Prospective Randomized Trial of Docetaxel Versus Mitomycin Plus Vinblastine in Patients With Metastatic Breast Cancer Progressing Despite Previous Anthracycline-Containing Chemotherapy

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Purpose: **This phase III study compared docetaxel with mitomycin plus vinblastine (MV) in patients with metastatic breast cancer (MBC) progressing despite previous anthracycline-containing chemotherapy.**

Patients and Methods: **Patients (n = 392) were randomized to receive either docetaxel 100 mg/m² intravenously (IV) every 3 weeks (n = 203) or mitomycin 12 mg/m² IV every 6 weeks plus vinblastine 6 mg/m² IV every 3 weeks (n = 189), for a maximum of 10 3-week cycles.**

Results: **In an intention-to-treat analysis, docetaxel produced significantly higher response rates than MV overall (30.0% *v* 11.6%; *P* < .0001), as well as in patients with visceral involvement (30% *v* 11%), liver metastases (33% *v* 7%), or resistance to previous anthracycline agents (30% *v* 7%). Median time to progression (TTP) and overall survival were significantly longer with docetaxel than MV (19 *v* 11 weeks, *P* = .001, and 11.4 *v* 8.7 months, *P* = .0097, respectively). Neutropenia grade 3/4 was more frequent with docetaxel (93.1% *v* 62.5%; *P* < .05); thrombocytopenia grade 3/4 was more frequent with MV (12.0% *v* 4.1%; *P* < .05). Severe acute or chronic nonhematologic adverse events were infrequent in both groups. Withdrawal rates because of adverse events (MV, 10.1%; docetaxel, 13.8%) or toxic death (MV, 1.6%; docetaxel, 2.0%) were similar in both groups. Quality-of-life analysis was limited by a number of factors, but results were similar in both groups.**

Conclusion: **Docetaxel is significantly superior to MV in terms of response, TTP, and survival. The safety profiles of both therapies are manageable and tolerable. Docetaxel represents a clear treatment option for patients with MBC progressing despite previous anthracycline-containing chemotherapy.**

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METASTATIC BREAST cancer (MBC) is essentially incurable with current chemotherapies, and patients usually have a median survival time of approximately 2 years after documentation of metastasis.[1] Many cytotoxic agents have shown some activity in advanced breast cancer, and first-line chemotherapy regimens often include an anthracycline such as doxorubicin or epirubicin.[1,2] Although substantial palliation is achieved in responding patients, remissions are generally short-lived. When patients present with disease progression despite previous treatment with anthracycline-containing chemotherapy, the prognosis is considered to be extremely poor, and salvage therapy has a modest impact on outcome.[3]

Various chemotherapeutic agents have been used alone or in combination in this setting, but there is currently no standard salvage chemotherapy. The options routinely used at the time of study design included cyclophosphamide, methotrexate, and fluorouracil; methotrexate and fluorouracil/

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leucovorin; continuous-infusion fluorouracil; platinum combinations; and mitomycin and vinblastine, given as single agents or in combination (MV). More recently, capecitabine, vinorelbine, and paclitaxel have been added to the available options. Several reports have shown that MV has a greater antitumor activity than either agent alone,[3-11] but no survival advantage has been observed in favor of the combination.[1] Response rates vary from 7% to 40%, median time to progression (TTP) ranges from 3 to 4 months, and the median survival time is usually between 6 and 9 months.[1-3] The variation in results may be explained by the heterogeneity of the patient populations studied and the different doses and schedules used.[3,6-11] Although response rate and survival do not change significantly with the different MV regimens, the toxicity profile (particularly cumulative toxicity) is worse at doses of mitomycin greater than 12 mg/m^2,[7,9] or when mitomycin is given more frequently.[3]

Of the new agents isolated in recent years, the taxanes seem to show most promise in the treatment of breast cancer. Docetaxel (Taxotere; Rhône-Poulenc Rorer, Collegeville, PA), used at a dose of 100 mg/m^2/1-hour intravenous (IV) infusion, has shown significant activity in the treatment of patients with MBC who received previous anthracycline therapy. In four phase II studies involving 134 patients classified as anthracycline-resistant, docetaxel produced response rates ranging from 29% to 54%, with an overall response rate of 41% (95% confidence interval [CI], 35% to 50%), a median TTP of 4.3 months, and a median survival time of 10.6 months.[12]

Given the level of activity shown by docetaxel in phase II clinical trials, a phase III study comparing docetaxel with a salvage regimen in current use (the MV combination) seemed appropriate to evaluate the benefits and risks of these two treatments in patients with MBC progressing despite previous anthracycline-containing chemotherapy.

PATIENTS AND METHODS

Patient Population

Women older than 18 years with histologically or cytologically proven metastatic progressive adenocarcinoma of the breast and measurable or nonmeasurable-but-assessable disease (evaluable disease) were eligible for entry onto the study. Other requirements included a performance status of at least 60 (Karnofsky index); adequate hematologic, renal (serum creatinine level $<$ 1.5 times upper normal limit [UNL]), and hepatic functions (total bilirubin $<$ 1.25 times UNL, AST $<$ three times UNL, ALT $<$ three times UNL, and alkaline phosphatase $<$ six times UNL [unless bone metastases were present in the absence of any liver disorder]); and previous treatment with anthracycline chemotherapy for advanced disease or disease progression within 12 months of the end of anthracycline chemotherapy given in the adjuvant setting. Patients were excluded if AST or ALT levels were more than 1.5 times UNL and associated with alkaline phosphatase levels more than 2.5 times UNL. Patients were classified as resistant or not resistant to previous anthracycline chemotherapy as follows: primary resistance (relapse during adjuvant chemotherapy or disease progression without response or stabilization); secondary resistance (relapse within 12 months of adjuvant therapy or disease progression during chemotherapy after complete response, partial response, or stabilization); not resistant (disease progression more than 30 days after chemotherapy). Normal cardiac function was confirmed by left ventricular ejection fraction in patients who had received a cumulative dose of doxorubicin of at least 550 mg/m^2 or of epirubicin of at least 900 mg/m^2.

