrast to the CALGB trial, where physical function declined in patients who received solvent-based standard

paclitaxel at 210 or 250 mg/m^2,[8] the QOL of patients treated with high-dose paclitaxel administered as ABI-007 in the present study was not compromised.

In conclusion, this phase III study documented improved efficacy and favorable safety of ABI-007 compared with standard paclitaxel. ABI-007, the prototype of a new drug delivery system based on the use of albumin particles to preferentially transport drugs to tumors, seems to overcome the limitations of solvent-based paclitaxel. ABI-007 can be administered safely over a short period (30 minutes) with no special tubing or premedication. ABI-007 allows administration of paclitaxel at increased dose with minimal need for dose modifications, offering significantly improved efficacy compared with the current standard of solvent-based paclitaxel, without compromising QOL or patient safety. The superior efficacy, favorable safety profile, and greater patient convenience of ABI-007 make this novel albumin-bound paclitaxel an important advance in the treatment of patients with MBC. ABI-007 warrants further investigation, using additional dosing regimens (eg, weekly) and in combination with other treatment modalities, as front-line treatment of breast cancer and other solid tumors.

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