Specific criteria for exclusion were as follows: more than one line of chemotherapy for advanced or metastatic disease; previous treatment with mitomycin, vinca alkaloids, or taxoids; history or presence of CNS metastases; previous or concurrent malignancies, with the exception of curatively treated in situ carcinoma of the uterine cervix and nonmelanoma skin cancer; inadequately assessable disease, defined as patients with only blastic bone metastases, lymphangitic carcinomatosis, ascites, or pleural effusion; and pre-existing motor or sensory neurotoxicity of grade 2 or more according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC).

Concomitant bisphosphonate treatment was not allowed unless it was initiated more than 3 months before the start of the study. Patients were recruited from 50 centers in Europe, Canada, and South Africa. The study was conducted in accordance with the Declaration of Helsinki (Hong Kong amendment). Ethics committee approval and informed patient consent were obtained before the start of the trial. Study investigators other than those listed as authors are shown in the Appendix.

Study Design

This was a randomized, multicenter, nonblinded, prospective phase III study. The randomization was centralized at Rhône-Poulenc Rorer, Antony, France, with a block design by institution. There was no stratification for patient characteristics. However, anthracycline resistance was prospectively defined. Patients were assigned randomly at inclusion to receive an IV infusion of docetaxel 100 mg/m^2 for 1 hour every 3 weeks, or an IV infusion of mitomycin 12 mg/m^2 for 2 to 5 minutes every 6 weeks plus an IV bolus injection of vinblastine 6 mg/m^2 every 3 weeks. A cycle was defined as 3 weeks for both arms of the study. Premedication for hypersensitivity reactions and fluid retention was specified for patients in the docetaxel group and consisted of oral dexamethasone 8 mg administered 13 hours, 7 hours, and 1 hour before docetaxel infusion and for a further 4 days at a dose of 8 mg twice daily, starting immediately after docetaxel infusion. Antiemetic premedication for the MV group was given according to each center's normal practice. Prophylactic administration of granulocyte colony-stimulating factor was not allowed in either treatment group. Treatment of neutropenic complications was left to the discretion of the investigator. For the next cycle, after a neutropenic complication, dose reduction was the action planned in the protocol.

A maximum of 10 treatment cycles was set for both groups; fewer cycles were given if progression or unacceptable toxicity occurred. If no response to treatment was observed after six cycles, therapy was to be stopped. If a patient failed to respond to the assigned treatment, further treatment was administered at the discretion of the investigator. The choice of further antitumor treatment was again at the discretion of the investigator and could include switching to the alternative study treatment; however, this study was not designed with a cross-over portion in mind. Patients withdrawn from the study before disease progression could not receive other antitumor therapy until progression was documented, unless considered necessary by the investigator. The choice of treatment was at the discretion of the investigator. Patients

were observed for 1 month after their last study treatment infusion to document any late adverse events, with a follow-up visit every 3 months until death to document TTP and survival.

Dose reductions from 100 to 75 mg/m^2 and from 75 to 55 mg/m^2 for docetaxel, from 12 to 8 mg/m^2 and from 8 to 5 mg/m^2 for mitomycin, and from 6 to 4 mg/m^2 for vinblastine were planned for severe hematologic and nonhematologic toxicities other than alopecia and anemia, graded according to NCI-CTC.

Assessments

A complete tumor assessment, consisting of chest radiography and/or chest computed tomography scan, bone scintigraphy, bone radiography (if bone scintigraphy was positive), abdominal computed tomography scan or ultrasonography, and physical examination, was performed in the 3 weeks before the first infusion of study medication. Bone scintigraphy could be performed 4 weeks before the first infusion of study medication. All measurable and evaluable lesions were to be assessed at the end of cycles 3, 6, 8, and 10, or at discontinuation of study treatment, and then at least every 3 months until disease progression in the follow-up period.

Response was classified according to World Health Organization criteria. Complete response (no detectable tumor, including bone) and partial response ($\geq$ 50% reduction) had to be confirmed by a second evaluation more than 28 days later. Patients with no disease progression at least 6 weeks after the start of therapy were considered to have stabilization of disease. In addition, patients who did not have a response confirmed by a second evaluation more than 28 days later were classified as having stable disease. Patients with disease progression before the end of the second treatment cycle were considered to have early progression. Patients with inconsistencies between overall response and tumor measurements reported by the investigator were reviewed by an independent panel of two radiologists and an oncologist. This independent review was necessary for 10% of patients (the results after this review are reported).

Weekly blood counts were performed. Febrile neutropenia was defined as fever ($\geq$ 38°C) with grade 4 neutropenia that required IV antibiotics and/or hospitalization, without documented infection.

Fluid retention was monitored at each cycle and during follow-up until resolution. Severity of fluid retention was defined according to the following scale: mild (asymptomatic edema or effusion), moderate (edema that was pronounced or caused moderate functional impairment, or effusion that was symptomatic and possibly required drainage), and severe (edema that caused significant impairment or effusion, resulting in dyspnea that required urgent drainage).

Quality of life (QOL) was assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30).[13,14] A 30-item core questionnaire was completed by the patient in the 3 days before the first infusion, at every two cycles before receiving the study treatment, and at each visit during follow-up until the first disease progression occurred. Karnofsky performance status was used to assess patient condition from the physician's point of view.

Statistical Methodology and Analysis

The initial sample size of 194 patients per treatment group was selected to detect a 50% increase in median TTP with a 5% two-sided type 1 error and a 90% power. The sample size took into account the expectation that 10% of patients would not be assessable.

The intention-to-treat (ITT) population was defined as all randomized patients. The eligible and assessable population consisted of all patients who did not have a major deviation from the eligibility criteria, did not have an on-study deviation, received at least two cycles of treatment, and had at least one complete tumor assessment after the baseline evaluation. Analyses of response rate and TTP were performed on both the ITT population and on the eligible and assessable patient population. Analyses of survival and time to treatment failure were performed on the ITT population only.

Response rate was defined as the percentage of patients in each treatment group who achieved a complete or partial response. Patients who did not have an objective response confirmed 28 days later were censored at the date of last tumor assessment on-study. TTP was calculated from the date of randomization until disease progression or death. Patients who received any further antitumor treatment before disease progression were censored in the TTP analysis at the date of last tumor assessment before the start date of the new antitumor treatment. Time to treatment failure was calculated from the date of randomization until the date of disease progression, death for any reason, withdrawal because of adverse event, patient refusal, patient lost to follow-up, or further anticancer therapy before documentation of disease progression, whichever occurred first. Survival was calculated from the date of randomization until the date of death for any reason.

Categoric data such as response rate and adverse events were compared using the χ^2 test. CIs for response rates were computed using the exact method. Time-to-event variables were analyzed using the Kaplan-Meier method. Comparisons of efficacy variables, such as TTP and survival, were performed using the log-rank test and Wilcoxon test.

Multivariate analyses were performed on TTP and survival using a Cox proportional hazards model and on response rate using a logistic regression model, to analyze the treatment effect when adjusting for prospectively chosen covariates (resistance to previous anthracycline agents [not resistant, secondary resistance, primary resistance]; age [$\leq$ 49 years, $\geq$ 50 years]; Karnofsky performance status [100%, 90% to 80%, $\leq$ 70%]; time from first diagnosis to randomization [$\leq$ 12 months, $>$ 12 months]; time from last chemotherapy to randomization [$\leq$ 3, 3 to 12, $>$ 12 months]; visceral, liver, or bone involvement [no, yes]; number of organs involved [1, 2, $\geq$ 3]; intention of previous hormonal therapy [none, adjuvant, advanced $\pm$ adjuvant]; number of lines of hormonal therapy for advanced disease [none, 1, $\geq$ 2]; previous chemotherapy received as adjuvant [no, yes]; setting(s) in which previous chemotherapy was received [adjuvant, advanced, adjuvant + advanced]; and baseline QOL score [continuous variable]) or for the most significant covariates using the Collett selection strategy.[15]

Safety analyses were performed on all treated patients. For hematologic and biochemical changes, drug safety was analyzed directly from reported laboratory parameters. Analysis of hematologic parameters was performed for treated patients who had at least one blood count assessed between the second and 19th days of any cycle. Clinical signs and symptoms experienced on treatment were graded according to NCI-CTC, or as mild, moderate, or severe (COSTART [Coding Symbols for Thesaurus of Adverse Reaction Terms] classification) if NCI-CTC were not applicable.

All ITT patients who had an assessable baseline questionnaire and at least one further assessable variable on-study were considered assessable for QOL. The primary QOL variable was change in global health score, and the principal secondary variable was change in physical functioning score; changes in the other 13 dimensions in the questionnaire were also analyzed. The Wilcoxon rank sum test was used to compare differences between the two treatment groups. Median times to worsening of global health score by two points and Karnofsky performance status by 20 points were also analyzed by the Kaplan-Meier method.

All analyses were performed using the SAS software package (SAS Institute, Inc, Cary, NC). Differences at $P \leq .05$ were considered statistically significant.

RESULTS

Patients

Of the 392 patients randomized to receive study medication (docetaxel, n = 203; MV, n = 189), 200 patients in the docetaxel group (98.5%) and 187 patients in the MV group (98.9%) actually received treatment. The five patients who did not receive the study medication (docetaxel, n = 3; MV, n = 2) were included in the efficacy analyses, including survival.

The first patient was randomized on July 25, 1994, and the last was randomized on February 25, 1997. This report is based on data from all 392 randomized patients with follow-up until September 15, 1997. The median follow-up duration was 19 months, determined by the reverse survival Kaplan-Meier method.

The two groups were well balanced for pretreatment characteristics, except for number of organs involved (Table 1). The other important negative prognostic factors (age < 50 years, visceral and liver involvement, previous adjuvant chemotherapy, and resistance to previous chemotherapy) were well represented and equal in the two groups. Most patients (74% in each group) had at least one measurable lesion; 26% of patients in each group had evaluable disease only. All patients had metastatic disease.

Table 1. Baseline Characteristics of Randomized Patients

	Docetaxel (n = 203)		MV (n = 189)	
	No.	%	No.	%
Age, years				
< 35	7	3	6	3
35-49	80	39	73	39
50-65	94	46	92	49
> 65	22	11	18	10
Median	51.0		52.0	
Range	30-73		32-78	
Karnofsky performance status (%)				
Median	90		90	
Range	60-100		60-100	
No. of organs involved				
1	47	23	40	21
2	76	37	51	27
≥ 3	80	39	98	52
Site of metastases				
Soft tissue only	17	8	18	10
Bone	116	57	122	65
Viscera	153	75	138	73
Liver	102	50	88	47
At least one measurable lesion	151	74	139	74
Intention of previous chemotherapy				
Adjuvant only	34	17	40	21
Advanced only	100	49	94	50
Adjuvant + advanced	69	34	55	29
Response to previous chemotherapy				
Resistant	115	57	105	56
Primary resistance*	46	23	40	21
Secondary resistance†	69	34	65	34
Not resistant‡	88	43	84	44
Intention of previous hormonal therapy				
Adjuvant only	35	26	39	30
Advanced only	72	53	66	51
Adjuvant + advanced	28	21	24	19
Time from first diagnosis to first relapse, months				
Median	18		18	
Range	0-224		1-277	
Time from last chemotherapy to randomization, months				
Median	3.4		3.9	
Range	1-90		1-182	

*Relapse during adjuvant chemotherapy or progression as best response.

†Relapse within 12 months of adjuvant therapy, or progression during chemotherapy after complete response, partial response, or no change.

‡Progression > 30 days after chemotherapy for advanced disease.

Exposure to Study Medication

The median number of treatment cycles given was higher in the docetaxel group than the MV group (six cycles [range, one to 12 cycles] *v* four cycles [range, one to 12 cycles], respectively). Four patients (docetaxel, n = 3; MV, n = 1) received more than 10 cycles because the investigator thought that these patients might benefit from further treatment. The median relative dose-intensity was 0.94 (range, 0.01 to 1.05) for docetaxel, 0.99 (range, 0.65 to 1.43) for mitomycin, and 0.97 (range, 0.65 to 1.24) for vinblastine, with almost all patients in both treatment groups receiving a relative dose-intensity of more than 70% of the planned dose.

Of the 1,135 total cycles of docetaxel and the 860 cycles of MV administered, similar proportions of treatment cycles were delayed by at least 3 days in the two treatment groups (docetaxel, 9.9%; MV, 9.3%). Specifically, hematologic toxicity was the reason for treatment delay in 12 patients (6%) and 12 cycles (1%) in the docetaxel group and in 23 patients (12%) and 31 cycles (4%) in the MV group.

Most cycles in both treatment groups were administered at the initial planned dose (docetaxel, 80.3%; MV, 96.0%). Almost all dose adjustments were first-level dose reductions (docetaxel, 17.8%; MV, 2.9%). Fewer than 2% of patients in both treatment groups needed a second-level dose reduction. The main reason for dose reduction was hematologic toxicity (62% of dose-reduced cycles in the MV group and 51% of dose-reduced cycles in the docetaxel group).

Overall, 37 patients completed the maximum number of treatment cycles in accordance with the protocol; 24 in the docetaxel group and 13 in the MV group (11.8% *v* 6.9%, respectively). Reasons for treatment discontinuation were as follows: disease progression (docetaxel, 50.7%; MV, 65.1%; $P = .004$); adverse events (docetaxel, 13.8%; MV, 10.1%); withdrawn consent (docetaxel, n = 9.4%; MV, 6.3%); death (docetaxel, 5.4%; MV, 4.2%); protocol violation (docetaxel, 1.0%; MV, 0.5%); lost to follow-up (MV, 1.6%); other reasons unrelated to study medication (docetaxel, 6.9%; MV, 4.8%); and still on study (docetaxel, 1.0%; MV, 0.5%).

The adverse events that resulted in discontinuation most frequently were thrombocytopenia (5.3%) and constipation (1.6%) in the MV group and neurologic toxicity (5.5%) and fluid retention (2.9%) in the docetaxel group.

Efficacy

The overall response rate (complete responses plus partial responses) was significantly higher with docetaxel than with MV for both randomized and assessable patients (30.0% *v* 11.6% and 33.0% *v* 12.3%, respectively; $P < .0001$; Table 2). The complete response rate was also higher in the docetaxel group than in the MV group, and fewer patients in the docetaxel group had progressive disease without any response or stabilization. The response rate for patients treated within 3 months of last chemotherapy was 26% among 92 patients treated with docetaxel and 4% among 78 patients treated with MV. In the multivariate analysis, a significant treatment effect in favor of docetaxel was observed when adjusting for all covariates (odds ratio, 3.52; 95% CI, 2.0 to 6.18; $P < .001$) or adjusting for the most important ones using the Collett strategy (odds ratio, 3.3; 95% CI, 1.9 to 5.6). Docetaxel produced a higher response rate than MV in almost all subgroups analyzed, especially patients with a poor prognosis because of visceral (30.1% *v* 10.9%, respectively; $P < .01$) or liver involvement (33.3% *v* 6.8%, respectively; $P < .01$), or resistance to previous anthracycline agents (29.6% *v* 6.7%, respectively; $P < .01$; Fig 1).

Median TTP was significantly longer in the docetaxel group than in the MV group for both randomized (19 weeks *v* 11 weeks, respectively; $P = .001$; Fig 2) and assessable patients (19 weeks *v* 11 weeks, respectively; $P = .0004$). In the multivariate analysis using the Cox model, a significant treatment effect in favor of docetaxel was also observed when adjusting for all covariates or for the most important ones (risk ratio, 1.5; 95% CI, 1.2 to 1.9; $P < .001$). As previously noted, four patients (docetaxel, n = 3; MV, n = 1) received more than 10 cycles; an additional analysis of TTP, censoring these patients at cycle 10, gave the same results.

Table 2. Response to Treatment

Efficacy Variable	Randomized Patients		Assessable Patients	
	Docetaxel (n = 203)	MV (n = 189)	Docetaxel (n = 179)	MV (n = 171)
Response to treatment, % of patients				
Complete response	3.4	1.6	3.9	1.2
Overall response rate*	30.0†	11.6	33.0†	12.3
95% CI, %	23.7-36.4	7.1-16.2	26.1-39.8	7.4-17.2
Progression	26.6‡	46.6	29.6‡	50.9
Not assessable	8.4	7.9	0	0.6

*Complete responses + partial responses.
†$P < .0001$.
‡$P < .001$.

The median time to treatment failure was longer in the docetaxel group (16 weeks) than in the MV group (10 weeks); the difference between groups was significant according to the log-rank and Wilcoxon tests ($P = .0003$ and .0002, respectively; Fig 3).

The median overall survival of all randomized patients was significantly longer in the docetaxel group than in the MV group (11.4 months *v* 8.7 months; $P = .0097$; Fig 4). In the multivariate analysis, a significant treatment effect in favor of docetaxel was observed when adjusting for all covariates or for the most important ones (risk ratio, 1.4; 95% CI, 1.1 to 1.8; $P < .001$). No cross-over was planned, but at the time of progression, 47% of patients in the docetaxel group received further chemotherapy (12% with MV), and 54% of patients in the MV group received further chemotherapy (24% with docetaxel). The difference between treatment groups remained significantly in favor of docetaxel ($P = .007$) when overall survival was adjusted for the cross-over treatment as a time-dependent covariate.

Safety

The incidence of toxic deaths was similar in the two treatment groups (docetaxel, 2.0%; MV, 1.6%; Table 3). Hematologic adverse events related to study medication are listed in Table 4. Neutropenia occurred frequently in both groups. The incidence of grade 3/4 neutropenia was significantly higher in the docetaxel group than in the MV group (93% *v* 62%, respectively; $P \leq .05$). Febrile neutropenia and grade 3/4 infections also occurred significantly more frequently in the docetaxel group than in the MV group (9.0% *v* 0.5% and 11.0% *v* 1.1%, respectively; $P < .05$). The median time to neutropenic nadir was 7 days (range, 2 to 14 days) in the docetaxel group and 14 days (range, 6 to 22 days) in the MV group. The incidence of thrombocytopenia was significantly higher in the MV group than in the docetaxel group (overall incidence, 34% *v* 9%, respectively; $P < .001$; grade 3/4, 12% *v* 4%, respectively; $P = .004$). Prolonged thrombo-

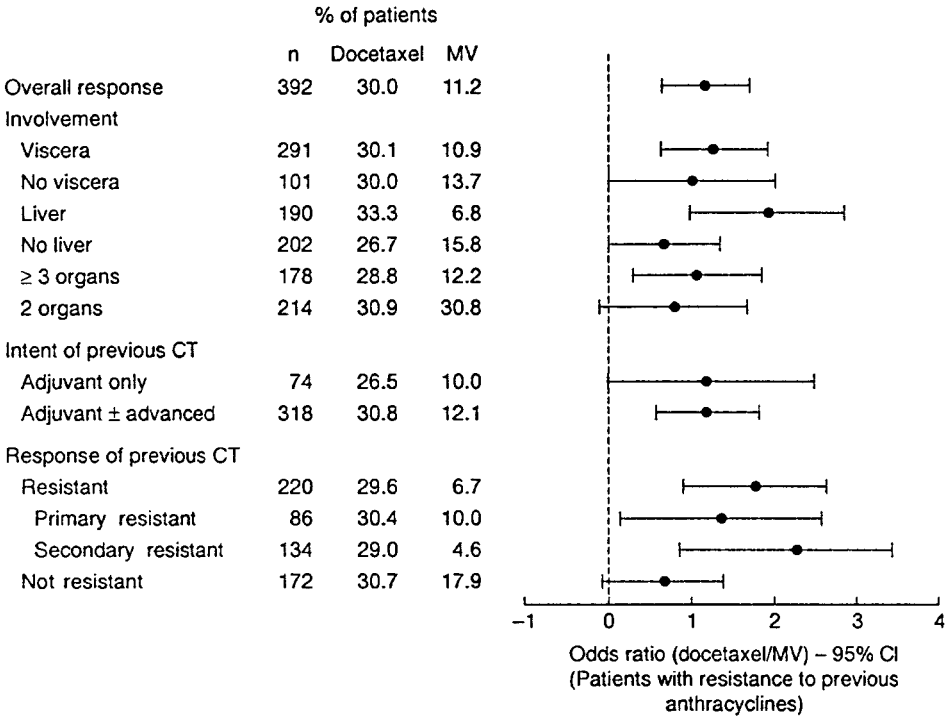


Fig 1. Odds ratio of response, docetaxel *v* MV.

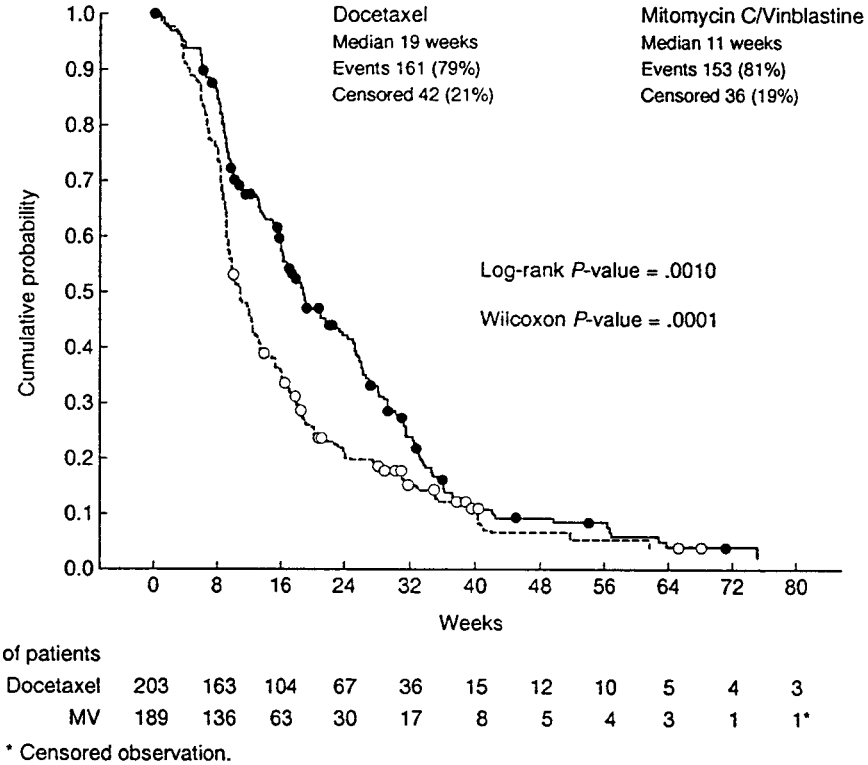
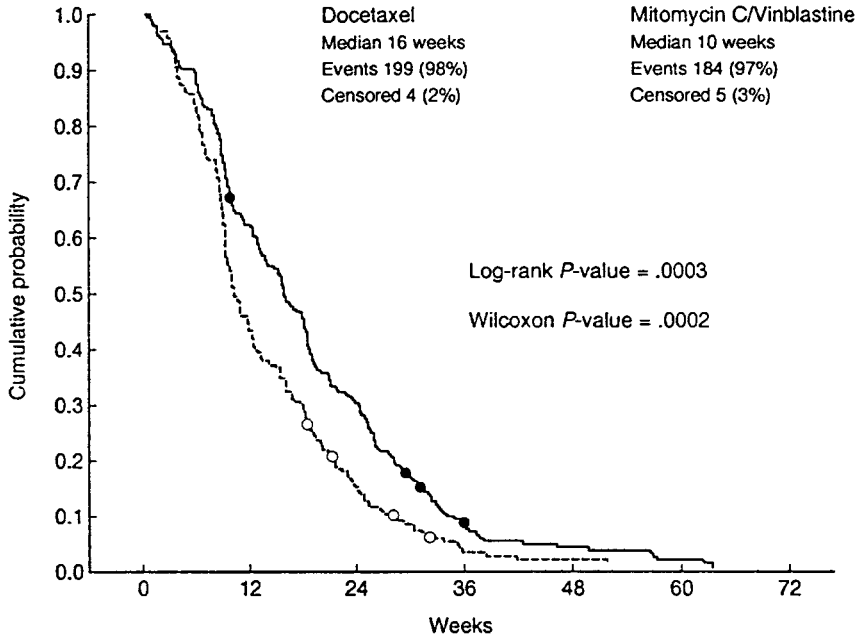


Fig 2. Kaplan-Meier estimate of the cumulative probability of remaining free of disease progression in each treatment group (ITT population) (●, docetaxel, n = 203; ○, MV, n = 189).

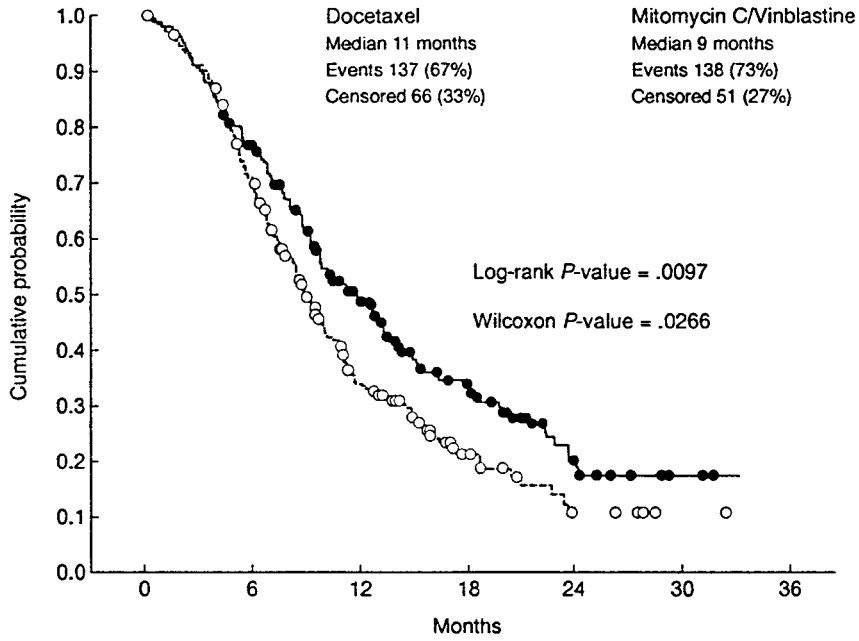


Number of patients

Docetaxel	203	125	60	12	6	2	0
MV	189	81	25	4	2	1	1*

* Censored observation.

Fig 3. Kaplan-Meier estimate of the cumulative probability of remaining free from treatment failure in each treatment group (ITT population) (●, docetaxel, n = 203; ○, MV, n = 189.



Number of patients

Docetaxel	203	150	78	41	14	3*	0
MV	189	123	48	17	5	1	0

* Censored observation.

Fig 4. Kaplan-Meier estimate of the cumulative probability of survival in each treatment group (ITT population) (●, docetaxel, n = 203; ○, MV, n = 189).

Table 3. Toxic Deaths

	Docetaxel (n = 203)		MV (n = 189)	
	No.	%	No.	%
Overall	4	2.0	3	1.6
On treatment	4	2.0*	2	1.1†
Off treatment	0		1	0.5‡

*Sepsis, pneumonia, unspecified infection, unexplained respiratory failure.

†Hemolytic uremic syndrome and progressive lymphangitic carcinomatosis possibly potentiated by mitomycin toxicity.

‡Interstitial pulmonary toxicity.

cytopenia caused treatment discontinuation in 10 patients treated with MV. There were four episodes of NCI grade 1 hemorrhage: one on the docetaxel arm and three on the MV arm. Neither neutropenia nor thrombocytopenia led to treatment discontinuation in the docetaxel group.

Nonhematologic adverse events related to study medication are listed in Table 5. Nausea, vomiting, local toxicity, and constipation occurred more frequently in the MV group, whereas allergy, diarrhea, stomatitis, myalgias, alopecia, skin toxicity, nail disorder, asthenia, and neurosensory toxicity occurred more frequently in the docetaxel group.

With regard to dose-cumulative toxicities specific to the two drugs, severe pulmonary toxicity occurred in 5% of the MV group and led to two toxic deaths, and severe fluid retention occurred in 8% of the docetaxel group. The median cumulative dose to onset of any fluid retention symptom was 477 mg/m^2.

QOL

Overall compliance, defined as the ratio between the number of assessable patients for QOL analysis and the number of patients on treatment at each cycle, was relatively similar in both groups. Compliance was high at baseline and at cycle 2 (docetaxel, 72%; MV, 68%) but decreased thereafter, reaching 59% for docetaxel and 61% for MV at cycle 8. Attrition (cumulative missing scores by cycle) was observed and was more evident in the MV group. When calculated for each cycle, the proportion of missing questionnaires was higher in the MV group than in the docetaxel group (55% *v* 40% and 71% *v* 55% at cycles 4 and 6, respectively). The attrition did not occur at random, and missing scores should therefore be considered to some extent as informative censoring. Overall, a significantly higher proportion of patients in the MV group than in the docetaxel group discontinued study treatment because of reasons associated with deterioration in condition, ie, progression of disease, patient refusal (in association with a variety of toxicities), adverse event, or death (MV, 82%; docetaxel, 63%; $P = .0004$). We therefore deduce that it was patients in the poorest condition of health who did not complete their QOL questionnaires. It follows that the decrease in QOL scores may have been underestimated in both groups, but particularly in the MV group.

At baseline, the two groups were similar in terms of global health score and physical functioning, with the exception of role functioning, where there was a significant imbalance in favor of docetaxel (means scores, 67.7 *v* 57.4, respectively; $P = .01$). The two groups were also similar with regard to symptom scales, with the exception of diarrhea (docetaxel mean score, 8.8; MV mean score, 2.9; $P = .01$).

With these limitations, longitudinal analysis showed that the global health status score was not different between the two treatment groups (mixed modeling approach, treatment effect; $P = .67$). Figure 5 shows the median of the mean change from baseline in all 15 dimensions of EORTC QLQ-C30 among all assessable patients. In assessments of the difference between groups for each dimension, patients treated with docetaxel fared significantly better than those treated with MV in terms of nausea/vomiting and appetite loss, whereas patients in the MV group fared significantly better than those in the docetaxel group in terms of role functioning and social functioning.

Table 4. Hematologic Adverse Events

	Docetaxel		MV	
Adverse Event	No.	%*	No.	%*
Neutropenia				
Overall	188	98.9	176	89.2
Grade 3/4	188	93.1‡	176	62.5
Febrile neutropenia†	200	9.0‡	187	0.5
Infection grade 3/4	200	11.0‡	187	1.1
Thrombocytopenia				
Overall	194	8.8	183	34.4‡
Grade 3/4	194	4.1	183	12.0‡

*Incidence of events possibly/probably related to study medication.

†Fever ≥ grade 2 and grade 4 neutropenia requiring hospitalization and/or antibiotics.

‡$P \geq .05$.

Table 5. Nonhematologic Adverse Events

	Overall (% of patients*)		Grade 3/4 or severe (% of patients*)	
Adverse Event	Docetaxel	MV	Docetaxel	MV
Acute				
Nausea	32.5	41.7	4.5	2.1
Vomiting	18.0	23.0	2.5	2.7
Stomatitis	56.0†	18.2	9.0†	0.5
Diarrhea	37.5†	7.5	7.5†	0
Skin toxicity	32.0†	1.6	4.0†	0
Local toxicity	9.0	13.9	1.5	2.1
Chronic				
Asthenia	62.5†	39.0	16.0†	6.4
Constipation	7.5	21.4†	0.5	3.2†
Nail disorder	41.0†	2.1	2.5†	0
Neurosensory	49.5†	19.8	5.0†	0.5

*Docetaxel, n = 200; MV, n = 187; incidence of events possibly/probably related to study medication.

†$P \geq .05$.

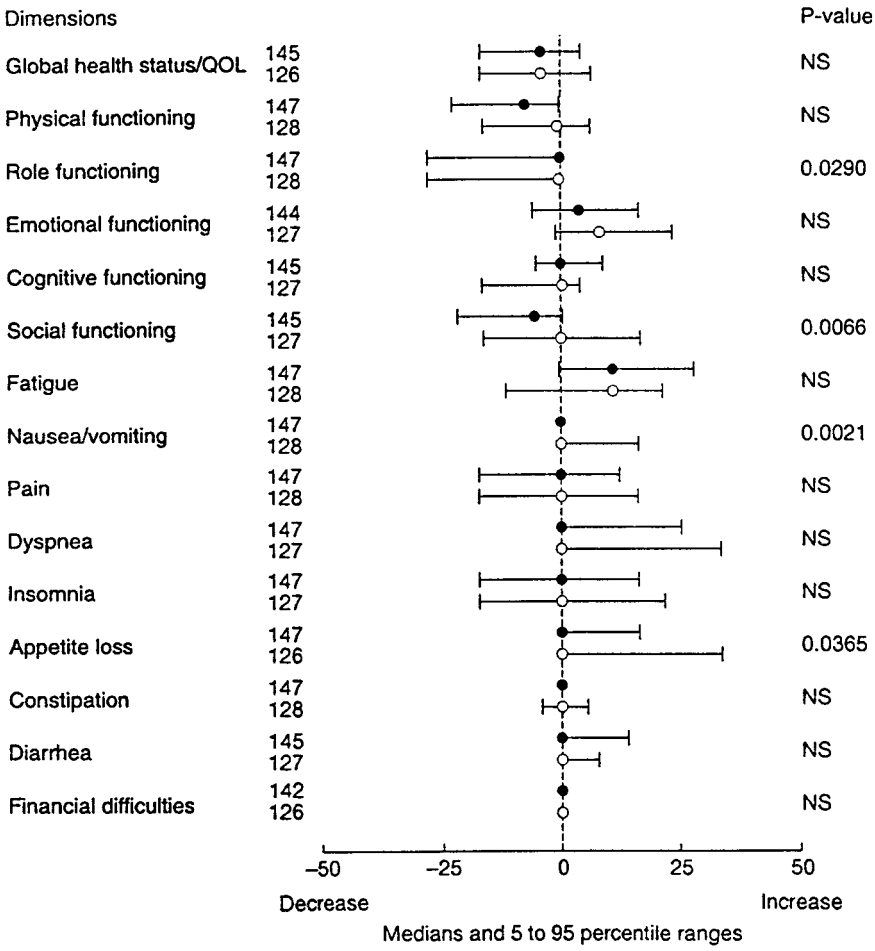


Fig 5. Median values of the mean changes in QOL scores from baseline (all assessable patients) (●, docetaxel, n = 147; ○, MV, n = 128).

The median time to worsening of the global health score by two points was longer in the docetaxel group, but this trend did not reach statistical significance (32 weeks in the docetaxel group [range, 6 to 33 weeks] and 24 weeks in the MV group [range, 4 to 32 weeks]). In addition, there was a similar trend in favor of docetaxel in the median time to worsening of the Karnofsky performance status by 20 points (34 weeks in the docetaxel group [range, 3 to 36 weeks] and 25 weeks in the MV group [range, 2 to 41 weeks]).

DISCUSSION

To our knowledge, this is the first large-scale, multicenter, prospective, comparative phase III trial in which a chemotherapeutic agent (docetaxel 100 mg/m^2/1-hour infusion) has been found to significantly increase TTP and survival more than another recognized chemotherapeutic regimen (MV, one of the widely used salvage chemotherapies) in the treatment of patients with MBC progressing despite previous anthracycline-containing chemotherapy. In this study, in which results are reported on the basis of an ITT analysis, docetaxel was significantly superior to MV in terms of overall response rate, TTP, and, most importantly, overall survival time.

The significantly higher objective response rate for docetaxel is especially notable because it is associated with a lower incidence of patients with progressive disease. However, the objective response rate achieved with docetaxel in our study was lower than that observed in phase II studies (median response rate, 41%).[12,16] Such a discrepancy between phase II and III studies is not uncommon, and in our trial may be attributable to a number of factors: a heavily pretreated study population with almost 40% of patients treated in adjuvant and metastatic settings; a high incidence of resistance to anthracyclines; and a high incidence of visceral metastases, specifically liver metastases. In addition, our study differed from phase II studies in that patients with evaluable disease were eligible for inclusion, which may have impaired the identification of partial responders.

In line with phase II trials in second-line MBC, we observed that response rates in subpopulations of patients with poor prognoses were consistently and significantly higher with docetaxel than with MV.[12] Of particular note were results in patients with liver, visceral, or multiorgan involvement and in those with previous exposure to multiple chemotherapies. Docetaxel produced a significantly higher response rate than MV in patients with liver metastases. For docetaxel, the response rate was similar in patients with or without liver involvement (33.3% and 26.7%, respectively). All patients had normal liver functions as per protocol entry criteria; therefore, this activity represents the effectiveness of docetaxel in patients with liver metastases and normal liver function. Response rates by category of resistance showed docetaxel to be consistently superior to MV regardless of anthracycline resistance subgroup, confirming the phase II findings that there is incomplete clinical cross-resistance between docetaxel and anthracyclines.

Although response to treatment is recognized as a valuable end point for assessing efficacy in MBC, TTP and, most importantly, overall survival are of paramount importance. Both TTP and overall survival were significantly longer with docetaxel than with MV. Moreover, the survival benefit with docetaxel seemed to persist beyond the 12-month time point: there were 49%, 58%, and 98% more survivors in the docetaxel group than the MV group at the 12-, 18-, and 24-month survival time points, respectively.

The differences between the groups in terms of outcome were confirmed by multivariate analysis. Treatment with docetaxel seemed to be an independent predictor of outcome when adjusting for all prognostic factors: the odds for response were 3.5 times higher in patients who received docetaxel, and the risk of death and progression were 1.4 and 1.5 times higher, respectively, in patients who received MV.

In designing this study, a literature review did not identify strong arguments in favor of any particular standard chemotherapy in this setting, which led to the choice of MV as the control group, because it was potentially neither better nor worse than any other salvage regimen.

Only direct comparative trials, such as this study, provide clear data on the superiority of one option over another. However, the comparative studies in the literature have not, to date, provided convincing arguments for the use of any particular regimen in this patient population. It has been shown that taxanes, including paclitaxel and docetaxel, are both partially non–cross-resistant with anthracyclines, and might therefore be a therapeutic option after anthracycline failure. In a limited phase II series,[17-20] and in a subgroup analysis in a large randomized phase II trial,[21] paclitaxel (various schedules and doses) produced response rates ranging from 6% to 48%. Comparative data are only available from a randomized phase II study in which paclitaxel (175 mg/m^2/3-hour infusion for 3 weeks) was compared with mitomycin alone (12 mg/m^2 for 6 weeks) in a small patient population (n = 81) that was similar to ours.[22] The overall results were poor in both groups, with response rates of 15% for paclitaxel and 5% for mitomycin, and median TTPs of 3.5 months for paclitaxel and 1.6 months for mitomycin.

Paclitaxel has also been evaluated in two phase III studies with a cross-over design. The first study was performed by the EORTC.[23] Of the 331 patients recruited, 68% were chemotherapy-naive and 32% had received alkylating chemotherapy with adjuvant intent. Patients were randomized to receive either doxorubicin (75 mg/m^2 bolus infusion for 3 weeks) or paclitaxel (200 mg/m^2 3-hour infusion for 3 weeks); 62 patients who experienced treatment failure with doxorubicin therapy were crossed over to receive paclitaxel. In the ITT analysis, the response rate for paclitaxel after doxorubicin failure was 13%, the median TTP was 13 weeks, and the median survival time from cross-over was 10 months.

The second study was performed by the Intergroup. In this large-scale three-arm trial (n = 739), doxorubicin 60 mg/m^2 bolus infusion for 3 weeks was compared with paclitaxel 175 mg/m^2 24-hour infusion for 3 weeks, and the combination of doxorubicin 50 mg/m^2 bolus infusion for 3 weeks plus paclitaxel 150 mg/m^2 24-hour infusion with granulocyte colony-stimulating factor.[24] Patients who experienced treatment failure with doxorubicin were crossed over to paclitaxel, and in the assessable patients' analysis, the response rate was 20%.

With regard to other types of chemotherapeutic agents, the semisynthetic vinca alkaloid vinorelbine has also been evaluated in this setting. Vinorelbine (30 mg/m^2/wk) was compared with melphalan (25 mg/m^2/4 weeks) in 183 patients with anthracycline-refractory advanced breast cancer.[25] Vinorelbine, although significantly superior to melphalan, produced a response rate of only 16%, a median TTP of 12 weeks, and a median survival time of 8.3 months. These results, together with the choice of control (melphalan), failed to provide convincing evidence of the advantage of vinorelbine for this patient population.

The safety profiles of both docetaxel and MV were as expected from phase II trials. The MV regimen is considered to be relatively mild in terms of toxicity.[3,6] It was particularly notable, therefore, that the rate of withdrawal because of adverse events (docetaxel, 13.8%; MV, 10.1%) and incidence of toxic death were similar in the two groups. In addition, a higher median number of treatment cycles was given in the docetaxel group (six cycles *v* four for MV), which illustrates the feasibility of the docetaxel dose.

The principle docetaxel-related hematologic toxicities were grade 4 neutropenia and clinically relevant associated complications, all of which occurred significantly more frequently in the docetaxel group than in the MV group.

Thrombocytopenia was significantly more frequent in the MV group than in the docetaxel group and resulted in treatment discontinuation in 5.3% of patients who received MV.

With regard to nonhematologic toxicities, nausea and vomiting were mild in both groups, as in phase I and II trials. Diarrhea and stomatitis were more frequent in patients who received docetaxel, whereas constipation was more frequent in the MV group. The incidence of grade 3/4 adverse events was low in both groups. The most typical taxane-associated toxicities (eg, allergic reactions and neurologic effects) occurred more frequently with docetaxel than with MV and at incidences similar to those in phase I and II trials. The finding that neurosensory toxicity was more frequent with docetaxel than with MV but was generally mild and reversible supports previously published data for docetaxel, and compares favorably with data from a large-scale trial evaluating paclitaxel (3-hour infusion schedule), in which the incidence of neurosensory toxicity (predominantly low grade) was approximately 70%.[21]

As expected, docetaxel-specific toxicities, such as nail changes and fluid retention, occurred more frequently in the docetaxel group than in the MV group, and severe changes were observed in only a small number of patients who received docetaxel. These results confirm the effectiveness of corticosteroid premedication to control fluid retention. It should be noted that this study used the 5-day corticosteroid premedication, whereas a 3-day premedication is now known to be equally effective and is associated with a lower incidence of infections and stomatitis.[26]

The evolution of QOL was not clinically significantly different between the two groups and was relatively stable for the entire duration of the two study treatments, despite the longer length of exposure to study medication in the docetaxel group. Compliance was similar in the two groups, but the attrition rate was higher in the MV group. These observations limit the interpretation of the changes in QOL scores from baseline, and any conclusions should therefore be drawn with caution. However, within these limitations, decreases in global health and physical functioning scores from baseline were not found to be clinically significant in either group.

In conclusion, this study not only shows the superiority of one treatment over another, but also shows that a more efficacious treatment can improve survival in patients with MBC. Additionally, these results confirm prospectively the concept of potential non–cross-resistance between anthracyclines and docetaxel and provide a compelling rationale for studies evaluating docetaxel/anthracycline–based combinations in the first-line treatment of MBC and, most importantly, in the adjuvant setting. Such studies will further establish the role of taxanes in the management of breast cancer and evaluate the real impact of these agents on the natural history of the disease.

APPENDIX
Other Study Participants

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